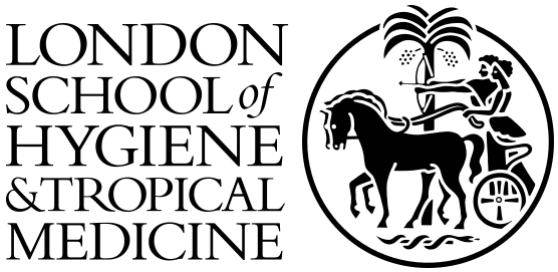


Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

Harriet Forbes

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy

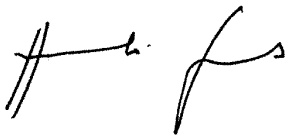
May 2016

Department of Non-Communicable Disease Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
University of London

Research group affiliation: Electronic Health Records Group
Funded by the National Institute of Health Research

Candidate declaration

I, Harriet Forbes, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed 

Thesis abstract

Background: Herpes zoster affects millions of people worldwide each year and many go on to suffer long-term pain, called postherpetic neuralgia (PHN). As zoster is common and PHN is difficult to treat, preventing zoster through vaccination is important. This thesis aims to better understand risk factors for zoster and PHN, in order to inform vaccination policy.

Methods: Three large observational studies were carried out using primary care data from the UK Clinical Practice Research Datalink and linked secondary care data from the Hospital Episodes Statistics. First, a matched case-control study quantified the effects of possible risk factors for zoster and explored whether their effects differed by age group. Second, a descriptive study looked at antiviral prescription patterns and patient characteristics associated with antiviral receipt after zoster diagnosis. Third, a cohort study assessed risk factors for PHN and investigated whether their effects were modified by antiviral use.

Results: The *case-control study of zoster risk factors* included 144,959 zoster patients and 549,336 controls and found an increased risk of zoster among patients with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression and type 1 diabetes; odds ratios ranged from 1.14 to 1.72. In general, the relative effects of these risk factors on zoster decreased with increasing age. In the *descriptive study of antiviral use*, of 142,216 zoster cases, only 58.1% received an antiviral prescription at zoster diagnosis. Antivirals were even under-prescribed among the immunosuppressed and older individuals, for whom guidelines recommend routine treatment. The *cohort study of PHN risk factors* identified 119,413 zoster patients, 5.8% of whom developed PHN. An increased risk of PHN was found among patients with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, depression, type 2 diabetes, lower socioeconomic status, smoking and under- or overweight; odds ratios ranged from 1.13-1.82. Antiviral use was not associated with PHN risk overall. The *zoster case-control* and *PHN cohort study* showed that patients with severely immunosuppressive conditions were at greatest risk of both zoster and PHN.

Conclusions: A number of patient characteristics and comorbidities were associated with increased zoster and PHN risks. Patients at highest risk of zoster and PHN are those of older age and those with immunosuppression; currently, patients with immunosuppression are not eligible for vaccination, highlighting a need for alternative risk reduction strategies in this group. Low antiviral use at zoster diagnosis suggests treatment guidelines be revised to encourage greater use, especially among the immunosuppressed and older individuals who are recommended, but not routinely given, antivirals. Research on the cost-effectiveness of vaccinating patients with specific risk factors is needed.

Acknowledgements

Thank you to my supervisors, Sinéad Langan and Krishnan Bhaskaran, for their guidance and encouragement throughout. Thanks also to Sara Thomas, Liam Smeeth and Tim Clayton, for being part of my advisory committee. I would also like to thank Caroline Minassian, Helen McDonald, Jenni Quint and CALIBER for providing previously developed code lists, from which I was able to work from.

Role of the candidate, ethics and funding

The candidate was employed under an NIHR Clinician Scientist fellowship awarded to Sinéad Langan entitled, “The natural history and management of herpes zoster: the role of moderate immunosuppression from common diseases”. The research aims and objectives of this thesis grew from this fellowship, and from discussion between the candidate and supervisors. The candidate conceptualised the research and designed the studies, with input from supervisors. The candidate was responsible for all data management and analysis.

Regarding the research papers included in the thesis, the candidate did all the analysis and wrote the initial draft for all papers, and incorporated comments from co-authors in an iterative process.

This project was approved by the London School of Hygiene and Tropical Medicine Ethics Committee. The scientific protocol (included in full in appendix I) was by approved the Independent Scientific Advisory Committee for MHRA Database Research in April 2011, and further amendments were approved in May 2012 and April 2014.

This project was funded by the National Institute of Health Research, specifically an NIHR Clinician Scientist Fellowship (to Doctor Langan, grant number: NIHR/CS/010/014).The work was carried out independently of the funding bodies. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the UK Department of Health.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
COPD	Chronic obstructive pulmonary disorder
EHR	Electronic health record
GP	General Practitioner
HES	Hospital Episodes Statistics
HLA	Human leukocyte antigen
HR	Hazard ratio
HZ/su	Herpes zoster subunit vaccine
IBD	Inflammatory bowel disease
ICD	International Classification of Disease
ICS	Inhaled corticosteroids
IMD	Index of multiple deprivation
mg	milligrams
NDD	Numeric daily dose
NHS	National Health Service
OR	Odds ratio
PHN	Postherpetic neuralgia
PPV	Positive predictive value
QoF	Quality and Outcomes Framework
RA	Rheumatoid arthritis
SD	Standard deviation
SES	Socioeconomic status
SLE	Systemic lupus erythematosus
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States
VZV	Varicella-zoster virus
WHO	World Health Organisation

Chapter 1: Introduction

In this introductory chapter, I present a brief overview of herpes zoster and postherpetic neuralgia (PHN), followed by details of the zoster vaccine. The aims and objectives of the research are then described and an outline of the thesis is given.

1.1. Introducing herpes zoster and postherpetic neuralgia

1.1.1. Herpes zoster

1.1.1.1. Clinical presentation, diagnosis and treatment

Herpes zoster, more commonly known as shingles, typically presents as a painful, vesicular rash with a dermatomal distribution, preceded by tingling, itching or pain, termed prodromal pain. The rash usually abates within four weeks. Ophthalmic zoster occurs in approximately 10% of cases and occurs when the rash appears in the dermatome supplied by the ophthalmic nerve.[1]

Diagnosis of zoster is largely made clinically in primary care; hospitalization is rare, occurring in around 1 to 4% of cases.[2] Antiviral therapy is recommended for patients deemed at risk of severe zoster, including all patients with immunosuppression and some immunocompetent patients.[3] However, it is not known if these antiviral treatment guidelines are adhered to in the United Kingdom (UK). Antiviral therapy has been shown to limit the duration and severity of zoster and accelerates healing.[4]

Zoster patients can experience a number of complications, the most common of which is PHN (see below). Other complications include; cranial and peripheral nerve palsies, encephalitis, and myelitis and, for ophthalmic zoster, chronic eye conditions and loss of vision;[4] few data exist describing the frequency of these complications, however they are believed to be very rare. More recent research has also suggested that zoster may be associated with increased risk of stroke; ophthalmic zoster was associated with over three times the risk of stroke in the 6 months after zoster onset.[5,6]

1.1.1.2. Pathogenesis of zoster

Primary varicella-zoster virus (VZV) infection manifests itself as varicella (chickenpox) infection, which is a highly infectious disease usually occurring before the age of ten in temperate

climates, after which the VZV lies dormant in sensory ganglia for many decades.[4] Zoster arises from the reactivation of latent VZV in sensory nerve cells,[7] whereupon the virus spreads along the nerve to the dermatome (an area of skin supplied by a single spinal or cranial nerve).

Over fifty years ago Hope-Simpson proposed that immunity played a role in zoster reactivation.[8] VZV-specific T cell-mediated immunity is understood to prevent reactivation of latent VZV and plays a greater role in suppressing reactivation than humoral immunity.[9,10] The importance of cell-mediated immunity is supported by several lines of evidence, including: (1) the decline in VZV-specific cell-mediated immunity with age,[11,12] correlating with the increased frequency of zoster in older individuals. This contrasts to VZV-specific antibodies which remain relatively constant as people age;[13] (2) immunocompetent individuals having lower VZV-specific immunity at the start of their zoster episode, compared to non-zoster controls;[14-16] (3) patients with immunosuppressive conditions affecting cell-mediated immunity being at greater risk of zoster;[17,18] and finally, (4) that vaccination of adults with the live VZV vaccine reduces the incidence of zoster and PHN, suggesting that augmentation of the cellular immune response to VZV can reduce reactivation.[19]

Cell-mediated immunity involves mostly T cells recognising VZV-infected cells and bringing about their destruction. No small-animal model replicates the signs and symptoms of varicella and zoster, therefore understanding of zoster pathogenesis is limited.[9,12] VZV-specific CD8+ (or cytotoxic) T cells have been detected, which recognise VZV antigens and destroy the infected cell.[20] VZV-specific CD4+ (or helper) T cells, which recognize VZV antigens and release cytokines (predominantly interferon-γ[12]) to activate other immune responses, are also believed to play a role in suppressing VZV reactivation.[12,21]

1.1.1.3. Epidemiology and risk factors

In the pre-varicella vaccine era in North America, over 95% of adults (age>20 years) were seropositive for VZV[22], putting the majority of these populations at risk of zoster. The lifetime risk of zoster is around 25%, increasing to around 50% for those reaching 80 years of age.[23] The annual rate of zoster is around 3 to 4 cases per 1000 persons across all ages, and an estimated 88,650 zoster cases occur each year in the UK among immunocompetent individuals aged over 60.[24] These numbers are expected to increase as the population ages.

Waning cell-mediated immunity is understood to lead to viral reactivation; therefore increasing age, due to a general waning of cell-mediated immunity during life, and severe immunosuppression are well-established risk factors for zoster.[23] However, these risk factors

do not explain the vast majority of zoster cases; over half of all zoster cases occur in people under 64 years of age,[13,25] so zoster is not exclusively a disease affecting older individuals, and over 90% of zoster cases occur among immunocompetent patients.[26] Despite this, predictors of zoster beyond age and severe immunosuppression are not fully understood. A full review of risk factors for zoster can be found in chapter 2.

1.1.2. Postherpetic neuralgia

1.1.2.1. Clinical presentation, diagnosis and treatment

PHN is a neuropathic pain syndrome which can develop after an episode of zoster.[27] Definitions of PHN vary, though the most commonly used classification is persistent pain 90 days or longer following onset of zoster rash.[27] Diagnosis of PHN is made clinically, on the basis of a patient's history and a physical examination of sensory function. The pain experienced by patients with PHN is described as a burning or stabbing pain, and can be accompanied by allodynia (pain triggered by contact with non-painful stimuli). This pain can last for months, years, or until death.[27] The pain associated with PHN can thus have a significant effect upon a patient's quality of life, physical functioning and mental health.[28-30]

PHN is a challenging condition to treat and strategies focus on pain management rather than resolution.[27] There are currently no therapies which can modify the course of the condition. Medications shown in randomized trials to reduce pain associated with PHN include topical lidocaine, anticonvulsant agents, opioids, tricyclic antidepressants and capsaicin.[4] In clinical trials of available therapies, fewer than half of patients with PHN have a 50% or greater reduction in pain and adverse effects are common, particularly in older individuals.[27] Some evidence exists suggesting antivirals administered during the acute zoster episode may reduce the risk of PHN, however the findings are inconclusive.[31]

1.1.2.2. Pathogenesis of PHN

Acute zoster infection undoubtedly results in nerve damage to both the peripheral and central nervous system, yet the nature of the damage and the specific mechanism resulting in persistent pain are not fully understood.[32] There are two non-mutually exclusive hypotheses for the development of PHN; the first is that a persistence of the VZV following acute zoster, at higher levels than during latency, causes continued pain; and the second, after acute zoster infection there is increased neuronal excitability and an alteration of pain perception caused

by neural damage.[33,34] A recent study showed that greater VZV cell-mediated immune responses in the first week after zoster onset was associated with less zoster morbidity and lower frequency of PHN.[35] This finding suggests that among patients with a better cell-mediated immune response, virus replication is limited and the underlying cell-mediated immune response plays an important part in PHN susceptibility.

1.1.2.3. Epidemiology and risk factors of postherpetic neuralgia

PHN is the most frequent complication of zoster, and the most common neuropathic pain following infection, developing in approximately 12.5% of patients with zoster aged over 50 years.[23]

The evidence regarding determinants of PHN is particularly limited. Increasing age is a clear risk factor for PHN[4] and PHN is rarely seen among those below 50 years of age. Certain features of the acute zoster episode, such as rash severity and prodromal pain,[36,37] are also commonly cited risk factors, although the evidence has never been systematically reviewed. A detailed systematic review and meta-analysis of risk factors for PHN can be found in chapter 6.

1.1.3. Preventing zoster and postherpetic neuralgia through vaccination

The importance of zoster and PHN morbidity has led to large-scale vaccination programmes in the United States (US), the UK, Australia and elsewhere.[38] A live-attenuated vaccine, called *Zostavax*, is currently used which works by boosting pre-existing cell-mediated immunity. Initially licensed in 2006 for patients aged 60 years and over, it is now approved for use in those 50 years and over.[39] Due to concerns that the live vaccine may lead to a varicella-like or herpes zoster illness from the vaccine virus strain, the vaccine is contraindicated in patients with conditions, or undergoing therapy, associated with severe immunosuppression.[40,41]

The vaccine demonstrated an efficacy of approximately 51% for zoster and 67% for PHN in a randomised controlled trial,[19] later substantiated in vaccine effectiveness studies.[42,43] Efficacy declines in older age groups and with time since vaccination.[44]

Due to the high-cost of the zoster vaccine, its use is limited. In the UK it is available to patients aged 70, 78 and 79 years of age and as of December 2014 uptake was estimated at around 60%.[45] Uptake in the US, where individuals over 60 years are eligible, reached 27.9% in 2014,[46] having previously been very low;[42] low uptake has in part been attributed to the high-cost of

the vaccine and difficulties around patient reimbursement, as well as low public awareness and logistic issues relating to vaccine supply.

More recently a recombinant subunit vaccine (HZ/su) has been developed and shown in a large randomised placebo-controlled trial (n=15,411) among patients ≥50 years to have a vaccine efficacy of 97.2%.[47] The HZ/su vaccine was equally as effective in patients ≥70 years, as patients <70 years. As opposed to the live *Zostavax* vaccine, the HZ/su vaccine may also be suitable for patients with immunosuppression, because the risk of disease resulting from replication of the vaccine virus is prevented.

1.2. Aim, rationale and research questions

The overall aim of this research is to better understand risk factors for zoster and PHN to inform vaccination policy. Considerable research has been carried out demonstrating the effect of older age and severe immunosuppression on the risk of zoster, and to a lesser extent PHN, however evidence regarding other risk factors is limited. Given the high frequency of zoster which is set to increase in the ageing population, and the intractability and lack of effective treatments for PHN, identifying groups who would benefit from the effective zoster vaccine could have important public health benefits (assuming the vaccine is safe, effective and sufficiently durable in these patients groups).

Three observational studies using electronic health records (EHR) data were conducted to answer the following research questions.

1.2.1. What are the risk factors for herpes zoster?

The first study of this thesis investigates the effects of possible risk factors for zoster. Many previous studies investigating risk factors for zoster have suffered from low power. Furthermore, few studies have evaluated multiple risk factors simultaneously, which has not enabled a consistent methodological approach to be applied to various factors.

A population based matched case-control study was therefore conducted, using data from the Clinical Practice Research Datalink (CPRD) to assess risk factors for zoster, namely autoimmune conditions including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD), and other medical conditions such as diabetes mellitus, chronic obstructive pulmonary disorder (COPD), chronic kidney disease (CKD), asthma and depression. A case-control study was carried out as its design makes it convenient to look at multiple exposures.

1.2.2. Who receives antiviral therapy following diagnosis of herpes zoster?

The second study aims to analyse antiviral prescription patterns after a zoster diagnosis. As PHN risk may be modified by antiviral use, an understanding of how commonly antivirals are used within UK general practice is an important preliminary step, before assessing risk factors for PHN. Research on the proportion of zoster individuals prescribed antivirals is limited and previous studies have reported overall use, rather than use by specific risk groups.

Therefore a descriptive study among zoster patients was carried out to calculate the proportion of zoster cases receiving antivirals. A risk factor analysis was also conducted to assess associations between patient characteristics and antiviral use.

1.2.3. What are the risk factors for postherpetic neuralgia?

The final research question of the thesis is to identify risk factors for the most common complication of zoster, PHN. For this question, a systematic review of risk factors for PHN was carried out. Following the review, a cohort study was conducted among previously identified zoster patients to identify those at higher risk of developing PHN. A cohort study design was chosen as it allowed the estimation of the incidence of PHN following zoster. This approach also allowed inclusion of all zoster cases, thus maximising the power of the study and reducing the possibility of selection bias.

1.3. Outline of thesis

The thesis follows the research paper style format, with articles incorporated into the chapters. Five articles have been written, four of which are published and one accepted, in peer-reviewed journals. Each chapter containing a research article is opened with a concise introduction describing the structure of the chapter. The original formatting of the journal articles has been kept. In some chapters the paper is followed by additional analyses and discussion, which could not be included in the published or submitted paper, due to length restrictions. There is some repetition in the thesis, as the chapters were written as separate publications.

Below is an outline of the thesis, describing the content of each chapter:

Chapter 2 presents a published literature review of the epidemiology and prevention of zoster, with an in-depth discussion of risk factors for zoster.

Chapter 3 provides a detailed account of the general methods which are relevant to the three key research questions. Specifically, it initially describes the data sources utilised in the thesis. It goes on to outline how zoster and PHN were defined. Finally, it outlines the definitions of other explanatory variables in the thesis.

Chapter 4 incorporates the first research paper; a population-based case-control study of risk factors for zoster.

The second research paper, a description of who is getting treated with antivirals in UK primary care, after a zoster diagnosis, is presented in *chapter 5.*

Chapter 6 contains a systematic review and meta-analysis of risk factors for PHN.

Chapter 7 presents the study investigating risk factors for PHN, nested within zoster patients.

In *Chapter 8* the findings from the thesis are summarised and discussed in the context of what was previously known on this topic. The suitability of the data sources for answering the research questions are then discussed and the implications of the findings on future research and clinical practice are explored.

1.4. Chapter summary

Introduction

- Zoster is a common dermatological condition caused by the reactivation of VZV, during periods of suppressed T cell-mediated immunity. It is more common in older and immunosuppressed individuals.
- Zoster can cause a number of complications, the most common of which is PHN, a neuropathic pain which can last for months to years, and affects approximately 12.5% of zoster patients over 50 years of age. The pathogenesis and risk factors for PHN are poorly understood.
- Zoster, and thereby PHN, can now be prevented through vaccination. However, the vaccines high-cost means its use is limited to older individuals, and because it is a live vaccine, it cannot be administered to immunosuppressed individuals.
- This thesis aims to better understand risk factors for zoster and PHN.

Chapter 2: Epidemiology and prevention of herpes zoster: literature review

2.1. Introduction

This chapter provides a general overview of the epidemiology and prevention of zoster, with a particular focus on describing risk factors for zoster. Current Dermatology Reports invited a literature review on this topic, and it appears below. As the review was carried out in 2011, evidence on zoster risk factors published between 2011 and 2016 has been gathered, and is summarised after the paper.

2.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Harriet Forbes
Principal Supervisor	Sinead Langan
Thesis Title	Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Current Dermatology Reports		
When was the work published?	18th January 2012		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I carried out all background reading and wrote first and subsequent drafts. My co-authors contributed to this work in an advisory capacity, commenting on and editing drafts.

Student Signature: _____ **Date:** 9/5/2016

Supervisor Signature: Sneed Kanjan Date: 4/3/2016

Curr Derm Rep (2012) 1:39–47
DOI 10.1007/s13671-011-0004-4

EPIDEMIOLOGY (J GELFAND, SECTION EDITOR)

The Epidemiology and Prevention of Herpes Zoster

Harriet J. Forbes · Sara L. Thomas · Sinéad M. Langan

Published online: 18 January 2012

Abstract Herpes zoster is a common disease among older individuals, affecting approximately 25% of people in their lifetime and resulting in appreciable morbidity. The risk of zoster increases sharply with age and immunosuppression, yet relatively little is known about other risk factors for zoster. A vaccine for zoster is now available that holds the potential to reduce incidence of zoster and its complications. In this review, the recent literature on zoster incidence and potential risk factors for the disease are summarized. Current methods of preventing zoster and its associated morbidity are discussed, including zoster vaccine and the use of antivirals.

Keywords Shingles · Herpes zoster · Epidemiology · Incidence · Vaccine

Introduction

Herpes zoster is a common disease among older individuals, with a lifetime risk of 10% to 30% that rises to 50% among those living to ≥85 years [1•]. It is caused by the reactivation of latent varicella zoster virus (VZV), which can lie dormant for many decades after varicella (chickenpox) infection. Reactivation is thought to result from waning cell-mediated immunity. Zoster typically presents as a painful unilateral vesicular dermatomal rash (Fig. 1) that causes acute morbidity lasting between 2 weeks and 1 month [2].

The most common complication of zoster is post-herpetic neuralgia (PHN), which develops in around 20% of individuals aged ≥50 years [3]. PHN is often defined as pain persisting for >90 days after the onset of the rash; the pain can be very severe and remain for years [4]. Although zoster is rarely fatal, the pain associated with the acute phase of the disease and subsequent PHN significantly reduces quality of life [5]. Other rarer complications of zoster, such as cranial and peripheral nerve palsies [6], encephalitis and myelitis [7], and stroke [8, 9], have been described but few data exist about the frequency and severity of these complications.

There are two main reasons to present an update of the epidemiology and prevention of zoster. Firstly, zoster predominantly affects older populations, and with an increasingly aging population, it is likely to become increasingly common. Secondly, a vaccine to prevent zoster has recently been introduced for adult immunocompetent individuals in the United States and Australia, so this is an exciting era for zoster epidemiology and warrants increased research focus.

In this review, we summarize the literature on zoster, using key articles and reviews up to 2003 with more detailed investigation of recent research. We cover incidence of zoster and risk factors for the disease. Current methods for preventing zoster and its associated morbidity are discussed, including antivirals and the recently developed vaccine. Important unanswered clinical questions identified during the review are listed in Table 1.

Epidemiology

Incidence

Incidence in General Population

A systematic review published in 2004 found the overall incidence of zoster among immunocompetent subjects ranged from 1.2 to 4.8 per 1000 people per year [1•]; recent

H. J. Forbes (✉) · S. L. Thomas · S. M. Langan
Faculty of Epidemiology & Population Health,
London School of Hygiene and Tropical Medicine,
Keppel Street,
London WC1E 7HT, UK
e-mail: Harriet.forbes@lshtm.ac.uk

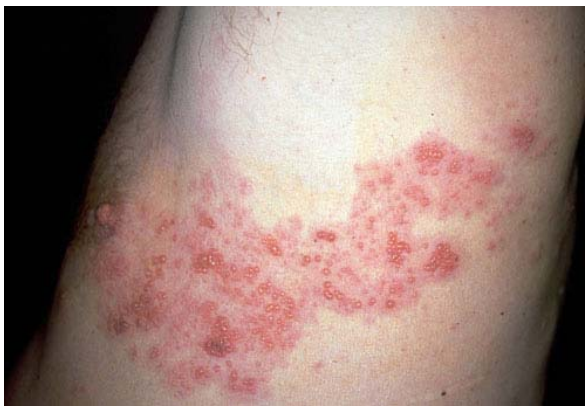

Fig. 1 Acute herpes zoster. (Courtesy of Professor Dr Thomas Diepgen, Heidelberg, Germany)

studies from the United States [10, 11] and France [12] have also reported disease incidences within this range. The incidence of zoster increases markedly with age, with estimated incidences of up to 14.2 per 1000 people per year in those aged ≥50 years in the United States [1•], the United Kingdom [3], Italy [13], and Germany [14].

Incidence Among Immunosuppressed

The incidence of zoster among people with a generalized loss of cell-mediated immunity either from immunosuppressive disorders, such as HIV and cancer, or from the use of immunosuppressive therapies is much higher than in the general population, with incidence rates ranging from 14.5 to 53.6 per 1000 person-years [15–20]. In a retrospective cohort study using the Veteran Affairs administrative databases in the United States, the rate of zoster following a solid organ transplant was estimated at 22 per 1000 person-years overall, with higher rates seen among African American patients (37.6 per 1000 person-years) and heart transplant patients (40 per 1000 person-years) [17].

The incidence of zoster among patients on biologic drugs is of interest due to the increased use of these drugs and their potential impact on cellular immunity. A retrospective cohort study in Israel among psoriasis patients found zoster incidence was higher among patients treated with biologics such as infliximab (19.1 per 1000-person-years) compared to patients not on systemic therapy (4.6 per 1000 person-years) [21], but the difference in incidence did not reach statistical significance. Data from registries of patients with rheumatic diseases treated with biological agents in Spain [22], Germany [23], and France [24] suggest an increased risk of zoster when these patients are treated with monoclonal antibody–tumor necrosis factor (TNF) inhibitors. However residual confounding may contribute to these findings. A longitudinal study from the United States of patients in the National Data Bank for Rheumatic Diseases found biologics were not a risk factor for zoster [25], whereas a retrospective cohort study using an American administrative data source of people with rheumatoid arthritis reported those taking biologic therapy were at higher risk of zoster (adjusted odds ratio [OR] 1.54; 95% CI, 1.04–2.29) compared to patients not taking disease-modifying drugs or corticosteroids (but those taking oral corticosteroids were at even higher risk (adjusted OR 2.51; 95 CI, 2.05–3.06)) [26]. Disentangling risk associated with disease severity and impact of therapy remain challenging.

Recurrent Incidence

It is widely believed that second episodes of zoster are very uncommon, except among immunosuppressed individuals for whom recurrent zoster is well described. Therefore, a surprising finding from a recent population-based, retrospective cohort study in Minnesota was that of 1530 individuals diagnosed with zoster and deemed "immunocompetent" at the time of diagnosis, a second zoster episode was recorded in 5.7% in the subsequent 8 years [27]. Misclassification of immune status is possible in this study: immune status was determined only at the time of the first zoster episode and individuals with HIV infection who had not yet developed AIDS-defining illnesses and those taking low doses of systemic corticosteroids (<5 mg/d) were deemed immunocompetent. Thus, the immunocompetent group may have included some individuals with moderate immunosuppression at baseline as well as some who became immunosuppressed during follow-up [27, 28]. In addition, a small proportion of the clinically diagnosed zoster cases could have had herpes simplex rather than zoster. Research using larger datasets and more detailed characterization of immune status over time would be useful to confirm these findings. As expected in

Table 1 Unanswered questions

What is the risk of zoster among older patients with specific co-morbidities?
Can newer antiviral agents, such as famciclovir and valacyclovir, reduce the duration and severity of post-herpetic neuralgia?
What is the absolute risk of zoster directly related to treatment with biologic medications?
What approach should clinicians take regarding interruption of therapy in patients receiving biologics to administer the live zoster vaccine?

the Minnesota study, risk of recurrent zoster was almost three times higher among the 139 immunosuppressed patients compared to those classified as immunocompetent (hazard ratio [HR] 2.80; 95% CI, 1.84–4.27).

Temporal Changes in Incidence

Despite an expectation that aging populations and increasing use of immunosuppressive therapies during the course of the 20th century could have caused an increase in occurrence of zoster, reports of temporal changes in zoster incidence are conflicting [1•]. Interest in trends in zoster incidence over time heightened after the introduction of the varicella vaccine because of concerns that by removing exogenous boosting of VZV immunity from varicella contacts [29], zoster incidence could rise among older unvaccinated individuals with latent VZV infection [30].

Varicella vaccine became available in the United States in 1995 for healthy children aged over 12 months, susceptible adolescents, and adults. Vaccine uptake in the United States was slow during the first 5 years but increased from 68% in 2000 to 89% in 2006 among 19- to 35- month-old children [31]. Studies of the impact of introduction of the varicella vaccine on zoster incidence have shown inconsistent findings. Jumaan et al. [32] report no increase in zoster incidence between 1993 and 2002 among patients enrolled with a health insurance organization in Washington state [32]. In contrast, two further US studies report increases in zoster incidence rates following varicella vaccination. A telephone survey in Massachusetts found an increase in zoster incidence from 2.77 to 5.25 cases per 1000 people between 1999 and 2003 [33]. A study using the Veterans Administration database reported that between 2000 and 2007 (when vaccine coverage was higher), zoster increased from 3.10 to 5.22 episodes per 1000 people aged ≥40 years, although rates per year were not standardized for age [34]. Interpretation of the impact of the vaccine on zoster also has to consider background trends in zoster incidence. A further US study described greater increases in zoster incidence rates before varicella vaccine licensure compared to post-licensure periods, although interpretation was complicated by exclusion of Medicare enrollees (ie, older individuals receiving Medicare health insurance) from the earlier estimate [31]. As most older individuals in the US are enrolled in Medicare and the majority of zoster episodes occur in this age group, the true incidence rates may be distorted. Increases in zoster incidence prior to varicella vaccine introduction have also been described in Canada [35], Australia [36], and Spain [37]. Whether population-based varicella vaccination affects zoster incidence remains controversial.

Risk Factors for Herpes Zoster

Any factor impacting on VZV-specific or general cell-mediated immunity may affect risk of zoster. However, beyond the two key risk factors of age and immunosuppression, relatively little is known. Potential risk factors for zoster are outlined below.

Factors Affecting General Cell-Mediated Immunity

Age

The most important risk factor for zoster is increasing age, with incidence rates rising among older individuals (see above). This is likely to be due to immunosenescence (the generalized waning of cell-mediated immunity over the life course), which puts individuals at greater risk of many infections [38], as well as waning of VZV-specific immunity with increasing time since primary infection.

Immunosuppression

As discussed in the section on zoster incidence, the incidence of zoster among patients with immunosuppressive diseases is far greater than among the general population. Patients with HIV have up to 10 times the risk of developing zoster compared to the general population [18], and in specific young African populations, the positive predictive value (PPV) for underlying HIV infection when zoster is present is 85% to 90% [39, 40]. The PPV will vary depending on HIV prevalence in the population; reported PPVs of zoster for HIV vary from 3.7% in Brazil to 91% in a Ugandan study population [41, 42]. The risk of zoster is also markedly increased among those with leukemia, lymphoma, and metastatic malignancies and among those with selected autoimmune disorders, although disentangling immunosuppression related to disease pathology from immunosuppressive therapies for these conditions (discussed below) is challenging [15, 26, 43–47]. Recent studies have indicated that diseases associated with less marked immune suppression may also increase the risk of zoster. A retrospective hospital-based cohort study in Japan showed an increased risk of zoster among diabetic patients (HR 2.38; 95% CI, 2.04–2.78) [48] as did a nested case–control study from Israel (OR 1.53; 95% CI, 1.44–1.62) [49]. Chronic obstructive pulmonary disorder (COPD) has also been associated with increased risk of zoster, again possibly reflecting the therapies used [50]. Although the magnitude of the risk is smaller than among patients with severe immunosuppression, the high prevalence of common diseases means that the absolute number of people affected may be significant.

Increased zoster incidence is also reported in specific high-risk groups with iatrogenic immunosuppression following treatment with cytotoxic drugs or therapies affecting the immune response. The increased risk of zoster identified among individuals with COPD or with autoimmune disorders such as rheumatoid arthritis, Wegener's granulomatosis, or systemic lupus erythematosus mentioned above may partly reflect use of corticosteroids or disease-modifying drugs. Recent observational data from a German and Spanish biologics registry has suggested additional increases in zoster incidence related to use of monoclonal drugs inhibiting TNF-α in rheumatoid arthritis treatment [22, 23], consistent with findings from randomized controlled trials and observational studies in large databases in the United Kingdom and United States. Findings from psoriasis biologic registries are awaited to identify the long-term effect of biologic therapies on zoster risk. Although the relative risk among people with major immunosuppression from specific diseases and/or therapeutic interventions is high, these individuals account for <10% of cases with zoster in most population-based studies [10, 51] from Europe and North America.

Gender

Thomas and Hall's [1•] systematic review suggested that female sex may be a risk factor for zoster. Subsequent studies from the United States, United Kingdom, Italy, France, and Germany have reported significantly higher incidence rates among women [3, 10, 12–14]. It is unclear to what extent the reported increased incidence rates in women reflect a bias due to differences in health-seeking behavior as opposed to biological mechanisms affecting cell-mediated immunity that could put women at higher risk [1•].

Diet, Smoking, and Alcohol Use

Diets low in micronutrients may increase zoster risk by diminishing cell-mediated immunity and hastening immunosenescence among older individuals. A UK case–control study found no association between intake of single micronutrients and risk of zoster; however, among individuals aged ≥60 years, combined low micronutrient intake and low vegetable intake were associated with increased risk of zoster, as was lower fruit intake (at all ages) [52]. These results suggested that a mixture of nutrients in the diet may be necessary to maintain immune system health. Accurate measurement of micronutrient and diet intake is notoriously difficult; however, the study found strong dose–response associations that give credence to the findings.

Smoking and alcohol can affect cell-mediated immunity [53, 54], although no studies have been specifically designed to look at their effect on zoster risk. A cohort study in North Carolina found smoking was associated with a markedly lower risk of zoster [55], whereas another study using routine data from UK general practices from 1991 to 92 found no association between smoking and zoster risk [1•].

Stress

Stress may increase risk of zoster as it affects a number of neuroendocrine functions that can affect cell-mediated immunity [56]. A case–control study in North Carolina found stressful life events were more common in zoster cases within the 6 months prior to rash onset than in age-matched controls (2.64 vs 1.82 events; P=0.008), although recall bias may have contributed to this finding [57]. Analyses of the same population using a cohort study design found some evidence that negatively perceived life events were weakly associated with risk of subsequent zoster (risk ratio [RR] 1.38; 95% CI, 0.96–1.97), although the study lacked power to detect a significant effect [55]. A retrospective cohort study in Taiwan found patients with a psychiatric illness were more likely to have an episode of zoster (HR 1.29; 95% CI, 1.18–1.38) [58], which may reflect increased stress among these patients.

Factors Affecting Varicella Zoster Virus-Specific Immunity

Age at Primary Infection

Individuals acquiring varicella later in life have been hypothesized to be at lower risk of zoster as their immunity to VZV may last to older ages. No published studies have looked at this hypothesis directly, but country of birth has been taken as a proxy for age at varicella infection. Typically, in temperate areas, varicella onset is during childhood, whereas onset is often delayed until adolescence or even adulthood in some tropical areas such as southern India, Sri Lanka, and the Caribbean. Late varicella acquisition has been suggested as the reason why people of black ethnicity in a US study of older individuals had around one third the risk of zoster compared with those of white ethnicity (OR 0.35; 95% CI, 0.24–0.51) [55].

There is also some evidence that very early acquisition of varicella, in utero or in early infancy, may increase the risk of zoster during childhood and adolescence, perhaps because the immune system is not able to establish VZV immunity at such a young age [59].

Varicella Contacts

Hope-Simpson [29] hypothesized in 1965 that exposure to individuals with varicella could naturally boost VZV-

specific immunity in individuals with latent VZV infection and thus could protect against zoster [29], leading to the concern, as outlined in the section on zoster incidence, that population-based varicella vaccination might lead to changes in the incidence of zoster. Hope-Simpson's theory has been supported by a UK population-based case–control study of incident zoster cases and age- and sex-matched controls. The study found increasing protection against zoster with increasing number of varicella contacts in the 10 years before zoster, and a similar association with child contacts (used as proxies for unrecognized varicella contacts) [1•]. In contrast, a recent US case–control study of individuals interviewed 2 months to 5 years after zoster diagnosis found no evidence that varicella contacts or child contacts protected against zoster [60]. Even participants with three or more varicella contacts over the past 10 years were not associated with a significantly increased* risk of zoster compared with participants with no contacts (OR 1.37; 95% CI, 0.82–2.27). However the incidence of varicella at the time of the US study was low in comparison to that in the UK study, due to the US population-based varicella vaccination program. Few participants in the US study had more than two contacts with varicella in the previous 10 years (2% of controls compared with 17% of controls in the UK study), and some of these contacts could have been mild cases of breakthrough varicella in vaccinated children. Thus, participants in the US study perhaps had insufficient exposure to varicella to provide exogenous boosting.

Other Risk Factors

Genetics

The possibility of genetic susceptibility to zoster and its associated morbidity has some support from genetic association studies. Zoster cases in Finland and Korea were more likely to carry certain polymorphisms of the interleukin-10 gene, an immunomodulatory cytokine that suppresses cell-mediated immunity, compared to healthy controls [61, 62]. A study in Japanese zoster patients also found an association between human leukocyte antigens (HLA) haplotypes and PHN cases [63]. Two case–control studies using family history of zoster as an indicator for genetic susceptibility to zoster found opposing results. Hicks et al. [64] reported finding a family history of zoster more commonly among incident zoster cases in the United States compared to controls with other skin diseases, whereas Gatti et al. [65] found no difference in family history of zoster between cases with PHN and controls without a history of zoster presenting with hypertension in Italy. Further research is needed to clarify whether there is inherited susceptibility to zoster or to PHN among those who develop zoster.

*error: should read decreased

Mechanical Trauma

Mechanical trauma has long been thought to be a risk factor for zoster, based largely on case reports. A case–control study published in 2004 found that mechanical trauma in the 6 months before rash onset was associated with an eightfold increased risk of zoster at the site of the trauma (OR 8.02; 95% CI, 2.24–28.69), and trauma within 1 month before rash onset was associated with a 12-fold increased risk (OR 12.07; 95% CI, 1.49–97.63) [66].

Immunotoxin Exposure

A cross-sectional study in the United States of people living close to a pesticide dump site found those living closer to the dump were more likely to report a history of zoster; however, the sequence between zoster events and residence near the dump was not ascertained [67].

Prevention

Vaccine

The zoster vaccine has been a significant breakthrough in this field. The live-attenuated VZV vaccine works by boosting pre-existing cell-mediated immunity, providing protection against zoster and PHN. It was initially shown to be efficacious in the Shingles Prevention Study (SPS), a US-based randomized, double-blind, placebo-controlled trial among 38,546 individuals aged 60 years and older, in which it reduced the incidence of zoster by 51% and PHN by 67% [68•]. Vaccine effectiveness was subsequently shown in a retrospective cohort study of 75,761 vaccinated individuals insured by the Kaiser Permanente health plan in California, with each matched to three unvaccinated controls; the incidence of zoster was reduced by 55% among individuals over 60 years of age [69•]. Using population-based data in Canada, the estimated number of 65-year-old individuals needed to vaccinate to prevent a case of zoster and a case of PHN is 11 (90% CI, 10–13) and 43 (90% CI, 33–53) [70].

The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination among all persons over 60 years of age, excluding patients with major immunosuppression or those with an allergy to any vaccine components [71]. In the context of dermatology clinics, the vaccine should not be given to individuals receiving high-dose prednisolone and safety is unknown in relation to biologic drugs, for which the ACIP recommends vaccinating those in target age groups at least 1 month prior to commencement of treatment in the absence of contraindications. A US observational study assessing the use of zoster vaccination in older individuals with inflammatory and

autoimmune diseases identified 32 patients taking biologic drugs at the time of zoster vaccination; none developed zoster in the subsequent month [72]. Research using Medicare data from 2006 to 2009, currently available in abstract form only, report that among 387 biologic users there were no cases of zoster in the 6 weeks following zoster vaccine administration [73]. Further testing in a clinical trial is required before acceptable safety margins for the use of the live zoster vaccine in patients receiving biologics can be given or specific recommendations on safe intervals for temporary discontinuation of therapy prior to administration. The current literature does not provide clear answers regarding safety in individuals taking other immunosuppressants. The vaccine has also been introduced in Australia. Although the vaccine has not yet been introduced in the United Kingdom, the Joint Committee on Vaccinations and Immunisations (JCVI) has recommended that the zoster vaccine be introduced for immunocompetent individuals aged 70 to 79 years [74].

Vaccine side effects were assessed in 97% of the study participants in the SPS and the frequency of serious adverse events within 42 days of inoculation was the same in vaccinated (1.4%) and placebo groups (1.4%) [68•]. A further substudy of 6616 SPS participants (3345 vaccinated and 3271 placebo) gathered more detailed information on short-term events and hospitalizations over the entire follow-up period [75]. Local side effects at the inoculation site (eg, erythema, pain, swelling, rash, and pruritus) were more frequently reported in vaccinees (48%) than the unvaccinated group (16%), and having ≥1 inoculation-site adverse event was more common among those aged 60 to 69 years (56.6%) compared to individuals aged ≥70 years (39.2%). However, events were rarely long lasting or severe. Longer-term follow-up showed rates of hospitalization and death did not differ between the two groups [75].

Modelling work has suggested that zoster vaccine is cost-effective. Using data from the SPS and population-based data from Canada, Brisson et al. [76] suggested the most cost-effective strategy was vaccinating adults aged 65 to 75 years, with the main cost benefits being reduced PHN morbidity. One of the main challenges in calculating cost-effectiveness is uncertainty regarding duration of vaccine efficacy, due to the short duration of the SPS trial (mean follow-up of SPS was 3.4 years) [76]. The US Food and Drug Administration have also recently expanded the age range for the zoster vaccine to individuals aged 50 to 59 years on the basis of a large unpublished, multinational, randomized controlled trial showing efficacy of 70% in terms of reduction of incident zoster; further observational data of vaccine effectiveness are awaited from this age group, and previously discussed ACIP recommendations remain unchanged [77].

Despite the efficacy of the vaccine, its uptake in the US target population has been disappointing. Data from a US household survey from 2007 found 1.9% of adults aged 60 years and older were vaccinated against zoster, rising in 2008 to 6.7% [78]. In 2008, rates were lower among Hispanics (2.1%) and non-Hispanic blacks (2.5%) than non-Hispanic whites (7.6%). Both patient and provider barriers have been suggested as explanations for the low uptake of the zoster vaccine, such as the high vaccine cost, complex methods for reimbursement, and requirement for freezer storage [79, 80].

Vaccination coverage levels could be higher if the zoster vaccine was given at the same time as other vaccines. In December 2009, the US Food and Drug Administration stipulated that the zoster vaccine should not be given concurrently with the pneumococcal vaccine, after results from a randomized, double-blind, placebo-controlled trial by the manufacturer on 473 individuals aged ≥60 years found VZV antibody levels were lower among patients receiving concomitant zoster and pneumococcal vaccinations compared to those receiving the zoster vaccine 4 weeks after pneumococcal vaccine (VSV geometric mean titers ratio [concomitant/non-concomitant] 0.70; 95% CI, 0.61–0.80) [81]. A retrospective cohort study in a US state compared incidence rates of zoster, rather than antibody levels, over a 3-year period among individuals receiving both vaccines either concomitantly (n=7187) or with at least a 30-day gap (n=7179). The study found no difference in the incidence of zoster between the groups (HR 1.19; 95% CI, 0.81–1.74) [82]. The authors suggested that a thorough assessment be undertaken before introducing rules placing barriers on administration of the zoster vaccine, especially considering its low uptake.

Antivirals

Antivirals are used to limit pain of an acute zoster episode, and some evidence suggests they might also reduce the risk of developing PHN. A recent Cochrane review of five trials comparing acyclovir to placebo and one trial comparing famciclovir to placebo found little difference in prevalence of PHN 6 months after rash onset; however, the meta-analysis was limited to two of the acyclovir trials with the required data (summary RR 1.05; 95% CI, 0.87–1.27) [83]. This finding partly contrasted previous reviews in which different definitions of PHN were used. These meta-analyses found some evidence of an effect of acyclovir on reducing frequency of PHN [84]. A randomized controlled trial of 419 adults showed a significant reduction in median duration of PHN (although no reduction in PHN incidence) when famciclovir was given using a standard regime [85]. The authors of the Cochrane review suggested further trials be conducted on famciclovir and valacyclovir to clarify their role in reducing duration and

severity of PHN [83]. These newer agents are, however, significantly more expensive compared to acyclovir and are currently infrequently prescribed.

Antivirals may also be effective in protecting against incidence of zoster among severely immunosuppressed patient groups. For example, a double-blind, placebo-controlled trial of 77 patients undergoing allogenic hematopoietic cell transplant showed that 800 mg of acyclovir, given twice daily for 1 year after the procedure, significantly reduced the risk of zoster (HR 0.16; 95% CI, 0.04–0.74) [86]. With increasing numbers of people becoming immunosuppressed from modern therapies, antiviral use may be proven effective in reducing the incidence of zoster and its associated morbidity in certain high-risk groups.

Conclusions

The lifetime risk of zoster is high and has important consequences. The greatest breakthroughs in this field have arguably been the development of a highly effective, safe zoster vaccine that has the potential to significantly reduce incidence and morbidity of zoster and PHN, as well as a vaccine to prevent varicella, which could eventually lead to the appreciable reduction of the burden of zoster. Further research focusing on cost and logistics of the zoster vaccine needs attention due to its current low uptake in the United States. Despite the relatively high incidence of zoster in older individuals, relatively little is known about risk factors for zoster, and recent questions have been raised about risks associated with specific co-morbidities. Better understanding of the determinants of zoster could be an important step in preventing herpes zoster episodes and identifying target groups for the vaccine.

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2.3. Risk factors for zoster: 2016 literature review update

Research exploring risk factors for zoster appearing after the publication of the above article, "The Epidemiology and Prevention of Herpes Zoster" (and herein referred to as the "2011 review"), are briefly summarised below. Table 2 below provides an overview of how literature published between 2011 and 2016 corroborates, challenges or extends the conclusions from the 2011 review.

Briefly, the 2016 literature review update has substantiated the findings from the 2011 review regarding older age[1,48] and severe immunosuppression[48-51] as major risk factors for zoster. The increased risk of zoster associated with female sex,[48,50-53] autoimmune conditions[49,54-60] and mechanical trauma[61,62] was similarly corroborated.

Since the 2011 review, the effects of anti- tumour necrosis factor (TNF) drugs, have been further investigated. Evidence from a systematic review suggests anti-TNF drugs increase the risk of zoster among RA patients by 60% (compared to conventional disease modifying anti-rheumatic drugs),[63] with some evidence that monoclonal antibody anti-TNFs pose greatest risk. However, in the review there was significant statistical heterogeneity between studies (I^2=80%) and one of the largest studies in the review concluded there was no evidence that new users of biologics were at greater risk of zoster, compared to new users of conventional DMARDs.[64] The effect of anti-TNF drugs among patients with psoriasis and IBD is similarly inconsistent.[58,64-66]

The 2011 review also suggested that more common medical conditions, associated with moderate immunosuppression, might increase the risk of zoster. The 2016 update found supporting evidence indicating that diabetes[48,50,52,67] and COPD[48,52] are associated with increased risks of zoster, of up to 45%. Additional research has suggested that other medical conditions may be risk factors for zoster including asthma,[48,51,68] CKD,[69-71] cancer,[48,51,72] cardiovascular disease[48,51,52] and peptic ulcer disease.[73] The risk of zoster was 5-80% greater for patients with these conditions, compared to the general population. However, a number of limitations were identified in these studies, including: 1) small study sizes; 2) inadequate adjustment for confounders; 3) lack of data on whether the associations were driven by the conditions themselves, or the use of immunosuppressive drugs; and 4) lack of data on how these risk factors varied by age. Therefore, the effect of these risk factors on zoster is not fully understood.

The 2016 update also identified two studies exploring recent negative life events as risk factors for zoster, in order to investigate the effects of stress. However, the effects of these life events were inconsistent between the studies.[74,75] This finding demonstrates that the very commonly cited risk factor for zoster, psychological stress, has yet to be comprehensively demonstrated as a risk factor in the epidemiological literature. The effect of varicella contact exposure,[1,76] age of primary varicella infection[48,51] and genetics[30,39] on zoster risk also remains unclear. Black ethnicity was substantiated as a protective factor against developing zoster, reducing the risk by 5 to 30%.[51,53,72]

Table 2: Overview of how literature published between 2011-2016 on zoster risk factors either corroborates, challenges or extends conclusions from the 2011 review

Exposure	Findings from main "2011 review"	2016 update: findings from papers published since 2011
Factors affecting general cell-mediated immunity		
Age	Increasing age is a risk factor for zoster with an estimated incidence of up to 14.2 per 1000 person years in those ≥50 years old in North America and Europe.	The effect of increasing age on risk of zoster was corroborated in a systematic review of zoster incidence studies, which confirmed a steep rise in zoster incidence after 50 years of age, with some suggestion that the incidence peaks around 75 years of age, whereupon it starts to plateau or decline.[1,48]
Gender	Female sex may be a risk factor for zoster.	Further studies support female sex as a risk factor for zoster; effect estimates ranged from 1.22 to 1.39.[48,50-53]
Severely immunosuppressive conditions/therapies	Zoster incidence in patients with severe immunosuppression is greater than in the general population; incidence rates range from 14.5 to 53.6 per 1000 person years.	Further research supports findings from the "2011 review".[48-51] The incidence of zoster in HIV patients is reducing, perhaps due to modern antiretroviral drugs; the rate of zoster among HIV patients using French hospital data reduced from 2955 per 100,000 person years in 1992-96 to 628 per 100,000 person years in 2009-2011.[17,77,78]
Autoimmune conditions	The risk of zoster is markedly increased among patients with autoimmune disorders, specifically RA, Wegener's granulomatosis, or SLE.	Further evidence supports the increased zoster risk in autoimmune conditions, compared to the general population, including RA (risk 2 fold greater),[57] IBD (risk 1.5 times greater),[58] SLE (risk 1.5 to 2.3 times greater),[49,59,60] primary Sjögren's syndrome,[54] bullous pemphigoid,[55] dermatomyositis and polymyositis.[56] Anti-TNF drugs appear to increase zoster risk among RA patients,[63] yet the effect in psoriasis[64-66] and IBD patients[58,64] is less clear.
COPD	One study suggested zoster risk was greater among patients with COPD, compared to the general population.	Two studies demonstrated an increased risk of zoster associated with COPD of around 20 to 30%.[48,52]
Diabetes	Two studies indicated diabetes was associated with increased risk of zoster, with effect estimates ranging from 1.53 to 2.38.	Four further studies found diabetes was associated with an increased risk of zoster, with effect estimates ranging from 1.04 to 1.45,[48,50,52,67] and a further study distinguished between diabetes type and reported only type 2 diabetes was associated with zoster.[79]

Table 2: (continued)

Exposure	Findings from main "2011 review"	2016 update: findings from papers published since 2011
Mental health problems	Negative life events and psychiatric disease were identified as risk factors for zoster in single studies.	Two studies assessed the effect of negative life events on zoster risk; one reported these events increased the risk of zoster,[74] whilst another found no evidence of increased risk.[75] Two case-control studies found depression was associated with an increased risk of zoster, ranging from 1.5-4 times the odds,[52,74] whilst an Australian cohort study found no association with depression or anxiety.[51]
Asthma	*No evidence in 2011 review.*	Three studies have reported an increased risk of zoster associated with asthma, with effect estimates ranging from 1.12 to 1.70.[48,51,68]
CKD	*No evidence in 2011 review.*	Recent studies indicate CKD is a risk factor for zoster,[69] associated with 20 to 60% increased risk, with greater risk among CKD patients on dialysis.[70,71] All studies used Taiwanese health records.
Factors affecting general cell-mediated immunity (continued)		
Cancer	*No evidence in 2011 review.*	Non-haematological cancers were associated with over 10% increased risk of zoster in two studies,[48,72] whilst an Australian cohort study assessed all cancers (excluding non-melanoma skin cancer) and found a 35% increased risk of zoster.[51]
Cardiovascular disease	*No evidence in 2011 review.*	Since the review, studies have indicated a small but significantly increased risk of zoster associated with coronary heart disease[48,51,52] (effect estimates range from 1.09 to 1.24).
Statins	*No evidence in 2011 review.*	Three studies reported a small but significantly increased risk of zoster with statin use, with effect estimates ranging from 1.13 to 1.28.[80-82]
Peptic ulcer disease	*No evidence in 2011 review.*	One cohort study identified peptic ulcer disease as a risk factor for zoster, with almost 80% increased risk of zoster.[73]
Liver disease	*No evidence in 2011 review.*	There is no evidence that patients with cirrhosis are at increased risk of zoster.[83]
Diet, body mass index (BMI) smoking and alcohol use	Diets low in micronutrients may increase zoster risk, smoking may be associated with lower risk of zoster and no studies have assessed alcohol use as a risk factor for zoster.	An Australian cohort study[51] found an 18% decreased risk of zoster in current compared to never smokers in line with previous research, along with a 6% increased risk of zoster among past smokers. This same cohort study found no association with alcohol use or BMI, and zoster.

Table 2: (continued)

Exposure	Findings from main "2011 review"	2016 update: findings from papers published since 2011
Factors affecting VZV-specific cell-mediated immunity		
Age at primary infection / ethnicity	Later age of primary varicella infection may reduce the risk of zoster, potentially explaining the reduced risk of zoster in patients of black ethnicity originating from countries where varicella is contracted later in life.	The reduced risk of zoster in patients of black ethnicity was corroborated, with protective effects ranging from 5 to 30%.[51,53,72] A Spanish study reported a lower incidence of zoster in foreign born participants with those born in sub-Saharan Africa at 60% reduced risk,[48] however in an Australian cohort study, participants born in countries where varicella onset is late were not at decreased risk of zoster in univariate analysis.[51]
Varicella contacts	Natural boosting of VZV-specific immunity through exposure to varicella contacts was partially supported by epidemiological evidence.	A systematic review assessing exposure to varicella contacts and zoster risk found mixed results,[76] whilst two systematic reviews concluded zoster incidence has not clearly increased following the introduction of the varicella vaccine.[1,76]
Other risk factors		
Genetics	Evidence regarding genetic susceptibility to zoster is scare and inconsistent.	Two studies reported greater risk of zoster for patients with family history of zoster,[74,84] however the effect of genetics on zoster susceptibility remains unclear.
Mechanical Trauma	A single case-control study found mechanical trauma six months pre-zoster was associated with eightfold increased risk of zoster, though the study may suffer from recall bias.	Two studies using routinely collected data reported physical trauma was associated with over three times the risk of zoster.[61,62] The effect appeared relatively immediate, specifically during the first week following trauma.
Physical limitation	*No evidence in 2011 review.*	An Australian cohort study reported that patients with a severe physical limitation were 30% more likely to develop zoster.[51]
Health-seeking behaviour	*No evidence in 2011 review.*	An Australian cohort study found patients attending cancer screening programmes and taking supplements were up to 17% more likely to develop zoster, and patients living in regional areas, rather than cities, were less likely to develop zoster.[51]

2.4. Chapter summary

Epidemiology and prevention of herpes zoster

- A review of the epidemiology and prevention of zoster was carried out in 2011, and evidence regarding zoster risk factors was updated in 2016.
- The lifetime risk of zoster is high and it can have significant consequences.
- The greatest breakthrough in this field has been the development of an effective, safe zoster vaccine, which has the potential to significantly reduce the incidence and morbidity of zoster and PHN.
- Well demonstrated risk factors for zoster include age, severe immunosuppression and mechanical trauma. Newer evidence indicates biologics may increase the risk zoster.
- Various common conditions, including diabetes, asthma, COPD, CKD, cardiovascular disease, cancer and peptic ulcer disease, have been indicated as zoster risk factors. However, a number of limitations were identified and the effect of these risk factors on zoster remains unclear.
- Better understanding of the determinants of zoster could be an important step in preventing zoster episodes and identifying target groups for the vaccine.

Chapter 3: Data sources and variable definitions

This chapter summarises the data sources utilised in this thesis and outlines how the main outcomes of interest (zoster and PHN) and the explanatory variables were defined.

3.1. Data sources

This study will utilise data from two EHR databases: the UK CPRD and the Hospital Episode Statistics (HES) database.

3.1.1. The Clinical Practice Research Datalink

3.1.1.1. Overview

CPRD is a large computerised database of anonymised patient records from UK primary care. At the time this research project was carried out, over 600 general practices contributed data from over 12 million patients and over 5 million currently registered patients. Approximately 7% of the UK population were represented, making it one of the largest sources of electronic primary care data in the world for research. Enrolled practices use a specific information technology (IT) system, called Vision, which uses coded and free text data to record information. Practices agree to participate, however individual patients may opt out upon request. Over 98% of the UK population are registered at a general practice and studies have shown that patients in CPRD are broadly representative of the UK population in terms of age, sex and ethnicity.[85]

The general practitioner (GP) in the UK acts as the gatekeeper of primary care and specialist referrals, therefore the majority of patients will seek care initially from their GP for health-related issues. This system results in a rich source of patient-level health data, including all consultations, diagnoses, prescriptions, tests, immunizations, referral to hospitals and hospitalizations. Unlike many administrative databases, particularly those collected for insurance purposes, CPRD also contains some lifestyle and anthropometric data, such as smoking behaviours and BMI.

3.1.1.2. Data structure and coding

CPRD release new database builds on a monthly basis. For this thesis the January 2012 build was used, except for the descriptive study of antiviral use (chapter 5) in which the June 2011 build was used. The data are split into several files and Table 1 below describes the main file types in CPRD used for this study, along with their contents. The patient-level files can be linked using a unique patient identifier, present in each file. The last three characters of this identifier also constitute a unique practice identifier, for linkage to the practice-level data.

Table 1: Description and contents of files types available and utilised in this thesis

File type	File contents
Patient	*Patient level demographic details including*; year of birth, gender, registration status (acceptable/unacceptable), death date, transfer out date.
Practice	*Practice level data including*; geographical region, 'Up to standard' date (date CPRD have classed the practice data sufficient quality for research), last data collection date (for the practice).
Consultation	*Patient level data on consultations with GP*; date of consultation, type of consultation and duration of consultation.
Clinical	*Patient level data on clinical events including*; date of clinical event, diagnosis given or symptom recorded.
Additional Clinical Details	Additional detail regarding clinical events, such as number of cigarettes smoked per day and test results. The file is split into entity type, which relates to a specific type of data. There are a total of 460 different entity types. For example, entity “type one” records information on blood pressure.
Referral	*Patient level data on referrals to specialist services including*; date of referral, diagnosis given, method of referral, referral specialty, urgency of referral.
Therapy	*Patient level data on drug prescriptions and apparatus including;* date of prescription, CPRD product code for the prescription.

GPs in the UK record medical and non-medical events using the hierarchical Read code classification system.[86] This system covers a range of areas including symptoms, diagnoses and administrative processes. The Read code hierarchy is organised into chapters and subchapters, with initial values representing high-level categories and following values specifying further detail on the event. Therapy prescriptions are recorded using the Multilex product dictionary, and include pharmaceuticals, drug appliances or devices. CPRD have translated these Read and Multilex codes into medical and product codes respectively, and created dictionaries that can be easily searched. For this thesis the dictionary versions 1.3.2 were used.

Defining follow-up for individual patients

Although records go back many years, CPRD recommend restricting the start of follow-up period to be the latest of practice 'up to standard' date or the date the patient first registered at the practice. They also recommend ending follow-up at the earliest of the following; when the patient died, transferred out of the practice, or when data were last collected on that practice.

3.1.1.3. Data Quality and Validity of Information

CPRD data undergoes some checks to ensure the data meet certain standards before release.[87] These checks occur at the practice and patient level. Practices are assessed and labelled 'up to standard' when the practice is considered to have continuous high quality data, fit for research. The practice must meet various criteria, such as a minimum referral rate per 100 patients. Patient level data are marked as "acceptable" for research, where certain criteria are met, such as: 1) age at end of follow-up is below 115 years; and 2) year of birth is recorded.

Guidance documents for practices contributing to CPRD ask GPs to record various aspects of a patients' medical details including; all significant clinical events from a patients history at registration and as they occur, indications for therapy prescriptions, all known hospitalisations and cause of death. However, data completeness may vary substantially over time, by population or type of data.

Recording of certain data types has been improved by the introduction of the Quality and Outcomes Framework (QoF), which encourages recording of key data items through an incentivised payment programme for GPs.[88] QoF was introduced in 2004 and sets out a series of data fields for collection, such as the BMI status of diabetes patients and the delivery of services to patients with severe mental health conditions. The completeness of data for factors included in QoF increased following the introduction of this programme.

Diagnostic validity in the CPRD is generally considered to be an advantage of the database. A systematic review of studies validating a variety of disease diagnoses found the median proportion of CPRD-defined cases with a confirmed diagnosis was 89%[89] (positive predictive value (PPV) of a recorded diagnosis). However, the PPVs ranged from 24 to 100% for individual diseases and the review acknowledged that validation studies were limited due to their size and frequently restricted to specific populations. Furthermore, the same systematic review noted that negative predictive values (NPV) are very rarely assessed in CPRD validation studies,

due to the financial implications of sampling a vast number of patients without the diagnostic codes of interest. The lack of information on the NPV is an acknowledged weakness of CPRD data.

3.1.2. Linked Hospital Episodes Statistics

3.1.2.1. Overview

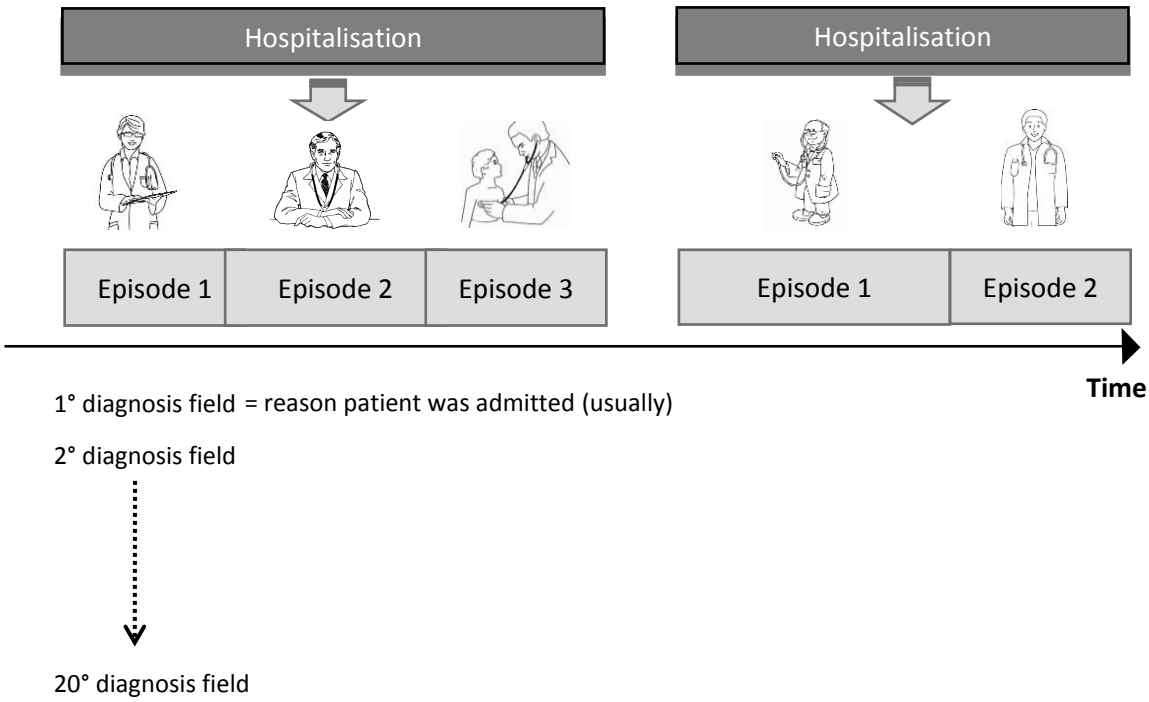
A subset of English CPRD practices participate in a linkage scheme, where related datasets are linked to CPRD. One of these datasets is HES, a secondary care database of hospital admissions from all National Health Service (NHS) trusts throughout England. Patients in CPRD are linked to HES data using deterministic matching (where all or some identifiers are required to match exactly) on a combination of the patient's NHS number, gender, and partial date of birth. The research in this thesis uses hospitalisation data from April 1997 to March 2012, during which time 375/497 (75%) of English practices participated in the linkage scheme. Linked HES data contains information on inpatient admissions only (limited outpatient data did not become available until September 2014). HES contains comprehensive diagnostic information, however prescription data are not currently available.

3.1.2.2. Data structure and coding

The structure of HES data are demonstrated in Figure 1 below. HES data are divided into "hospitalisations", which relate to a stay in hospital. For each hospitalisation there may be one to many "episodes", an episode being a time period for which a patient is under the care of a particular consultant. Within an episode, a patient has a primary diagnosis and up to 20 further secondary diagnoses; the primary diagnosis field usually relates to the reason the patient was admitted. The data are provided to researchers as files relating to hospitalisations or episodes.

Clinical diagnoses in HES data are coded using the International Classification of Disease, tenth revision (ICD-10) system, developed by the World Health Organisation (WHO). It is organised into chapters, themed on particular medical areas, covering diagnoses and procedures. ICD-10 codes are made up of 6 or 7 digits; the first three digits indicate the medical category, the next three give information on the location, severity or aetiology and the 7th digit is optional, depending on the chapter.

Figure 1: HES data structure



Note: "hospitalisations" relate to a stay in hospital and "episodes" relate to a time period for which a patient is under the care of a particular consultant.

3.1.2.3. Data quality

HES data are collected during a patient's hospital stay, and are processed to allow hospitals to be paid for the care they deliver. HES data are also designed to enable secondary use, that is use for non-clinical purposes, such as research. Trained clinical coders input ICD-10 codes from unstructured, hand-written clinical notes. Data input by clinical coders are then sent to a data warehouse. At pre-arranged time-points in a year, HES then extracts a copy of the data, and carry out validation and data cleaning. Each variable undergoes a set of cleaning rules, for example each patients date of birth must lie between 1/1/1885 and the last day of the period being processed, and where invalid codes appear, they are overwritten with the code for "Unknown".[90]

Errors and omissions within HES data are acknowledged to occur;[91,92] in 2013/14 an audit of 8,990 episodes of care from 50 NHS trusts compared case notes to clinical codes, and estimated the error rate of clinical codes in admitted patient care data at 10.8%.[93] The errors may be entirely incorrect codes, or codes lacking detail of the clinical event.[94] The main reasons for errors are thought to be incomplete paper records and the lack of involvement from front-line clinicians in the coding process.[91] The impact of this level of coding inaccuracy on epidemiological research is difficult to quantify and is likely to vary according to the hospital

specialty and the study question. Despite this, data quality is improving over time and is considered sufficiently robust for health research.[95,96]

3.2. Creating code lists

To identify patient characteristics in CPRD and HES, such as diagnoses or therapies, code lists are created. A code list refers to a list of all codes indicating the patient characteristic or drug of interest. Code lists can be merged with the raw data to identify all patients with the characteristic or all patients prescribed the drug.

For this project, a systematic approach was used when creating diagnosis and product code lists. The relevant dictionaries of codes were searched using a STATA do file, such that all decisions on inclusion and exclusion criteria were recorded and were easily replicated.

The approach to creating a diagnosis code list was as follows:

- *All possible codes* were identified by creating a set of search terms (synonyms of the medical event) and looking for these in the entire Read or ICD-10 dictionary, within the Read term data field or ICD-10 Terms field. The Read code or ICD-10 hierarchy was additionally utilised to identify all codes within relevant chapters or sub-chapters. Codes not meeting the search criteria were dropped.
- *Final diagnosis codes* were selected by reviewing the possible codes with a clinician (in the majority of cases Dr Sinéad Langan, dermatologist) and collating a list of exclusion terms, which were then applied. Remaining codes were then compared to any available pre-existing code lists (for example if a code list for the medical condition had been created for a previous study) and discrepancies were assessed.

The approach to creating a product code list was as follows:

- *All possible codes* were identified by creating a set of search terms and looking for them within the entire product code dictionary, within the following data fields: product name, British National Formulary (BNF) header, drug substance and route of administration. Most codes were identified from the product name search, however if this data field was missing, searching the other data fields picked up extra terms. The hierarchical structure of the BNF dictionary was utilised by searching for codes within BNF chapters (using the BNF code data field). Product codes not meeting the search criteria were dropped.
- *Final therapy codes* were selected by reviewing the possible codes with a clinician (in the majority of cases Dr Sinéad Langan, dermatologist) and compiling a list of exclusion

terms, which were then applied. Remaining codes were compared to existing code lists where possible and discrepancies assessed.

All medical and product code lists can be found in appendix V.

3.3. Outcome definitions

3.3.1. Definition of zoster in CPRD and HES

Zoster diagnoses were identified in CPRD by Read codes in the clinical and referral files and in HES data by ICD-10 codes (listed in appendix V).

Patients were required to be ≥18 years of age at zoster diagnosis, as zoster among children is very rare. The zoster diagnosis had to occur within the patient's follow-up period (see section 3.1.1.3). It was also necessary to identify patients with a first ever episode of zoster, as recurrent zoster is rare and its aetiology and clinical course is believed to be different to the majority of zoster episodes.

It was important for the thesis' objectives to identify incident rather than prevalent cases of zoster, to ensure the optimal accuracy of diagnosis date. In order to ensure this, patients were required to have 12 months registration in CPRD without a zoster diagnosis. This 12-month threshold is in line with research by Lewis et al,[97] which reported that in routinely collected data, recording of prevalent cases is more likely shortly after registration at a general practice, therefore it is common practice not to include diagnoses recorded shortly after registration.

Incident zoster cases in HES data were identified by ICD-10 codes (B02, B02.0, B02.1, B02.31, B02.7, B02.8, B02.9, G53.0). Although the majority of zoster cases do not require in-patient care, a small proportion of cases require hospitalisation.[26] Identifying hospitalisations due to zoster is challenging, as it is not easy to determine whether zoster triggered the admission, occurred during hospitalisation or was associated with admission for another reason. HES data contain up to 20 diagnoses per episode, however hospitalisations were only considered to be related to zoster if the zoster diagnosis was recorded in the primary field of any episode during a hospitalisation (see Figure 1: HES data structure). This is because it is not possible to identify whether records in any of the secondary fields are incident zoster, history of zoster or misdiagnosis of zoster. For zoster cases identified in HES the date of hospital admission was taken as zoster date.

If zoster was identified in both HES data and CPRD, the earliest recorded zoster diagnosis was used.

3.3.2. Postherpetic neuralgia

This section describes some of the challenges of defining PHN in EHR data, as well as a summary of how researchers have identified PHN in previous studies. The method used to identify PHN patients in CPRD is then outlined in greater detail.

Background information on the management of PHN in UK primary care

The UK Clinical Knowledge Summary on the management of PHN (last revised February 2014)[98] suggests patients with zoster-associated pain are treated as follows: initially, with paracetamol in combination with codeine if necessary; where this proves ineffective, tricyclic antidepressants or anticonvulsants are recommended for 4-6 weeks. Clinicians are also encouraged to consider using capsaicin cream 0.075% and lidocaine 5% medicated plasters on the affected areas to relieve pain. For patients awaiting referral to pain specialists, if the above treatments have failed, GPs are recommended to consider prescribing a short course of tramadol. The chosen treatment depends on patient characteristics (such as their age, comorbidity and frailty), the phase of the illness (acute or established PHN), local prescribing preferences and physician preferences. The pharmacological management of PHN patients may therefore be heterogeneous.

Challenges in defining PHN using EHR data:

There are two main avenues for identifying PHN from CPRD records namely (1) looking for clinical records indicating a PHN diagnosis or continuous post-zoster pain that would meet the criteria for PHN, and (2) looking for prescriptions for treatments that are given for PHN.

Long-term pain due to PHN is difficult to capture in EHR databases such as CPRD, for a variety of reasons:

- *There is no single definition of PHN.* The definition of PHN varies in the literature, primarily in terms of when zoster-associated pain becomes classified as PHN. The most accepted definition of PHN is pain persisting beyond 90 days of rash onset, however some GPs and researchers may diagnose PHN 30 days following zoster.

- *PHN treatments have various clinical indications, therefore prescriptions for PHN medications may not be sufficient to confirm PHN.* PHN drug treatments such as codeine or anticonvulsants are not exclusively given for PHN. As clinicians in the UK are not required to record the indication for every prescription, it cannot be confirmed whether a prescription was given for PHN.
- *PHN pain codes are not always specific.* The pain codes available and used by some GPs to diagnose PHN are often non-specific (such as "neuralgia" or "neuropathic pain"), so again it is difficult to be certain the pain is due to PHN.
- *Patients may be referred to secondary care for pain management*. The UK Clinical Knowledge Summaries suggest that if pain is not controlled, despite medical advice and trials of two drug treatments (normally about 8–12 weeks [56-84 days] after starting treatment), or adverse effects limit treatment, doctors should consider referral to a pain clinic or seek specialist advice.[98] Therefore some PHN patients may be missed in CPRD if treatment is provided in secondary care. However, these patients would typically be referred back to primary care for ongoing treatment.
- *Patients may not attend primary care for pain-management.* Patients may not seek care from their GP for a number of reasons: (i) they may establish stable pain regimens before 90 days that no longer require repeated physician visits (many painkillers used in PHN pain management can be obtained over-the-counter); (ii) they may seek second opinions and alternative therapies outside the primary practice; (iii) they may resign themselves to pain as PHN is often refractory to treatment; (iv) or they may develop new health concerns that displace PHN pain as the focus of their visits. The implications of the above factors are that there is likely to be decreasing sensitivity of capturing PHN in EHR data with increasing time since zoster.

How researchers currently deal with PHN in EHR data

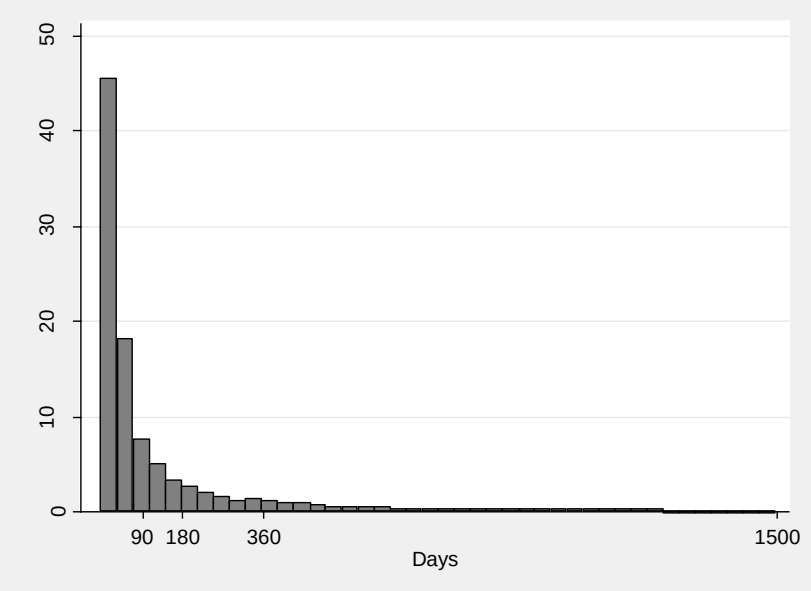
Researchers have used a variety of techniques to ascertain PHN patients in EHR data (see Table 2 below for some examples). Most researchers use evidence within a certain time-frame following zoster to define their PHN cases. The presence of PHN diagnosis codes (if available) and/or zoster plus neuropathic pain codes are widely used. Hall et al identified patients with a PHN code (without a requirement for previous zoster) or a code for neuropathy or neuropathic pain 3 to 6 months following an acute zoster code in CPRD. They validated their definition in a sample of 108 patients with PHN diagnosed between 2006 and 2010.[99] Questionnaires were sent to GPs to confirm PHN. The response rate was 86.8% and the PPV for PHN was 91%. This finding appears to suggest using PHN codes and zoster with a later nerve pain code is effective at identifying PHN patients in CPRD. However, this algorithm may not be reliable; it could be

argued that in CPRD, the majority of PHN codes may not indicate PHN itself, but zoster-associated pain shortly after zoster. Figure 2 below shows the distribution of time from zoster diagnosis to PHN code in patients with a first ever zoster code in CPRD. This figure suggests almost 70% of the codes occur within 90 days of zoster; as the most accepted definition of PHN is pain after 90 days, none of these codes alone would meet the criteria for PHN.

Table 2: Some examples of PHN definitions in previous studies using EHR data

First author, year	Database, country	Definition of PHN	Exclusions
Opstelten, 2002[13]	Primary care records, Netherlands	Any evidence of pain or analgesic prescription in patients' medical record 1 and 3 months following zoster	None
Gauthier, 2009[100]	CPRD, UK	Diagnostic code for PHN; *or* Neuropathic pain medication (topical analgesics, tricyclic antidepressants, anticonvulsants and tramadol) >1 to >12 months and >3 to <12 months post-zoster diagnosis. Assessed PHN severity from prescribed medications.	Diabetic neuropathy, epilepsy, recurrent zoster
Gialloreti, 2010[101]	Primary-care database and national hospital-discharge records covering four major regions in Italy 2003-05.	ICD9-CM code for zoster and a prescription for any drug commonly prescribed for PHN (tramadol, anti-epileptics, tricyclic antidepressants capsaicin cream or lidocaine) 3-12 months and 1-12 months after zoster diagnosis; *or* ICD9-CM code for PHN within the same time-frame	Immunosuppressed patients
Hall, 2013[99]	CPRD, UK	PHN code; *or* Code for neuropathy or neuropathic pain code 3-6 months following acute zoster code	None
Langan, 2013[42]	Medicare, USA	Zoster code 90 days following incident zoster, with a prescription of analgesia, anticonvulsant, antidepressant on the same day; *or* Non-specific neuralgia/neurological complications code 90 days following incident zoster.	None

Figure 2: Distribution of time from zoster diagnosis to PHN code appearing, in CPRD patients with first ever zoster



Some researchers have additionally used medications prescribed within a time frame following zoster to identify PHN cases. The use of relevant medications following zoster to identify PHN has not been validated in CPRD, however a US study by Klompas *et al*, developed an algorithm to identify PHN patients using administrative data, incorporating medication history into their final definition.[102] They used the Harvard Vanguard Medical Associates database, an ambulatory practice group that provides primary and specialty care to more than 550,000 patients in eastern Massachusetts. This database uses ICD version 9 (ICD-9), which has no code for PHN. Patients included were aged 20 years or older, with an ICD-9 code for zoster, in the calendar year 2008.

Klompas et al focused on identifying persistent pain 30 days following zoster and developed an algorithm with a sensitivity of 86% and PPV of 78%. In the algorithm, they required two or more visits with an ICD-9 code for zoster 21 days or more apart *and* a new prescription for an analgesic, antidepressant or anticonvulsant; *or* an ICD-9 code for zoster with nervous system complications; *or* an ICD-9 for neuralgia within 180 days of a visit for zoster. This validation study was carried out in an administrative data source, which differs from CPRD in so far as rule out codes are more commonly used and certain diagnoses may be under-reported if there are no financial incentives to record them. However, some high-level elements of this algorithm were used to help identify patients with PHN in CPRD; specifically, using a combination of diagnostic and "new" prescription codes within specified time periods following acute zoster diagnosis.

Strategy to identify PHN patients in CPRD

Methods previously used to define PHN were considered and an approach was developed to identify patients with PHN in the study. The approach was motivated by the specific study objective; that is to identify risk factors for PHN. A definition which prioritised high specificity (correctly identifying those without the disease) rather than high sensitivity (correctly identifying those with the disease) was required to reduce the chance of type I error (incorrect rejection of a true null hypothesis);[103] in other words, reporting spurious associations by rejecting the null hypothesis when it is actually true.

Underlying definition of PHN

The underlying definition of PHN on which the algorithm was based was *pain persisting for at least 90 days following zoster*. Patients were assumed to have PHN at 90 days following zoster, even where evidence of PHN was, say, 180 days after zoster.

Exclusions

As anticonvulsant prescriptions were to form part of the PHN algorithm (described in detail below), patients with other indications for anticonvulsants (e.g. epilepsy) recorded pre-zoster were excluded. Also excluded were patients without 365 days follow-up after zoster diagnosis; as the definition would use data within 365 days from zoster diagnosis, it would not be possible to know whether individuals censored before 365 days without PHN met the PHN definition.

Identifying zoster patients with and without PHN

The case definition of PHN was categorised into three groups; diagnosed, probable and possible.

- *Diagnosed PHN*: a PHN code 90-365 days following zoster within either; a) the clinical or referral files in CPRD or b) a primary diagnosis field within any episode of HES for linked patients.
- *Probable PHN*: a first ever non-specific neuralgia code 90-365 days following zoster in CPRD; *or* an additional zoster code 90-365 days following zoster with a drug prescription for an anticonvulsant, tricyclic antidepressant, capsaicin cream or lidocaine patch (see Table 3 below for drug descriptions) *on the same day* in CPRD.

Due to an unrealistically low number of PHN cases being ascertained using the above criteria (n=3110/119,413; 2.6% of zoster patients) drug prescription data were utilized further. As GPs

in UK primary care are not required to record the indication for every prescription, it is plausible patients are prescribed medications for PHN, without the diagnosis being recorded. The PHN medications searched for and their indications are described in Table 3. To increase the likelihood of the medication being prescribed for PHN, "new" prescriptions were searched for, defined as no previous prescriptions of the same medication type 12 months to two weeks prior to zoster (medications may have been prescribed for pain management two weeks prior to zoster, if zoster initially presented without a rash- "*zoster sine herpete*").

Table 3. Medications used to treat PHN

Medication type	Specific drugs	Indications[1]
Mild Painkillers	*Paracetamol*	*Mild to moderate pain*
	Ibuprofen	
	Aspirin	
Strong painkillers	*Codeine*	*Mild to moderate pain, diarrhoea, cough suppression.*
	Dihydrocodeine	
	Dextropropoxyphene	
	Tramadol tablets or injection	*Moderate to severe pain*
Tricyclic antidepressants	*Amitriptyline*	*Depressive illness, neuropathic pain, chronic pain and migraine prophylaxis*
	Nortriptyline	
	Imipramine	
	Desipramine	
	Duloxetine	
Anticonvulsants	*Pregabalin*	*Seizures, peripheral neuropathic pain and migraine prophylaxis*
	Gabapentin	
	Valproate	
	Oxcarbazepine	
	Carbamazepine	
	Phenytoin	
	Lamotrigine	
Other	*Lidocaine patches*	*No other indications*
	Capsaicin cream 0.075%	*No other indications*

[1]According to BNF 2014

Note on selection of medications: Mild painkillers included paracetamol as indicated for PHN in the Clinical Knowledge Summaries, and other commonly used painkillers ibuprofen and aspirin were additionally included. Stronger painkillers included codeine and tramadol, as indicated in the Clinical Knowledge Summaries, as well as dihydrocodeine and dextropropoxyphene which are indicated for treatment of neuropathic pain in the UK. Although other painkillers such as morphine and oxycodone can be used for neuropathic pain treatment, their use is not recommended for treating neuropathic pain in primary care[98]. Amitriptyline is clinically the most widely used tricyclic antidepressant for treatment of PHN yet nortriptyline, protriptyline, imipramine, desipramine were also included as they are occasionally used. Pregabalin and gabapentin are the most commonly used anticonvulsants in PHN treatment, yet others also indicated for PHN were included. Finally capsaicin cream 0.075% and lidocaine patch 5% were included, given specifically for PHN.

Medications appearing 90-180 days (rather than 90-365 days) were considered to further reduce misclassification of PHN. To get a sense of whether a PHN-medication was likely to have been given for PHN, or another condition, the *expected* number of "new" PHN-related prescriptions in similar patients without recent zoster was estimated. This was achieved by comparing the prescription patterns among the study cohort with age, sex and practice matched patients without zoster (using controls from the case-control study described in

Chapter 4 assessing risk factors for zoster). After applying the same exclusion criteria to the non-zoster controls as with the zoster cases (at least 365 days follow-up from their index date, no neuropathic pain syndromes or epilepsy prior to index date) and randomly selecting 1 control per zoster patient (see Table 4).

Table 4: Proportion of patients within the zoster cohort, and a similar non-zoster population, receiving a "new" PHN medication 90-180 days following zoster diagnosis

PHN medication	% of zoster study cohort (N= 117,815)	% of similar non-zoster sample (N= 117,815)
Anticonvulsants	1.65	0.25
Tricyclic antidepressants	2.84	0.69
Lidocaine patches	0.09	0.01
Capsaicin cream	0.25	<0.01
Strong painkillers	4.42	2.98
Mild Painkillers	2.51	2.05

Note: 1,598 patients from the study cohort had no matched control after exclusion criteria were applied

Table 4 demonstrates that "new" anticonvulsants, antidepressants, lidocaine patches and capsaicin creams were much more common among the zoster cohort than amongst controls. Patients with zoster had a slightly higher use of strong painkillers. On the basis of this evidence strong painkillers were not included in the definition of probable PHN, but instead possible PHN. Due to the comparable use of mild painkillers within the zoster and non-zoster samples, these medications were not used to identify further PHN patients. On browsing the clinical and therapeutic records of a selection of patients, two further criteria were added:

- *Further probable PHN*; patients with a "new" PHN drug prescription for an anticonvulsant, capsaicin cream or lidocaine patch 90-180 days following zoster; patients with a "new" tricyclic antidepressant 90-180 days following zoster with two additional criteria (to reduce misclassification of PHN, particularly with depression): firstly, no clinical diagnoses suggesting non-PHN indications on the same day as the tricyclic prescription [that is, any Read codes suggesting depressive diagnosis (symptoms of depression, such as "Crying all the time" or life-events with the potential to precipitate depression, such as divorce), a pain that may be chronic, or a need for migraine prophylaxis], as well as additional evidence of the drug being prescribed for zoster or PHN previously (in other words, a tricyclic antidepressant prescription 0-89 days following zoster, with a zoster/PHN code on the same day).

To capture other "possible" PHN patients, these criteria were added;

- *Possible PHN*: patients with a "new" tricyclic antidepressant prescription 90-180 days following zoster with no clinical diagnoses suggesting non-PHN indications on the same day as the tricyclic prescription (without additional evidence of the drug being prescribed for zoster or PHN 0-89 days after zoster); patients with a "new" strong painkiller 90-180 days following zoster with no clinical diagnoses suggesting non-PHN indications on the same day as the strong painkiller prescription (that is, any Read codes suggesting the presence of pain, diarrhoea, or cough) as well as additional evidence of the drug being prescribed for zoster or PHN previously (a strong pain killer prescription 0-89 days following zoster, with a zoster/PHN code on the same day); or patients with a neuropathic pain code 90-365 days following zoster.

The use of pain and symptom codes to diagnose PHN (e.g. "Chest pain", "Burning pain" or "Has tingling sensation") as well as referrals to pain clinics/specialists was considered; however their lack of specificity may have led to a number of false positive PHN cases. Finally, utilising information on the dosage of tricyclic antidepressant prescriptions was explored; when these drugs are given for neuropathic pain, patients are started on a low dose and graduated to a higher dose (compared to their use in patients with depression, who are more typically started on a high dose). Unfortunately the dosage information in the CPRD doesn't sufficiently capture information on graduated dose; therefore it was not possible to incorporate this into the definition.

The PHN definition, utilised in chapter 7, is summarised in Table 5 below.

Table 5: PHN definition used in this thesis

PHN classification	
Diagnosed PHN	PHN code* (90-365 days post-zoster)
Probable PHN	Zoster code and prescription consistent with PHN• on same day (90-365 days post-zoster)
	Non-specific neuralgia code (90-365 days post-zoster)
	NEW anticonvulsant or capsaicin cream or lidocaine patch prescription (90-180 days post-zoster)
	NEW tricyclic antidepressants 90-180 days post-zoster with no other indication on the day of the prescription, plus evidence of the drug being prescribed for zoster or PHN previously†
Possible PHN	**NEW** tricyclic antidepressants 90-180 days post-zoster with no other indication on the day of the prescription
	NEW strong painkiller 90-180 days following zoster with no other indication on the day of the prescription, plus evidence of the drug being prescribed for zoster or PHN previously†
	Non-specific neuropathic pain code (90-365 days post-zoster)

PHN: Postherpetic neuralgia.*Read code for PHN in CPRD or (for those with linked data) an ICD10 PHN code in the primary diagnosis field within any episode of linked HES. •Prescriptions included anticonvulsants, tricyclic antidepressants, capsaicin cream or lidocaine patch.
NEW prescriptions were defined as no previous prescriptions of the same medication type 12 months to two weeks prior to zoster, to increase the likelihood of the medication being prescribed for PHN (medications may have been prescribed for pain management two weeks pre-zoster, if zoster initially presented without a rash). †Here, previously is defined as a prescription 0-89 days following zoster.
Medications indicative of zoster were only considered in the 90-180 day period after zoster diagnosis (rather than 90-365 days) to reduce the chance of misclassifying other reasons for medication use as PHN.

3.4. Potential explanatory variables

Various other potential explanatory variables were defined for this thesis, including severe immunosuppressive conditions, autoimmune conditions, other comorbidities, demographic characteristics, lifestyle data and finally characteristics of the zoster episode. Below are detailed notes on how these variables were identified in CPRD records. HES data were not utilised to identify the medical conditions, as they are chronic, rather than acute conditions, and were thus assumed to be recorded in primary care records. All code lists are given in appendix V.

3.4.1. Severely immunosuppressive conditions

Severely immunosuppressive conditions were determined by the zoster vaccine contraindications set out by the Advisory Committee on Immunization Practices (ACIP), a group of medical and public health experts that develop recommendations on how to use vaccines in the US.[104] As the currently available zoster vaccine is a live vaccine, patients with primary or acquired immunodeficiency are assumed to be at risk of developing a varicella-like or zoster illness from the vaccine virus strain, if vaccinated. Therefore the contraindications

provide a list of conditions considered to result in severe immunosuppression. These contraindications are very similar to those set out in the UK's counterpart vaccine guidelines, the Green Book.[41]

The definition of severely immunosuppressive conditions used throughout this thesis therefore included a recent history (less than two years before the zoster diagnosis) of leukaemia or lymphoma, or any history of HIV, hematopoietic stem cell transplantation, myeloma or 'other unspecified cellular immune deficiencies' (e.g. pancytopenia). These diagnoses were all identified through the presence of Read codes in CPRDs clinical and referral files.

3.4.2. Immunosuppressive therapies

3.4.2.1. Corticosteroids

Definition

Two definitions of oral corticosteroid exposure were used: 1) a high-dose (≥20 milligrams (mg)/day), 14-day or longer course, in the month prior to zoster diagnosis (in keeping with the ACIP guidelines for zoster vaccine contraindications[104]); and 2) any dose of oral corticosteroids in three months prior to zoster diagnosis.

To identify high-dose prescriptions of 14 days or more in CPRD required some data cleaning. Below is some background information on how prescription data are collected in CPRD, how these data were cleaned, how prescription duration and prescription dose were calculated and finally, how missing data were handled.

Background on prescription data in CPRD

CPRD does not provide researchers with duration and dose for individual prescriptions. Instead, these must be generated using information from other variables.

Prescribing GPs select the drug, enter information on the prescription and can also enter free text. The drug name itself contains the dose in milligrams per tablet and the GP enters the total number of tablets to be prescribed, within in a field called *quantity*. The free text field contains the actual prescribing information; in other words how many tablets the patient should take each day, known as the *numeric daily dose*. Examples include, "take one daily" and "take one twice a day". To utilize this information, CPRD developed an algorithm to derive numeric daily dose from the free text and provide this to researchers.[105]

Data cleaning on oral corticosteroid prescriptions

A series of data-checking and data-cleaning tasks were carried out on oral corticosteroid prescriptions, including;

- Checking commonly occurring free texts; 500 of the most commonly used free texts were compared to the numeric daily dose for accuracy and 150 of the most commonly occurring free texts where numeric daily dose equalled zero were checked for accuracy. This approach captured over 90% of all prescriptions. Very few errors were found when checking the most commonly used free text against the numeric daily dose.
- The clinical and referral records for 20 randomly selected patients were browsed to verify that the duration and dose of the prescriptions were consistent with the diagnoses. For a single patient, consistency checks took on average 30 minutes, and 20 patients records were selected for review. This analysis demonstrated that patients prescribed short-term high-dose courses of oral corticosteroids tended to have codes consistent with an acute illness, such as an exacerbation of COPD or asthma. Longer term, lower doses were less easy to assign a reason for use.
- Tapering dose; the possibility of identifying tapering doses of oral corticosteroid prescriptions was explored by searching for words in the free text implying tapering doses, specifically, "*reduc*", *then*, *3*2*1*, *stop*. In total, 36 phrases were identified. However very few records had information about the actual reducing dose, therefore it was concluded that tapering doses could not be accurately identified.
- Unlikely values for quantity and numeric daily dose were excluded; for oral corticosteroids, individual prescription quantities of >1000 tablets and numeric daily dose's >40 were changed to missing.

Dealing with missing data

Although 99% of oral corticosteroid prescriptions had the quantity of tablets, as well as the dose of the tablets, data on numeric daily dose (required to calculate daily dose and duration of prescription) was missing for more than 30% of oral corticosteroid prescriptions. Steps were therefore taken to impute missing data for numeric daily dose.

Where numeric daily dose was missing for oral corticosteroids, the majority of the texts were "as directed". This suggests the dose may be uncommon. Alternatively, it may be the same as

a previously prescribed dose. It was agreed that clinically the best predictor of numeric daily dose was likely to be a person's previous prescriptions.

Several approaches were considered to handle missing numeric daily dose data:

1) Using the mode or median numeric daily dose: Most previous CPRD studies have used the mode or median numeric daily dose for oral corticosteroids where numeric daily dose is missing,[106,107] however this approach does not fully utilise the information available in the data.
2) Multiple imputation of numeric daily dose: This technique replaces each missing value with values representing the conditional distribution of the variable, based on observed data. These multiply imputed data sets are then individually analysed and the results are combined. In this instance, there were repeated measurements (i.e. several prescriptions), clustered within individual participants. This meant the data structure was multi-level.[108] Dealing with clusters would be statistically complex and is not handled by standard multiple imputation software commands, therefore this technique was not pursued.
3) An alternative multiple imputation approach was considered, whereby a single-variable summary of "numeric daily dose at other times" could be generated, perhaps using "last numeric daily dose" or "closest numeric daily dose". In this approach the data are no longer multi-level, therefore can be handled easily in STATA. The approach was taken in a recent paper by Fardet et al to impute daily dose.[109] However, use of this technique would not predict numeric daily dose for patients who only had a single prescription with missing numeric daily dose.

Another, computationally simpler, imputation approach called "Hot Decking" was instead used to address missing numeric daily dose. Hot Decking involves replacing missing data with observed data from a similar unit, or strata, for example patients of the same age and gender. The median numeric daily dose of the observed data, within the chosen strata, was used to replace missing numeric daily dose within that same strata. An algorithm was developed which reviewed each oral corticosteroid therapy record and imputed missing values, first where the strata were based on data within- persons, then where the strata were based on data from groups of patients. See Figure 3 for specific details.

Calculating duration and dose of oral corticosteroid prescriptions

Having cleaned the relevant variables and imputed missing data using the "hot decking" approach (see Figure 3), first the duration and dose of individual prescriptions were identified,

then, if patients had a series of prescriptions within a certain timeframe, continuous periods of use were defined.

The duration and daily dose of oral corticosteroid prescriptions were calculated as follows:

Duration = quantity ÷ numeric daily dose

Daily dose = dose per tablet x numeric daily dose

3.4.2.2. Inhaled corticosteroids

Definition

Inhaled corticosteroid (ICS) use 3 months prior to zoster diagnosis was identified. Prescriptions of any dose were included, as discrepancies are likely between the prescription and actual adherence, potentially making any calculated dose unreliable.

Background and data cleaning

Numeric daily dose for ICS represents the number of puffs a patient is directed to take on the inhaler per day. The variable "pack type" largely provided the number of puffs per inhaler, and the quantity variable represented the number of inhalers. Implausible values for ICS were identified; quantities > 4 (99% of ICS prescriptions had a quantity 1-4) were changed to the median value of one and numeric daily doses >40 (in other words, more than 40 puffs per day, as this was deemed a clinically plausible upper threshold) were changed to missing.

Missing data

Missing data for ICS were dealt with as follows;

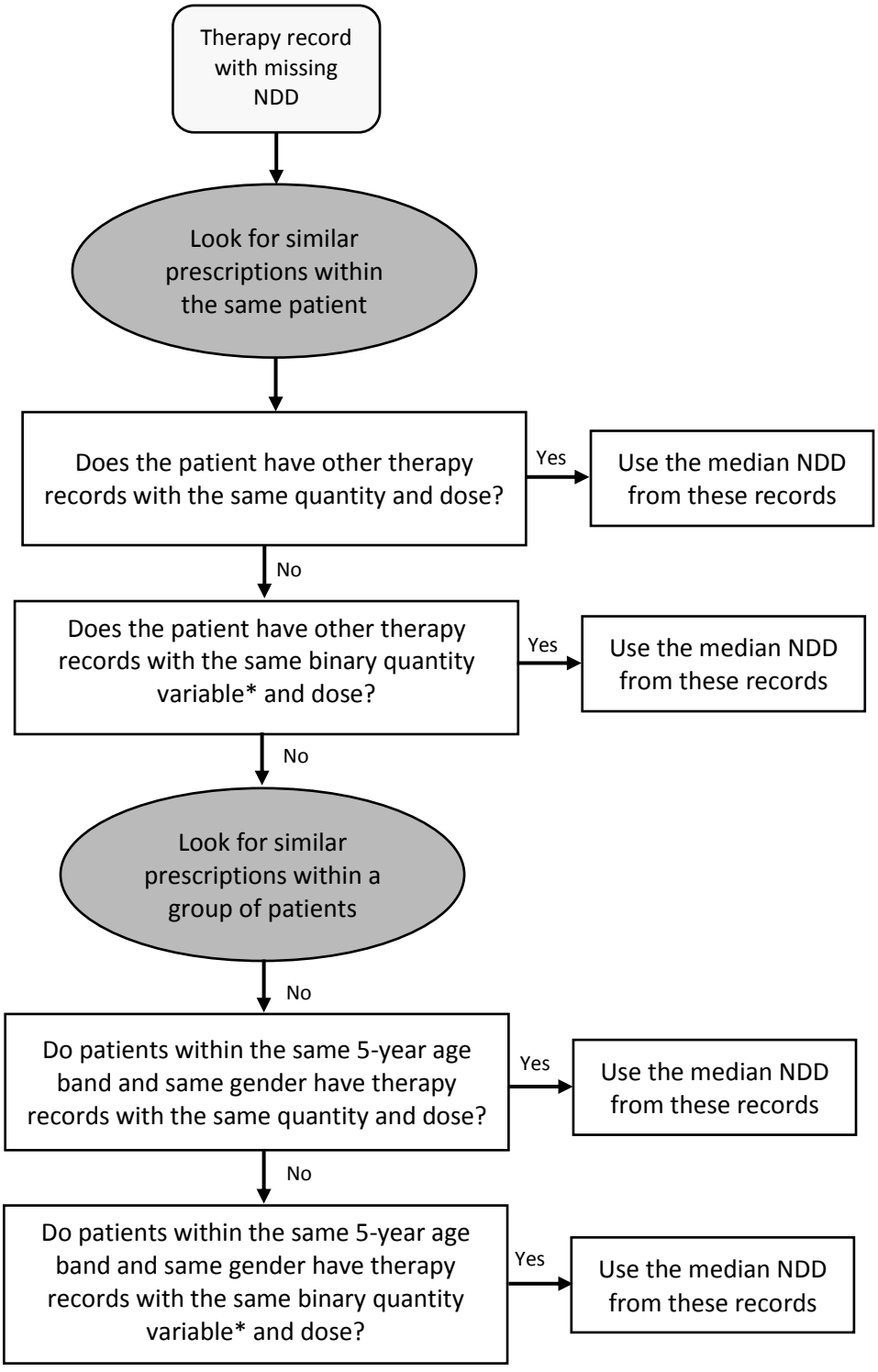
- Missing pack type: the most common pack type for the quantity and dose of each prescription, or if not available the median pack type value for all prescriptions of 200 was used.
- Missing numeric daily dose: the median value of 4 puffs per day was used.
- Missing quantity: the median value of 1 was used.

Calculating duration of inhaled corticosteroid prescriptions

Duration of individual inhaled corticosteroid prescriptions were calculated as follows:

(Quantity x pack type) ÷ numeric daily dose

Figure 3: Flow chart describing the "hot decking" imputation method used to impute missing values for numeric daily dose



Notes

(NDD, numeric daily dose, equivalent to number of tablets taken per day) *binary quantity variable refers to a variable that was created, which categorised quantity into low and high about the median quantity (42 tablets for oral corticosteroids, 36 tablets for other immunosuppressive drugs).

3.4.2.3. Other immunosuppressive therapies

In addition to corticosteroids, there are a number of other drugs which can cause immunosuppression, including: chemotherapy drugs such as antimetabolites, anthracyclines and alkylating agents; and drugs to treat autoimmune conditions such as anti-proliferative immunosuppressants.[110]

Definition

The primary definition of these *"other immunosuppressive therapies"* was any use in the month prior to zoster diagnosis. An alternative definition was also coded; which comprised any use in the three months prior to zoster diagnosis.

Data cleaning and imputing missing data

Where the variable quantity (total number of tablets prescribed) had a value of >1000 tablets, quantity was coded to missing. As with oral corticosteroid prescriptions, quantity was 99% complete and numeric daily dose had around 30% missing data. The hot-deck method was used to impute missing numeric daily dose, in the exact same way as for imputing numeric daily dose for oral corticosteroids (see Figure 3); the only difference being the binary quantity variable that was created used the median value 36 tablets (rather than 42 tablets).

Calculating duration of other immunosuppressive therapies

Duration was calculated as follows:

Quantity ÷ numeric daily dose

3.4.3. Autoimmune conditions

Three autoimmune conditions were defined: *RA, SLE,* and *IBD.* These disorders were defined through the presence of a Read code in CPRD any time prior to the zoster diagnosis.

3.4.4. Other clinical conditions

3.4.4.1. Diabetes

The diabetes definition required either: a definite diabetes diagnosis identified by Read codes in the CPRD clinical or referral files; or a possible diabetes Read code [e.g. self- monitoring of

blood glucose] with a subsequent diabetes-specific prescription [insulin or oral anti-diabetics]; or ≥2 diabetes drug prescriptions prior to the zoster diagnosis. Gestational diabetes and drug-induced diabetes were excluded as these are usually temporary, rather than chronic conditions.

Patients were categorised as type 1 or type 2 diabetes where possible. Distinguishing between type 1 and type 2 diabetes is not always possible using diabetes codes as patients are frequently given a non-specific code. Furthermore, where type of diabetes is assigned within a Read code, it has been found to be unreliable.[111] Therefore Read code data for type 1 and type 2 diabetes were not used, but instead age at first diagnosis, age at first treatment and, finally, treatment received was used to classify diabetes type, as in previous CPRD studies.[112,113]

Type 1 diabetes was assigned where:

- age at first diagnosis was ≤35 years and treatment ever was exclusively insulin; or
- patients received at least two insulin prescriptions ≤35 years, but had no diabetes diagnosis.

Type 2 diabetes was assigned where:

- age at first diabetes diagnosis was >35; or
- patients received exclusively oral anti-diabetics after 35 years of age.

Patients with age at diagnoses >35, but treated exclusively with insulin or any others not fitting into these categories were assigned as “Unknown type”.

3.4.4.2. Chronic obstructive pulmonary disorder

COPD patients were defined as anyone with a Read code for COPD prior to zoster diagnosis and aged ≥35 years at the time of diagnosis. Diagnostic READ codes used to identify COPD included chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation.[114]

Previous studies of COPD patients in UK primary care databases have used diagnostic codes or diagnostic codes[115-118] along with prescription data, for example having a minimum number of treatments following COPD diagnosis.[119] In this study, prescription data were not included because: 1) patients with mild COPD may not receive treatment (despite guidelines suggesting all COPD patients are given bronchodilators); 2) patients may be receiving treatment in

secondary care; 3) treatment is non-specific to COPD; prednisolone, the oral corticosteroid most commonly used in COPD treatment, is also used in other inflammatory and allergic disorders such as RA, asthma and IBD; bronchodilators and ICS are used in asthma treatment and other respiratory diseases; and finally 4) a recent validation study in CPRD of COPD diagnoses, concluded that use of COPD Read codes alone is sufficient to identify COPD patients.[120] Using medication in the definition of COPD does not appreciably improve the accuracy of the diagnoses.

The use of spirometry data were also considered, however, the above mentioned validation study found that using spirometry recordings did not significantly improve the accuracy of COPD diagnoses.

3.4.4.3. Asthma

Although asthma can be chronic, patients may not continuously experience symptoms. Therefore it was decided to identify patients who were likely to have "active" asthma at the time of zoster diagnosis. Patients were considered to have "active" *asthma* if they had an asthma diagnosis prior to zoster diagnosis and additionally an asthma-related prescription within the 12 months prior to the zoster diagnosis. This definition matches the criteria required to be on the asthma register in the UK.[121] Patients with a COPD diagnosis ever in their medical history were also unable to be defined as asthma patients; differentiating between these two conditions is challenging and this criteria helped exclude COPD patients misdiagnosed as asthma. Asthma related prescriptions included the following respiratory drugs; short and long-acting beta-2 agonists and short and long-acting antimuscarinics, ICS, cromoglycates and nedocromil, theophyllines, leukotriene receptor agonists and omalizumab.

3.4.4.4. Chronic Kidney Disease

CKD was defined as any patient with a clinical diagnosis of mild, moderate or severe CKD, or evidence of having received kidney dialysis, any time prior to zoster diagnosis. CKD diagnosis is mostly based on serum creatinine tests which can be used to obtain the glomerular filtration rate (how much blood passes through the kidneys each minute), and estimate the stage of kidney disease. However, these tests were not included in the definition of CKD as certain groups, such as elderly patients with diabetes, may be more likely to be tested, potentially leading to a non-representative sample of CKD patients.

3.4.4.5. Depression

As depression tends to occur in episodes, the aim was to identify recent depression. In this study, depression was defined as any patient with a Read code within one year prior to the zoster diagnosis for new onset or current symptomatic depression. Read codes for both diagnoses and symptoms were included. Symptoms were included, in addition to diagnoses, due to the trend post-2004 of using symptom, rather than diagnosis codes, in UK primary care.[122] Antidepressants were not used in the definition of depression as these drugs are used in a wide range of other disorders, including the management of chronic pain and stroke recovery.

3.4.5. Demographic factors

3.4.5.1. Age

All "acceptable" patients in CPRD have a year of birth, and some patients born after 1990 have a month of birth. Where month of birth was missing, July was used, and all patients were allocated a birth date of the 1st of the month, as day of birth is not available.

3.4.5.2. Gender

Gender is provided in CPRD and there was no missing information for gender. Patients with indeterminate gender were excluded (in the January 2012 CPRD build, 0.0001% were indeterminate gender).

3.4.5.3. Socioeconomic status

Socioeconomic status (SES) was analysed using quintiles of the Index of Multiple Deprivation (IMD) score. The IMD combines a number of indicators, chosen to cover a range of economic, social and housing issues, into a single deprivation score.[123,124] IMD is available at the practice and patient level. The practice postcode or patient's home postcode is mapped at the lower level super output level to the corresponding IMD score; a low quintile represents the least deprived, while a higher quintile the most deprived. Patient level IMD data are available for patients registered at English practices agreeing to link medical records with other databases and who have a valid and linkable postcode in their medical records. The papers on zoster risk factors (chapter 4) and antiviral use (chapter 5) used the IMD dataset released in 2007, whilst the paper on PHN risk factors (chapter 7) used the IMD dataset released in 2010. Practice level

IMD was available for all practices within the IMD 2010 dataset, whereas only for English patients in the IMD 2007 dataset.

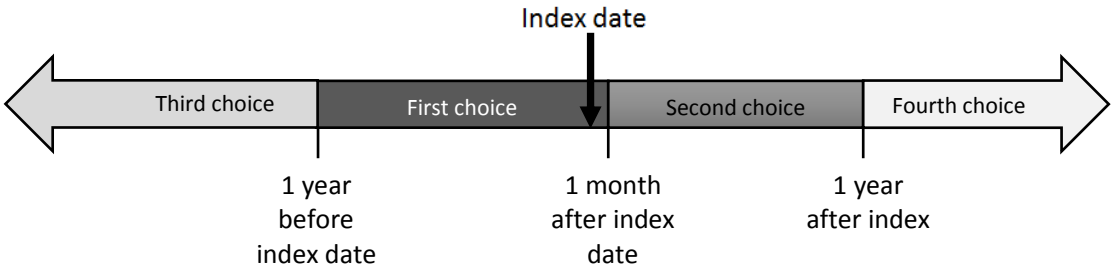
3.4.6. Lifestyle data

3.4.6.1. Smoking status

Smoking was defined at zoster diagnosis using three categories; non-smoker, current smoker and ex-smoker. Data were derived from: 1) medical Read codes such as "tobacco dependence in remission" and "stopped smoking"; and 2) data from structured data fields in the additional details file, specifically entity type number four records information on smoking, including the patients smoking "status" (yes, no or ex) and the "number of cigarettes per day" smoked. These data were extracted for each patient along with the date the status was assigned.

Smoking status was then classified by the algorithm shown in Figure 4.

Figure 4: Algorithm used to define BMI, smoking and alcohol status



Note: the nearest record to the index date from the first choice period was taken if available, otherwise from the second choice period and so on. If patients had any evidence of smoking or alcohol prior to zoster diagnosis, but were defined by the algorithm as a non-smoker or non-drinkers, they were reclassified as ex-smokers or ex-drinkers.

3.4.6.2. BMI category

BMI is a metric used to classify people as under- or overweight. It is derived from patients weight in kilograms / (height in meters)^2. In this study BMI was defined at zoster diagnosis, according to adult BMI cut-offs defined by the WHO, as underweight (BMI <18.5), healthy weight (BMI 18.5-24.9), overweight (BMI 25+) or obese (BMI ≥30).

Height and weight are recorded opportunistically in UK primary care and are contained in the CPRD additional details files, in entity types 104 and 140. Data cleaning was based on that described in the paper by Bhaskaran et al on BMI recordings in CPRD.[125] Any records taken when the patient was <16 years old were dropped, as the patient would still be growing.

Implausible values were excluded, specifically height records <4 and >7 foot were dropped, and weight records <20 kilograms were dropped. For each weight record, a BMI was calculated using first, height recorded on that day, otherwise, last observation of height, or if no previous height records were available, then first future height.

BMI status was then classified by the algorithm shown in Figure 4.

Read codes exist classifying patients by BMI category, however they are very rarely used (around 3% of patients have a clinical code that would enable classification into WHO BMI categories),[125] therefore Read codes were not incorporated into the definition of BMI.

3.4.6.3. Alcohol use

Alcohol use was defined at zoster diagnosis and classified as non-drinker, ex-drinker, or current drinker using: 1) medical Read codes, such as "alcohol problem drinking"; and 2) data from structured data fields in the additional details file, specifically entity type 5 records data on alcohol use, including the patients alcohol "status" (yes, no or ex) and the number of alcohol "units per week" consumed.

Alcohol status was then classified by the algorithm shown in Figure 4.

3.4.7. Characteristics of the acute zoster episode

3.4.7.1. Antiviral use during acute zoster episode

Antiviral medications are recommended for all immunosuppressed and some immunocompetent patients following zoster diagnosis. Guidelines specify they must be given within seven days of a zoster diagnosis.[126] Therefore antiviral medications given up to a week following zoster diagnosis were identified from CPRD therapy records. Three different antivirals were searched for; aciclovir, famciclovir and valaciclovir.[3] If zoster patients had two different antivirals prescribed on the same day, this was recorded.

3.4.7.2. Site of zoster

The site of zoster is not routinely recorded in CPRD or HES. However, some Read and ICD codes which identify zoster also contain the location of zoster, for example, "Herpes zoster with ophthalmic complication". The level of detail contained in the diagnostic codes allowed

zoster patients to be categorised as, “ophthalmic zoster”, “non-truncal zoster” or “site unspecified”.

As patients may have more than one interaction with their GP or hospital regarding their zoster episode, particularly for complicated zoster involving the eye, all zoster codes in the year following the first zoster diagnosis were extracted from CPRD and HES, and their site determined. Site was then assigned in order of priority; ophthalmic, non-truncal and finally site unspecified.

In the study of PHN risk factors (described in chapter 7) ophthalmic zoster was identified through a revised algorithm, to improve identification of ophthalmic zoster. In a US study of an administrative data source (specifically, all adult residents of Olmsted County, Minnesota, aged ≥22 years seeking medical care for zoster between 1996 and 2001) just 10% of patients whose full medical records reported zoster affecting the eye, also had an ICD-9 code indicating an ophthalmic complication. In the study described in chapter 7, ophthalmic zoster was therefore additionally defined as patients with non-specific zoster, plus a diagnosis of, or treatment for, acute eye infection (such as keratitis or conjunctivitis) within 2 weeks of zoster onset or from records of first-ever specific chronic eye conditions known to be associated with zoster (such as, conjunctival scarring or episcleritis), within 3 months after zoster onset. This was in line with a previous study in CPRD.[5]

3.5. Chapter summary

Data sources and variable definitions

- This study utilises data from a UK primary care database called CPRD, which holds data on over 12 million patients and is largely representative of the UK population. The study also uses a linked secondary care database called HES, which holds data on all hospital admissions throughout England.
- Zoster was defined through the presence of Read codes in CPRD and ICD-10 codes in HES.
- PHN was defined as pain for at least 90 days following zoster diagnosis, and identified through the presence of diagnosis codes in CPRD and HES, along with prescription data in CPRD.
- The other explanatory variables utilised in this thesis were identified from data in CPRD, and included: severely immunosuppressive conditions, immunosuppressive therapies, autoimmune conditions (RA, SLE and IBD), other clinical conditions (diabetes, COPD, asthma, CKD and depression), demographic factors (age, gender and SES), lifestyle data (BMI category, smoking and alcohol use) and characteristics of the acute zoster episode (antiviral use during acute zoster and site of zoster rash).

Chapter 4: Quantification of risk factors for zoster: population based case-control study

4.1. Introduction

Understanding the risk factors for zoster is important when planning vaccination campaigns. A large case-control study was therefore carried out to quantify the effects of various proposed risk factors for zoster and explore whether their effects differed by age group. Such investigations may help to identify any groups of patients at high risk of zoster, who are not currently targeted for vaccination.

This research, which was published in the British Medical Journal, is presented below, along with its published appendices which were too detailed for the main paper. The paper is followed with some additional information on: 1) how controls were selected in this study; 2) the relative risk of zoster according to smoking, BMI and alcohol status; and 3) additional biological evidence indicating impaired cell-mediated immunity, associated with the risk factors of interest.

4.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Harriet Forbes
Principal Supervisor	Sinead Langan
Thesis Title	Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	British Medical Journal		
When was the work published?	13th May 2014		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I was responsible for preparing the dataset, designing the study, and conducting the statistical analysis. I was also primarily responsible for writing this work. My co-authors supported this work in an advisory capacity, commenting on research design and

	drafts of the paper.

Student Signature: _____ **Date:** 9/5/2016

Supervisor Signature: Sinead Kangan **Date:** 4/5/2016.

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RESEARCH

Quantification of risk factors for herpes zoster: population based case-control study

Harriet J Forbes *research fellow in epidemiology*, Krishnan Bhaskaran *lecturer in statistical epidemiology*, Sara L Thomas *clinical senior lecturer*, Liam Smeeth *professor of clinical epidemiology*, Tim Clayton *senior lecturer in medical statistics*, Sinéad M Langan *NIHR clinician scientist and clinical senior lecturer*

Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

Abstract

Objectives To quantify the effects of possible risk factors for herpes zoster at different ages.

Design Case-control study.

Setting UK Clinical Practice Research Datalink primary care data.

Participants 144 959 adults diagnosed with zoster between 2000 and 2011; 549 336 age, sex, and practice matched controls.

Main outcome measures Conditional logistic regression was used to generate adjusted odds ratios to estimate the strength of association of each potential risk factor with zoster and assess effect modification by age.

Results The median age of the cases and controls was 62 years. Factors associated with increased risk of zoster included rheumatoid arthritis (3111 (2.1%) *v* 8029 (1.5%); adjusted odds ratio 1.46, 99% confidence interval 1.38 to 1.55), inflammatory bowel disease (1851 (1.3%) *v* 5118 (0.9%); 1.36, 1.26 to 1.46), chronic obstructive pulmonary disease (6815 (4.7%) *v* 20 201 (3.7%); 1.32, 1.27 to 1.37), asthma (10 243 (7.1%) *v* 31 865 (5.8%); 1.21, 1.17 to 1.25), chronic kidney disease (8724 (6.0%) *v* 29 437 (5.4%); 1.14, 1.09 to 1.18), and depression (6830 (4.7%) *v* 22 052 (4.0%); 1.15, 1.10 to 1.20). Type 1, but not type 2, diabetes showed some association with zoster (adjusted odds ratio 1.27, 1.07 to 1.50). The relative effects of many assessed risk factors were larger in younger patients. Patients with severely immunosuppressive conditions were at greatest risk of zoster—for example, patients with lymphoma (adjusted odds ratio 3.90, 3.21 to 4.74) and myeloma (2.16, 1.84 to 2.53), who are not eligible for zoster vaccination.

Conclusions A range of conditions were associated with increased risk of zoster. In general, the increased risk was proportionally greater in younger age groups. Current vaccines are contraindicated in people at the greatest risk of zoster, highlighting the need for alternative risk reduction strategies in these groups.

Introduction

Herpes zoster (commonly known as shingles) is caused by the reactivation of latent varicella zoster virus when specific cell mediated immunity becomes compromised. It is a common disease in older people,[1] with a lifetime risk of up to 30% rising to 50% among those living to 85 years.[2] Zoster typically presents as a painful unilateral vesicular dermatomal rash that causes acute morbidity lasting two to four weeks.[3] A severe complication—postherpetic neuralgia—although uncommon in patients aged under 50, develops in 12% of zoster patients aged 50 years or over[1 4]; it causes intense pain that can last from months to years and is associated with considerable impairment of quality of life.

A live vaccine that reduces the risk of zoster and postherpetic neuralgia has recently been developed.[4] The vaccine is licensed in peoople aged over 50 years. In the United States and Australia, it is recommended in people aged 60 years or over. In the United Kingdom, it is routinely available for patients aged 70, with a catch-up campaign for 72-79 year olds (on the basis of cost effectiveness studies[5]); the current catch-up cohort is those aged 79. Table 1⇓ shows some examples of recommedations on vaccination in major countries. As the zoster vaccine is expensive, targeting vaccination towards groups at high risk of zoster is necessary. Age is the most important risk factor for zoster and postherpetic neuralgia, so it drives vaccination policies. The incidence of zoster rises from 3.5 per 1000 person years among 50-54 year olds to 7.1 per 1000 person years among 75-79 year olds in the UK.[6] However, whether people with other risk factors, particularly in younger age groups, might also benefit from vaccination is not clear.

Several clinical conditions not listed as contraindications for the zoster vaccine have been associated in some studies with an increased risk of zoster; these include autoimmune conditions such as rheumatoid arthritis,[7] systemic lupus erythematosus,[8]

Correspondence to: H Forbes harriet.forbes@lshtm.ac.uk

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and inflammatory bowel disease,[9] and chronic conditions such as diabetes mellitus,[10 11] chronic obstructive pulmonary disease,[11 12] chronic kidney disease,[13-15] asthma,[16] and depression.[2 17] Large, adequately powered studies investigating the association of these conditions with zoster are lacking.

This study therefore aimed to quantify the effects of various proposed risk factors for zoster and explore whether their effects differ by age group, to help to identify any groups of patients at high risk who are not currently targeted for vaccination. We aimed to add to the existing literature by using a very large data source and a consistent methodological approach to help comparison between various risk factors.

Methods

We did a matched case-control study to quantify the effects of a range of individual level factors on the risk of zoster in a general population.

Data source

This study used data from the UK Clinical Practice Research Datalink, a primary care database of anonymised patients' records containing complete prescribing and diagnostic information and feedback from hospital referrals. Clinical diagnoses are coded in the Clinical Practice Research Datalink with Read codes.[18] It is one of the largest sources of continuous patients' records in the world, containing data on approximately 7% of the UK population, and is broadly representative of patients' and practices' characteristics in the UK.[19] Sixty per cent of patients in the Clinical Practice Research Datalink have data available in the Hospital Episode Statistics database, which is a linked computerised database of hospital attendances in England from 1997.

Selection of cases

The base study population consisted of all patients aged 18 years or over, under follow-up between 1 January 2000 and 31 December 2011, with no evidence of previous zoster (no codes for zoster or postherpetic neuralgia before the start of follow-up). We identified zoster cases by using the Clinical Practice Research Datalink and Hospital Episodes Statistics. Cases in the Clinical Practice Research Datalink were those with a zoster Read code and at least 12 months' follow-up before a first diagnosis of zoster, to exclude past cases of zoster recorded retrospectively after registration at a general practice.[20] Incident zoster in Hospital Episodes Statistics was identified by ICD-10 (international classification of diseases, 10th revision) codes (B02, B02.0, B02.1, B02.31, B02.7, B02.8, B02.9, G53.0) that appeared in the primary diagnosis field; we excluded patients with these codes recorded in secondary diagnosis fields, as this could reflect either incident zoster or sequelae of past zoster. For cases identified in Hospital Episodes Statistics, we took the date of hospital admission as the index date. If zoster was identified in both Hospital Episodes Statistics and the Clinical Practice Research Datalink, we took the earliest recorded zoster diagnosis as the index date.

Selection of controls

We identified all potential controls for each case and used incidence density sampling to select up to four controls per case at random.[21] Controls were registered with the practice at the index date of the case and for at least 12 months before and were matched to cases by practice, sex, and age (within 1 year). We selected controls before their exposure status for other risk factors was known. By matching on practice, we controlled for practice level socioeconomic status. Controls took the index date of their matched case. Controls had no history of zoster or postherpetic neuralgia at the index date, but they could go on to have zoster and therefore also be included as a case.[22] Controls with no contact with their practice (that is, no consultation record of any kind, including repeat prescriptions and face to face or telephone consultations) any time from six months before to 12 months after the index date were assumed inactive in the database and excluded.

Risk factors

Information on risk factors was based on records entered in the Clinical Practice Research Datalink any time before the index date. For each risk factor, we developed a definition and a list of relevant Read codes. A clinician reviewed all code lists, and these are available on request. Patients without Read codes for a clinical condition were assumed not to have the condition.

Key risk factors of interest

Our key risk factors of interest were rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, and diabetes (overall and by type) (see appendix section A for a full descriptions of how these risk factors were identified).

Severe immunosuppression

Our models included severely immunosuppressive conditions determined by the Advisory Committee on Immunization Practices to be contraindications to vaccination—namely, recent history (less than two years before index date) of leukaemia, lymphoma, or bone marrow transplant, or any history of HIV, haematopoietic stem cell transplantation, myeloma, or "other unspecified cellular immune deficiencies" (for example, pancytopenia).[23] We also included use of immunosuppressive treatment; we extracted all relevant prescriptions before the index date and calculated duration of prescription (using data on quantity of tablets prescribed and numeric daily dose). We defined oral corticosteroid exposure as a 14 day course of high dose (≥20 mg/day) oral corticosteroids in the month before the index date. We included exposure to other immunosuppressive treatments in the month before the index date as an additional covariate (see appendix section A for further details).

Other characteristics

Other characteristics of patients included smoking (ex-smoker, current smoker, non-smoker), alcohol consumption (non-drinker, current drinker, ex-drinker), and body mass index (underweight (<18.5), normal weight (18.5-24.9), overweight (≥25), obese (≥30)) (see appendix section A for further details). We captured exposure to inhaled corticosteroids within three months before the index date (see appendix section A for further details), as some evidence suggests that they may increase the risk of zoster.[24] We compared follow-up time (in years) for cases and controls, to check that the opportunity to record the exposures of interest in the two groups was equal.[25]

To explore whether the association between our risk factors of interest and zoster could be affected by ascertainment bias (that is, visiting a general practice for the risk factor may increase the likelihood of receiving a diagnosis of zoster), we investigated the association between zoster and treated epilepsy (an epilepsy Read code before index date and an epilepsy treatment (*British National Formulary* chapter 4.8.1) 12 months before the index

date). Epilepsy is a chronic condition requiring high level healthcare use[26]; it is not thought to be associated with zoster.

Statistical analysis

We described the characteristics of the study population by case-control status. The analysis accounted for the matched design by using conditional logistic regression, so all odds ratios accounted for the matching factors of age (within 1 year), sex, practice, and calendar time. Initially, we calculated univariable odds ratios to estimate the strength of association of each potential risk factor with zoster; 99% confidence intervals were generated to account for multiple testing and reduce the chance of picking up small and clinically unimportant associations. We then did multivariable analyses on patients with complete data for all variables (see also below for approach to missing data).

We investigated a potentially effect modifying role of age at diagnosis (index) date by calculating stratum specific odds ratios for each variable in the multivariable model by age groups (>50 years, 50-59 years, 60-69 years, and ≥70 years). We added interaction terms between age and other risk factors one at a time into the multivariable regression model and used likelihood ratio tests to investigate interactions.

To quantify the effect of our assessed risk factors, we estimated the age specific absolute rate of zoster for each factor by multiplying the age specific effect estimates by the age specific rate of zoster in the general population in 2010. We estimated the age specific general population rates within the Clinical Practice Research Datalink by dividing the number of incident cases of zoster in 2010 by the total person time contribution of the population at risk in that year, which included all patients in the Clinical Practice Research Datalink with at least one year of follow-up and no history of zoster.

We then evaluated to what extent combinations of risk factors could lead to a high risk of zoster, specifically within age groups not targeted for vaccination. We calculated the predicted risk of zoster for each person by summing the coefficients for their risk factors from the final model and multiplying their predicted odds ratio by the age specific rate of zoster in the general population. We were thus able to determine the number of cases aged under 70 but with a predicted risk of zoster equal to or higher than that of the general population aged at least 70 years (vaccination is currently offered to 70 and 79 year olds in the UK). We repeated this analysis with a 60 years age cut-off, to reflect vaccination policy from different countries. We restricted these calculations to people without severely immunosuppressive conditions.

Sensitivity analyses included use of a wider definition of exposure to oral corticosteroids and other immunosuppressive treatment (anyone exposed three months before the index date). We used multiple imputation by chained equations to account for missing data (11% of patients had missing data for alcohol or smoking).[27] The imputation model included all covariates from the main outcome model, together with matching variables of age and sex, and extra comorbidities as additional markers of alcohol or smoking related diseases. We created five imputed datasets and combined them for analysis. We further adjusted for patient level socioeconomic status in the subgroup of patients registered at English practices for whom these data were available (see appendix sections B-D for further details). We applied two different definitions of an "active" control. Firstly, we considered controls to be inactive if they had no contact with their general practice during any time from one year before to two years after the index date. Secondly, we considered controls to be inactive if they had not consulted their general practice in the previous three years. Finally, we calculated the mean yearly consultation rate before the index date (by dividing the total number of face to face or telephone consultations during follow-up by the total years of follow-up before the index date) among patients with our risk factors of interest and among patients with epilepsy.

Results

We identified a total of 145 397 incident cases of zoster. After matching, we removed inactive controls (n=27 928; 4.8% of all 577 264 matched controls). We excluded a small number of cases, as they had no eligible controls (n=438; 0.3%), largely owing to advanced age, leaving 144 959 cases.

Table 2⇓ shows descriptive details of the cases and controls; 59.4% of cases and 61.0% of controls were female (the higher proportion among controls was due to the variable number of controls per case). The median age at diagnosis of zoster was 62 (interquartile range 48-73) years for cases and 62 (49-74) years for controls. Approximately 45% of zoster cases occurred in patients under 60 years and 65% in those under 70 years. Registered follow-up time before the index date was equivalent in cases and controls (8.6 (4.3-12.1) years).

Table 3⇓ shows the proportion of cases and controls with our key risk factors of interest and other covariates. The strongest risk factors for zoster were the severely immunosuppressive conditions, although their overall prevalence was low—2.8% of cases and 1.2% of controls (table 3⇓). Odds ratios varied from 1.78 to 13.46, although the latter estimate (for haematopoietic stem cell transplantation) had a particularly wide 99% confidence interval, as it was based on only 29 exposed patients.

Among our key risk factors of interest, systemic lupus erythematosus had the strongest relative risk of zoster (adjusted odds ratio 1.72, 99% confidence interval 1.45 to 2.04) (table 3⇓), but the condition was very rare (0.3% of cases and 0.1% of controls). The risk of zoster was increased by more than 30% among patients with rheumatoid arthritis (adjusted odds ratio 1.46, 1.38 to 1.55) and chronic obstructive pulmonary disease (1.32, 1.27 to 1.37). Asthma, chronic kidney disease, and depression were associated with a greater than 10% increased risk of zoster. Although no association existed between zoster and diabetes overall (adjusted odds ratio 1.02, 0.99 to 1.05), we found strong evidence that patients classified as having type 1 diabetes were at increased risk of zoster (1.27, 1.07 to 1.50).

To assess whether some of the overall effect of these conditions was mediated by their treatments, we additionally adjusted for immunosuppressive treatments and inhaled corticosteroids (table 3⇓, final column). The associations between zoster and rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disorder, and asthma were attenuated after adjustment but did not disappear. Among conditions not commonly treated with these drugs (chronic kidney disease, depression, and diabetes), the association did not vary after this additional adjustment.

Treated epilepsy, not expected to be associated with zoster, was marginally more common among cases than controls (1420 (0.98%) *v* 5142 (0.94%)). We found little evidence of association with zoster in crude (odds ratio 1.05, 0.97 to 1.14) or adjusted analyses (1.06, 0.97 to 1.15), suggesting that other associations observed in this study are unlikely to be explained by ascertainment bias.

We explored how the effect of our risk factors varied by age (tables 4⇓ and 5⇓). We found some evidence of age interaction.

In general, the relative effects of these risk factors on zoster decreased with increasing age. For example, among patients with chronic kidney disease the odds ratio point estimate was 1.53, 1.21, and 1.11 among patients aged 18-49, 50-59, and 60-69 years respectively.

To quantify the effect of our key risk factors of interest, particularly among age groups not targeted for vaccination, we estimated absolute rates of zoster (table 6⇓). The rates remained low among patients aged 18-49 years (for example, for those with rheumatoid arthritis: 3.51 (99% confidence interval 2.40 to 5.13) per 1000 person years), despite the high relative risks in this age group. The absolute rates of zoster among patients aged 60-69 years were relatively high, particularly for those with chronic obstructive pulmonary disease and rheumatoid arthritis.

We calculated the predicted risk of zoster among 143 620 zoster cases (having excluded 1339 patients with severely immunosuppressive conditions) on the basis of their risk factor profile. Among these cases, 40 409 (28.1%) had at least one risk factor of interest. Of 97 789 zoster cases aged under 70 years, 3619 (3.7%) had a predicted risk as high as that for the general population aged 70 or over; 643 (0.96%) of 67 000 patients under 60 years had a predicted risk as high as those aged 60-69 years.

Sensitivity analyses imputing missing data for smoking and alcohol (see appendix section B), using different definitions for immunosuppressive treatment (see appendix section C), adjusting for patient level socioeconomic status (see appendix section D), and applying different definitions of an active control (see appendix section E) did not change the study findings. The consultation rate was similar among patients with epilepsy and those with our risk factors of interest (see appendix section F).

Discussion

In this large matched case-control study, a range of conditions were associated with increased risk of zoster, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, type 1 diabetes, and depression. The relative effects of many of these risk factors were larger among younger patients. This raises the question of whether vaccination of certain younger, high risk groups may be beneficial; cost effectiveness studies, also considering the risk of postherpetic neuralgia, would be needed to answer this question. Among a wide range of risk factors, people with contraindications to currently available vaccines were at the highest risk of zoster, highlighting the need to identify strategies to reduce the risk of zoster among these groups.

Strengths and limitations of study

This large study included all incident cases of zoster in the Clinical Practice Research Datalink over an 11 year period, providing high power to detect small effects, except for rare potential risk factors. We assessed a wide range of factors, allowing adjustment for many of the known as well as potential confounders, in addition to exploring interactions with age, which is of key public health relevance in terms of vaccination policy.

The study may be subject to ascertainment bias; regular general practice visits for a chronic condition such as diabetes may increase the likelihood of receiving a zoster diagnosis. However, we believe that most zoster cases would present to their general practice, owing to the extensive rash and considerable pain associated with zoster and free general practice attendance in the UK.[28] A survey about immunisation practices in the United States among people aged 60 and over found that 95% of those who knew they had zoster sought care.[29] Furthermore, we found little evidence to suggest that patients with epilepsy (who were visiting their general practice as frequently as patients with our risk factors of interest) were at increased risk of zoster.

As with any observational study, residual confounding may be present. For example, exposure to varicella contacts, hypothesised to naturally boost varicella zoster virus specific immunity in people with latent varicella zoster virus infection and thus protect against zoster,[30] was not available.

Some misclassification of zoster is possible. In UK primary care, diagnosis of zoster is clinically based with no laboratory testing. Validation of zoster diagnoses in primary care in the Netherlands found that 90.8% of cases had raised antibodies indicating recent zoster infection, suggesting that diagnosis of zoster has a high positive predictive value.[31] The frequency with which general practitioners wrongly reject the diagnosis of zoster has not, however, been investigated; this may be more common among younger patients in whom zoster is uncommon. However, the most common misclassification of zoster is as recurrent herpes simplex, which very rarely presents in a dermatomal distribution.[32] Zoster is typically a straightforward clinical diagnosis, so the extent of misclassification is likely to be minimal. Any misclassification is likely to be non-differential with respect to exposure status, thus leading to an underestimation of associations.

Finally, excluding "inactive" controls to remove patients who would not attend their general practice if they did develop zoster, may have resulted in healthier controls not being included and led to an underestimation of the odds ratios.

Comparison with other studies

The strength of association between the autoimmune conditions in this study and risk of zoster is broadly in line with previous studies.[7-9 33] The increased risk associated with these conditions may partly reflect exposure to immunosuppressive drugs, as well as the conditions themselves. When we adjusted for immunosuppressive treatments, the increased risk of zoster was attenuated, suggesting that these drugs contribute to the overall increased risk of zoster in these patients.

The effect of chronic obstructive pulmonary disease is also consistent with previous studies.[11 12] After adjustment for oral and inhaled corticosteroids commonly used to treat chronic obstructive pulmonary disease, the association reduced in these patients, again suggesting that these treatments add to their overall risk of zoster. Larger associations between zoster and depression have been reported.[11 17 34] No consensus exists on how to capture depression in electronic records; previous studies used different definitions, which may contribute to the varied findings. For example, a matched case-control study using commercial claims and encounters data in the United States found a higher risk of zoster among patients aged over 65 with depression (odds ratio 1.52, 95% confidence interval 1.46 to 1.58) but only included very severe cases (depressive disorder, chronic depressive personality disorder, or dysthymic disorder).[11] The association of zoster with chronic kidney disease was also smaller than previous studies have suggested.[15]

The risks of zoster are reportedly increased in patients with diabetes of unspecified type.[10 11 34 35] We found some evidence that type 1, but not type 2, diabetes was associated with an increased risk of zoster (although differentiating between type was not based on diagnostic codes, so misclassification is

possible). Patients with type 1 diabetes may be at higher risk of zoster owing to the immune dysregulation resulting from autoimmune pathogenesis.[36] The lack of effect found with type 2 diabetes must be interpreted cautiously, as negative confounding by ethnic group is possible; the type 2 diabetes population may have included South Asian patients (known to be at lower risk of zoster[2 37] and higher risk of diabetes). Ethnicity is poorly recorded for older patients not recently registered in the Clinical Practice Research Datalink, so we could not capture this characteristic.

The observed increased risks of zoster suggest that all these conditions are associated with some cell mediated immunosuppression. Disease induced immunosuppression has been proposed in chronic obstructive pulmonary disease and asthma patients,[38-42] although long term exposure to corticosteroids in these patients is also likely to contribute to immunosuppression. Patients with chronic kidney disease are known to have immune dysfunction,[43] particularly when the disease reaches end stage. For depression, stress may increase the risk of zoster as it affects several neuroendocrine functions that can affect cell mediated immunity,[44] and depression itself has been associated with poorer zoster immunity.[45 46]

Conclusions and policy implications

Severe immunosuppression is known to be associated with an increased risk of zoster.[11 47-49] What this study has highlighted, however, is that the strongest clinical risk factors for zoster are contraindications to its vaccine; the people arguably in most need of protection against zoster cannot currently benefit from vaccination. Alternative risk reduction strategies in these patients would help those at greatest risk of this disease and its complications.

Another important consideration regarding vaccination policy is whether the risk factors for zoster are also risk factors for zoster's main morbidity, postherpetic neuralgia. To date, very few studies have looked at this research question, and most have been underpowered. The role of severe immunosuppression as a risk factor for postherpetic neuralgia is inconclusive; three studies found that "general" immunosuppression was a risk factor for postherpetic neuralgia,[35 50 51] whereas another study found no association.[52] Autoimmune conditions have scarcely been assessed; one large cohort study in 34 280 zoster patients identified in Taiwanese health insurance records found that those with systemic lupus erythematosus were at greater risk of postherpetic neuralgia (rate ratio 2.27, 95% confidence interval 1.75 to 2.94).[35] Three studies found point estimates for the association between diabetes and postherpetic neuralgia greater than one in multivariate analyses, although the evidence was insufficient to confirm the association.[51 53 54] Some evidence suggests that depression is associated with postherpetic neuralgia.[55] Larger studies assessing these and other risk factors for postherpetic neuralgia are needed to improve our understanding of the risk factors for postherpetic neuralgia.

This study also raises the question of whether younger age groups at high risk of zoster may benefit from vaccination. Most cases of zoster occur in age groups too young for vaccination; this is because vaccination policy considers the risk of both zoster and postherpetic neuralgia, which is very uncommon in patients under 50. Deciding whether vaccination of groups of patients currently too young for vaccination would be cost effective will therefore require additional research on the risk factors for postherpetic neuralgia, specifically among patients aged under 50.

Our study has identified a range of conditions that are associated with an increased risk of zoster, raising the question of whether targeted zoster vaccination of specific high risk groups at younger ages is warranted. However, this study has also shown that patients at the greatest risk of zoster are not currently eligible to receive the vaccine.

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Transparency declaration: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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What is already known on this topic

A new herpes zoster vaccination campaign introduced in the United Kingdom in September 2013 is focused on older people only

Recent literature has suggested that a range of clinical conditions are associated with an increased risk of zoster, raising the possibility that some younger people may be at high risk

However, large, highly powered studies investigating the association of these clinical conditions with zoster are lacking

What this study adds

Conditions associated with increased risk of zoster included rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, type 1 diabetes, and depression

The increased risks were generally greater among younger age groups

The strongest risk factors are contraindications to vaccination, emphasising the need for alternative risk reduction strategies among these groups

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Tables

Table 1| Vaccine recommendations in United Kingdom, United States, Canada, Australia, and Sweden

Country	Groups recommended to receive vaccine	Contraindications
United Kingdom	People aged 70 years, with catch-up campaign for 72-79 year olds (current catch-up cohort is 79 year olds)	People with primary or acquired immunodeficiency state; active untreated tuberculosis infection; confirmed anaphylactic reaction to previous dose of varicella vaccine or any component of vaccine; pregnant women; people receiving immunosuppressive treatment (including high dose corticosteroids)
United States	Recommended for people aged ≥60 years	People with history of anaphylactic/anaphylactoid reaction to any component of vaccine; history of primary or acquired immunodeficiency state; people receiving immunosuppressive treatment, including high dose corticosteroids; women who are or may be pregnant
Canada	Recommended for people aged ≥60 years; also available for those aged 50-59 years	People with anaphylactic hypersensitivity to any of vaccine's componenets; congenital or acquired immune deficiency; active untreated tuberculosis; use of immune suppressive drugs; pregnant women; people with certain acute illnesses
Australia	Recommended for people aged ≥60 years; also available for those aged 50-59 years	People with anaphylactic hypersensitivity to any of vaccine's componenets; those receiving high dose systemic immunosuppressive treatment (such as chemotherapy, radiation therapy, or oral corticosteroids); people with malignant conditions of reticuloendothelial system; any person with similar immunosuppression due to disease or treatment
Sweden	Recommended for people aged ≥50 years	People with weakened immune systems due to drug treatment or other health conditions; allergy to gelatin or neomycin; moderate or severe illness; women who are or may be pregnant

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Table 2| **Description of cases and controls. Values are numbers (percentages) unless stated otherwise**

	Cases (n=144 959)	Controls (n=549 336)
Matching factors		
Sex:		
Female	86 071 (59.4)	335 272 (61.0)
Male	58 888 (40.6)	214 064 (39.0)
Age at index date (in years):		
18-29	10 849 (7.5)	38 761 (7.1)
30-49	28 762 (19.8)	104 708 (19.1)
50-59	27 833 (19.2)	105 157 (19.1)
60-69	31 134 (21.5)	121 108 (22.0)
70-79	28 025 (19.3)	110 097 (20.0)
80-89	15 891 (11.0)	61 566 (11.2)
≥90	2465 (1.7)	7939 (1.4)
Socioeconomic status (practice level)*:		
1 (least deprived)	28 938 (20.0)	109 663 (20.0)
2	28 853 (19.9)	109 253 (19.9)
3	29 811 (20.6)	112 888 (20.5)
4	30 550 (21.1)	115 678 (21.1)
5 (most deprived)	26 807 (18.5)	101 854 (18.5)
Other characteristics		
Mean (interquartile range) length of follow-up (in years)	8.6 (4.3-12.1)	8.6 (4.3-12.1)
Body mass index category:		
Underweight	2776 (1.9)	10 549 (1.9)
Normal weight	50 530 (34.9)	188 060 (34.2)
Overweight	47 886 (33.0)	177 603 (32.3)
Obese	29 581 (20.4)	109 440 (19.9)
Missing	14 186 (9.8)	63 684 (11.6)
Smoking status:		
Non-smoker	54 751 (37.8)	208 436 (37.9)
Current smoker	36 107 (24.9)	141 826 (25.8)
Ex-smoker	52 353 (36.1)	186 373 (33.9)
Missing	1784 (1.2)	12 701 (2.3)
Alcohol use:		
Non-drinker	14 481 (10.0)	56 774 (10.3)
Current drinker	103 113 (71.1)	383 976 (69.9)
Ex-drinker	12 786 (8.8)	45 242 (8.2)
Missing	14 579 (10.1)	63 344 (11.5)

*Measured by Index of Multiple Deprivation score.

Table 3| Relative risk of zoster in patients with key risk factors of interest and other covariates

	No (%)		Odds ratio (99% CI)		
	Cases (n=144 959)	Controls (n=549 336)	Model 1*	Model 2†	Model 3‡
Key risk factors of interest					
Rheumatoid arthritis	3111 (2.1)	8029 (1.5)	1.52 (1.43 to 1.60)	1.46 (1.38 to 1.55)	1.22 (1.15 to 1.30)
Systemic lupus erythematosus	387 (0.3)	818 (0.1)	1.85 (1.58 to 2.17)	1.72 (1.45 to 2.04)	1.60 (1.35 to 1.90)
Inflammatory bowel disease	1851 (1.3)	5118 (0.9)	1.38 (1.29 to 1.48)	1.36 (1.26 to 1.46)	1.28 (1.18 to 1.38)
Chronic obstructive pulmonary disease	6815 (4.7)	20 201 (3.7)	1.34 (1.29 to 1.39)	1.32 (1.27 to 1.37)	1.22 (1.17 to 1.28)
Asthma	10 243 (7.1)	31 865 (5.8)	1.24 (1.20 to 1.28)	1.21 (1.17 to 1.25)	1.11 (1.06 to 1.16)
Chronic kidney disease	8724 (6.0)	29 437 (5.4)	1.20 (1.16 to 1.24)	1.14 (1.09 to 1.18)	1.12 (1.08 to 1.17)
Depression	6830 (4.7)	22 052 (4.0)	1.19 (1.15 to 1.24)	1.15 (1.10 to 1.20)	1.15 (1.10 to 1.19)
Diabetes	11 430 (7.9)	41 320 (7.5)	1.07 (1.04 to 1.10)	1.02 (0.99 to 1.05)	1.02 (0.99 to 1.05)
Diabetes type:§					
No diabetes	133 529 (92.1)	508 016 (92.5)	1.00 (1.00 to 1.00)	1.00	1.00
Type 1	396 (0.3)	1054 (0.2)	1.37 (1.18 to 1.60)	1.27 (1.07 to 1.50)	1.26 (1.06 to 1.49)
Type 2	10 359 (7.1)	38 136 (6.9)	1.05 (1.02 to 1.09)	1.01 (0.98 to 1.04)	1.01 (0.98 to 1.04)
Unknown	675 (0.5)	2130 (0.4)	1.20 (1.07 to 1.35)	1.13 (1.00 to 1.27)	1.12 (0.99 to 1.27)
Other covariates					
Inhaled corticosteroids	12 996 (9.0)	38 902 (7.1)	1.31 (1.28 to 1.35)	—	1.13 (1.08 to 1.18)
Severe immunosuppression:					
HIV	128 (0.09)	97 (0.02)	4.74 (3.34 to 6.73)	5.07 (3.41 to 7.54)	5.07 (3.41 to 7.54)
Leukaemia	205 (0.14)	368 (0.07)	2.14 (1.71 to 2.68)	1.78 (1.39 to 2.28)	1.77 (1.38 to 2.27)
Lymphoma	444 (0.31)	386 (0.07)	4.41 (3.68 to 5.28)	3.90 (3.21 to 4.74)	3.89 (3.20 to 4.73)
Myeloma	492 (0.34)	816 (0.15)	2.35 (2.03 to 2.73)	2.16 (1.84 to 2.53)	2.13 (1.82 to 2.51)
Haematopoietic stem cell transplantation	26 (0.02)	3 (0.00)	32.82 (6.80 to 158.44)	13.46 (2.68 to 67.60)	13.71 (2.73 to 68.94)
Other unspecified cellular immune deficiencies	95 (0.07)	190 (0.03)	1.90 (1.37 to 2.63)	1.57 (1.10 to 2.22)	1.49 (1.05 to 2.12)
Oral corticosteroids	2164 (1.49)	3822 (0.70)	1.82 (1.58 to 2.10)	—	1.48 (1.27 to 1.72)
Other immunosuppressive treatment	502 (0.35)	1058 (0.19)	2.20 (2.05 to 2.36)	—	1.82 (1.67 to 1.98)

*Adjusted for matching factors only.

†Adjusted for HIV, leukaemia, lymphoma, myeloma, haematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, diabetes, smoking, and alcohol.

‡Additionally adjusted for oral corticosteroids, other immunosuppressive treatment, and inhaled corticosteroids.

§Separate model run for diabetes type (no diabetes, type 1, type 2, unknown) instead of diabetes (yes/no).

Table 4| **Numbers of cases and controls with various risk factors, stratified by age**

	<50 years		50-59 years		60-69 years		≥70 years	
Key risk factors of interest	**Case (n=39 611)**	**Control (n=143 469)**	**Case (n=27 833)**	**Control (n=105 157)**	**Case (n=31 134)**	**Control (n=121 108)**	**Case (n=46 381)**	**Control (n=179 602)**
Rheumatoid arthritis	283	614	515	1282	867	2224	1446	3909
Systemic lupus erythematosus	122	146	99	181	73	207	93	284
Inflammatory bowel disease	473	1003	394	1080	424	1225	560	1810
Chronic obstructive pulmonary disease	99	304	614	1815	1850	5301	4252	12781
Asthma	3447	9931	1990	6303	2140	6851	2666	8780
Chronic kidney disease	403	862	613	1774	1544	5090	6164	21711
Depression	2692	7983	1474	4944	1079	3722	1585	5403
Diabetes	881	2383	1632	5283	3093	11253	5824	22401
Diabetes type:								
Type 1	259	576	81	240	38	142	18	96
Type 2	422	1246	1431	4727	2922	10633	5584	21530
Unknown	200	561	120	316	133	478	222	775

Table 5| Association of various risk factors with herpes zoster, stratified by age

Key risk factors of interest	Adjusted odds ratio (99% CI)*				P value †
	<50 years	50-59 years	60-69 years	≥70 years	
Rheumatoid arthritis	1.69 (1.38 to 2.06)	1.45 (0.93 to 2.28)	1.49 (0.97 to 2.29)	1.41 (0.93 to 2.15)	0.203
Systemic lupus erythematosus	3.04 (2.14 to 4.31)	1.98 (0.86 to 4.58)	1.23 (0.52 to 2.89)	1.29 (0.56 to 2.93)	<0.001
Inflammatory bowel disease	1.73 (1.47 to 2.03)	1.40 (0.95 to 2.07)	1.30 (0.88 to 1.90)	1.18 (0.81 to 1.70)	<0.001
Chronic obstructive pulmonary disease	1.11 (0.80 to 1.54)	1.29 (0.65 to 2.53)	1.37 (0.71 to 2.66)	1.30 (0.68 to 2.51)	0.228
Asthma	1.24 (1.17 to 1.32)	1.19 (1.02 to 1.39)	1.22 (1.05 to 1.42)	1.18 (1.02 to 1.37)	0.465
Chronic kidney disease	1.63 (1.37 to 1.95)	1.26 (0.85 to 1.87)	1.14 (0.78 to 1.65)	1.10 (0.77 to 1.57)	<0.001
Depression	1.24 (1.16 to 1.33)	1.12 (0.94 to 1.33)	1.08 (0.90 to 1.30)	1.10 (0.93 to 1.30)	0.002
Diabetes	1.28 (1.15 to 1.43)	1.11 (0.87 to 1.42)	1.01 (0.80 to 1.28)	0.97 (0.77 to 1.22)	<0.001
Diabetes type:					
Type 1	1.51 (1.22 to 1.88)	1.16 (0.62 to 2.18)	0.98 (0.46 to 2.08)	0.62 (0.23 to 1.65)	<0.001
Type 2	1.22 (1.05 to 1.42)	1.09 (0.79 to 1.52)	1.02 (0.74 to 1.40)	0.97 (0.71 to 1.32)	
Unknown	1.20 (0.95 to 1.50)	1.30 (0.71 to 2.36)	1.02 (0.57 to 1.81)	1.07 (0.62 to 1.82)	

*Adjusted for HIV, leukaemia, lymphoma, myeloma, haematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, diabetes, smoking, and alcohol.

†P value for interaction.

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Table 6| **Estimated rate of zoster in patients with various risk factors, by age group**

	Rate of zoster/1000 person years (99% CI)			
Key risk factors of interest	**<50 years**	**50-59 years**	**60-69 years**	**≥70 years**
General population (2010)	2.08 (1.74 to 2.49)	4.37 (3.72 to 5.12)	6.69 (5.76 to 7.76)	8.84 (7.49 to 10.43)
Rheumatoid arthritis	3.51 (2.40 to 5.13)	6.35 (3.46 to 11.66)	9.96 (5.57 to 17.77)	12.47 (6.94 to 22.41)
Systemic lupus erythematosus	6.32 (3.73 to 10.74)	8.67 (3.20 to 23.46)	8.20 (2.99 to 22.45)	11.36 (4.22 to 30.60)
Inflammatory bowel disease	3.59 (2.56 to 5.04)	6.13 (3.55 to 10.58)	8.67 (5.10 to 14.74)	10.41 (6.10 to 17.74)
Chronic obstructive pulmonary disease	2.31 (1.40 to 3.84)	5.62 (2.44 to 12.94)	9.19 (4.09 to 20.62)	11.54 (5.08 to 26.20)
Asthma	2.58 (2.03 to 3.28)	5.20 (3.81 to 7.11)	8.16 (6.04 to 11.00)	10.44 (7.64 to 14.25)
Chronic kidney disease	3.39 (2.38 to 4.85)	5.51 (3.17 to 9.59)	7.60 (4.52 to 12.78)	9.70 (5.74 to 16.37)
Depression	2.59 (2.03 to 3.31)	4.89 (3.51 to 6.80)	7.22 (5.19 to 10.05)	9.71 (6.94 to 13.58)
Diabetes	2.66 (1.99 to 3.56)	4.84 (3.23 to 7.27)	6.79 (4.62 to 9.97)	8.55 (5.76 to 12.70)
Diabetes type:				
Type 1	3.14 (2.14 to 4.67)	5.08 (2.32 to 11.16)	6.55 (2.66 to 16.12)	5.49 (1.75 to 17.21)
Type 2	2.54 (1.84 to 3.54)	4.77 (2.93 to 7.78)	6.79 (4.25 to 10.84)	8.54 (5.28 to 13.79)
Unknown	2.49 (1.68 to 3.74)	5.66 (2.66 to 12.07)	6.80 (3.28 to 14.07)	9.43 (4.67 to 19.03)

4.3. Published appendices

Appendix (as published)

A: Further detail on defining risk factors
B: Dealing with missing data
C: Different definition of exposure to oral corticosteroids and immunosuppressive conditions
D: Association of various risk factors with zoster, after additionally adjusting for patient-level socioeconomic status
E: Different definitions of "active" controls
F: Consultation rate among patients with risk factors of interest

A: Further detail on defining risk factors

This information has been removed, as all risk factor definitions have been described in chapter 3, "Data sources and variable definitions". For transparency, the information can be found in Appendix III.

B: Dealing with missing data

We used multiple imputation to account for missing data. Missing data was present for alcohol and smoking. In total, 89% of patients had complete data for all variables. To maximise the use of the data while properly incorporating the extra uncertainty arising due to missing data, multiple imputation by chained equations[127] was used to impute missing values for alcohol and smoking from multinomial models. The imputation model included all covariates from the main outcome model, together with the matching variables age and sex. We also included extra comorbidities, identified using medical Read codes, to look for additional markers of alcohol or smoking related diseases. These included: stroke, peripheral artery disease, angina (stable and unstable), acute coronary syndrome, congestive heart failure, myocardial infarction, hypertension and alcoholic liver disease (including portal hypertension) and pancreatitis. Five imputed datasets were created and combined for analysis. Distributions of imputed values were visually checked for comparability with the observed data.

Table B1: Relative risk of zoster in patients with various risk factors, using a multiply imputed dataset

	Adjusted OR (99% CI)*
Clinical conditions	
Rheumatoid Arthritis	1.47 (1.39 to 1.56)
Systemic Lupus Erythematosis	1.71 (1.46 to 2.01)
Inflammatory Bowel Disease	1.35 (1.26 to 1.45)
COPD	1.34 (1.29 to 1.40)
Asthma	1.23 (1.20 to 1.27)
Chronic Kidney Disease	1.16 (1.12 to 1.20)
Depression	1.17 (1.13 to 1.22)
Diabetes	1.04 (1.01 to 1.07)
Diabetes Type	
No diabetes	1
Type 1	1.33 (1.14 to 1.56)
Type 2	1.02 (0.99 to 1.05)
Unknown	1.15 (1.03 to 1.29)

OR, odds ratio. CI, confidence interval. *Adjusted for HIV, Leukaemia, Lymphoma, Myeloma, HSCT, Other Immune deficiencies, RA, SLE, IBD, COPD, Asthma, CKD, Depression, Diabetes, Smoking and Alcohol.

C: Different definition of exposure to oral corticosteroids and immunosuppressive conditions

Rationale

The definition of exposure to oral corticosteroids and other immunosuppressive therapy in the main analysis was derived from guidelines on zoster vaccine contraindications (a 14-day course of high-dose oral corticosteroids or other immunosuppressive therapies, within the month prior to index date). The vaccine contraindications suggest patients remain immunosuppressed for one month following the end of their prescription. However we acknowledge this definition may not capture all patients with immunosuppression due to these medications.

Our sensitivity analysis therefore defined exposure as anyone taking an oral corticosteroid or other immunosuppressant within 3 months prior to the index date, and placed no restrictions on duration or dose of prescription.

Results

A much higher number of patients were defined as exposed to immunosuppressive therapy using this broader criterion (table C1). The overall effect of oral corticosteroids and immunosuppressive therapies was slightly lower when using the 3-month definition compared to the vaccine contraindication definition, however the confidence intervals overlapped (table C1). There were no major differences in the effect of our main risk factors after adjusting for the broader definition of exposure to immunosuppressive drugs, compared to the main analyses (table C2).

Table C1: Relative risk of zoster in patients taking immunosuppressive therapy, defined as exposure in the previous 3 months.

	Cases n (%)	Controls n (%)	Unadjusted OR (99% CI)	Adjusted OR (99% CI)
Oral corticosteroid**	5304 (3.7)	12341 (2.3)	1.69 (1.62 to 1.77)	1.37 (1.31 to 1.44)
Other immunosuppressant drugs **	2361 (1.63)	4151 (0.76)	2.21 (2.07 to 2.36)	1.71 (1.57 to 1.86)

OR, odds ratio. CI, confidence interval. *Adjusted for HIV, Leukaemia, Lymphoma, Myeloma, HSCT, Other Immune deficiencies, Oral corticosteroids (previous 3 months), Other Immunosuppressive (previous 3 months), ICS, RA, SLE, IBD, COPD, Asthma, CKD, Depression, Diabetes, Smoking and Alcohol.
** Within 3 months prior to index date

Table C2: Relative risk of zoster in patients with various risk factors

	Adjusted OR (99% CI)*
Clinical conditions	
Rheumatoid Arthritis	1.17 (1.10 to 1.25)
Systemic Lupus Erythematosis	1.52 (1.27 to 1.82)
Inflammatory Bowel Disease	1.26 (1.17 to 1.37)
COPD	1.20 (1.14 to 1.26)
Asthma	1.11 (1.06 to 1.16)
Chronic Kidney Disease	1.11 (1.07 to 1.16)
Depression	1.15 (1.10 to 1.20)
Diabetes	1.01 (0.98 to 1.05)
Diabetes Type	
No diabetes	1
Type 1	1.25 (1.05 to 1.48)
Type 2	1.00 (0.97 to 1.03)
Unknown	1.11 (0.98 to 1.26)

OR, odds ratio. CI, confidence interval. *Adjusted for HIV, Leukaemia, Lymphoma, Myeloma, HSCT, Other Immune deficiencies, Oral corticosteroids (previous 3 months), Other Immunosuppressive (previous 3 months), ICS, RA, SLE, IBD, COPD, Asthma, CKD, Depression, Diabetes, Smoking and Alcohol.

D: Association of various risk factors with zoster, after additionally adjusting for patient-level socioeconomic status

Rationale

In the main analyses patients were matched on practice and thereby the analyses controlled for practice-level socioeconomic status. For patients registered at English practices and agreeing to their medical records being linked to other dataset, a patient level socioeconomic status score is available. Socioeconomic status (at the patient and practice level) is captured using quintiles of the Index of Multiple Deprivation score. At the patient level, the patient's home postcode is mapped at the lower level super output level to the corresponding 2007 IMD score; a low quintile represents the least deprived.

Results

In total, 427,689 (61.6%) patients had a patient-level socioeconomic status score. The results from our sensitivity analysis which additionally adjusts for patient-level socioeconomic status are shown in Table D1. There were no major differences compared to the main analyses.

Table D1: Relative risk of zoster in patients with various risk factors

	Adjusted OR (99% CI)*
Clinical conditions	
Rheumatoid Arthritis	1.54 (1.42 to 1.65)
Systemic Lupus Erythematosis	1.82 (1.46 to 2.27)
Inflammatory Bowel Disease	1.39 (1.26 to 1.54)
COPD	1.33 (1.26 to 1.40)
Asthma	1.21 (1.16 to 1.26)
Chronic Kidney Disease	1.13 (1.08 to 1.19)
Depression	1.16 (1.10 to 1.22)
Diabetes	1.01 (0.98 to 1.06)
Diabetes Type	
No diabetes	1
Type 1	1.30 (1.05 to 1.61)
Type 2	1.01 (0.96 to 1.05)
Unknown	1.09 (0.93 to 1.27)

OR, odds ratio. CI, confidence interval. *Adjusted for HIV, Leukaemia, Lymphoma, Myeloma, HSCT, Other Immune deficiencies, RA, SLE, IBD, COPD, Asthma, CKD, Depression, Diabetes, Smoking and Alcohol and patient-level SES.

E: Different definitions of active controls

Rationale

In the main analyses we only included "active" controls, by ensuring controls had at least one consultation anytime within an 18 month period around the index date. In these sensitivity analyses, we applied different definitions of "active" controls. First we ensured controls had a consultation anytime from 1 year prior, to 2 years following the index date. Second, we required controls to have a consultation in the three years prior to index date.

Results

In the first analysis, 12,891 controls and 35 cases were excluded (compared to 27,928 controls and 88 cases in the main analysis). This meant 145,012 cases of zoster and 564,373 controls were included. In the second sensitivity analysis (where controls were required to have contact 3 years prior to index date), 31,551 controls and 303 cases were excluded; this left 144,744 cases of zoster and 545,713 controls in the analysis. There were no differences in the study findings compared to the main analyses (Table E1).

Table E1: Relative risk of zoster in patients with various risk factors

	Adjusted OR (99% CI)*once excluding controls without contact anytime from 1 year prior, to 2 years following the index date	**Adjusted OR (99% CI)* once excluding controls without contact 3 years prior to index**
Clinical conditions		
Rheumatoid Arthritis	1.47 (1.39 to 1.56)	1.45 (1.37 to 1.54)
Systemic Lupus Erythematosis	1.72 (1.46 to 2.04)	1.70 (1.43 to 2.01)
Inflammatory Bowel Disease	1.37 (1.28 to 1.48)	1.35 (1.26 to 1.46)
COPD	1.33 (1.27 to 1.38)	1.31 (1.26 to 1.36)
Asthma	1.23 (1.20 to 1.28)	1.21 (1.17 to 1.25)
Chronic Kidney Disease	1.14 (1.10 to 1.19)	1.13 (1.09 to 1.07)
Depression	1.17 (1.12 to 1.22)	1.15 (1.10 to 1.19)
Diabetes	1.03 (1.00 to 1.06)	1.02 (0.99 to 1.05)
Diabetes Type		
No diabetes	1	1
Type 1	1.32 (1.11 to 1.55)	1.29 (1.09 to 1.52)
Type 2	1.02 (0.98 to 1.05)	1.00 (0.97 to 1.04)
Unknown	1.15 (1.02 to 1.30)	1.13 (1.00 to 1.28)

OR, odds ratio. CI, confidence interval. *Adjusted for HIV, Leukaemia, Lymphoma, Myeloma, HSCT, Other Immune deficiencies, RA, SLE, IBD, COPD, Asthma, CKD, Depression, Diabetes, Smoking and Alcohol.

F: Consultation rate among patients with risk factors of interest

Rationale

We explored how frequently patients consulted the general practitioner as this may introduce ascertainment bias (i.e. patients visiting their general practitioner more frequently may be more likely to receive a zoster diagnosis). We calculated the mean yearly consultation rate prior to index date (by dividing the total number of face-to-face or telephone consultations during follow-up, by the total years of follow-up prior to index date) among patients with our risk factors of interest. We compared this to the mean consultation rate for epilepsy, to assess whether epilepsy patients had a similar likelihood of being diagnosed with zoster.

Results

The results are shown in Table F1. The consultation rates among patients with our risk factors of interest were very similar. The mean number of consultations per year among epilepsy patients was 10.2, suggesting these patients consult with similar frequency as patients with our risk factors of interest.

Table F1: Mean consultation rate prior to index date

	Mean number of consultations per year prior to index date
Clinical conditions	
Rheumatoid Arthritis	11.7
Systemic Lupus Erythematosis	10.9
Inflammatory Bowel Disease	9.7
COPD	11.7
Asthma	9.5
Chronic Kidney Disease	11.2
Depression	10.3
Diabetes	11.7

4.4. Additional methods: selecting controls

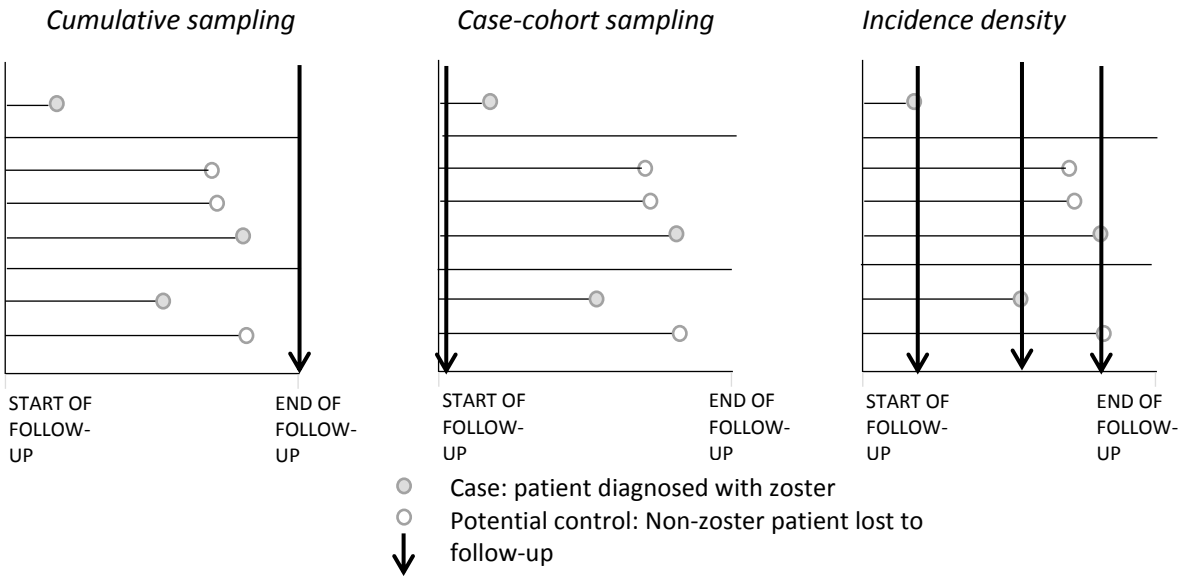
Appropriate control selection in case-control studies is key to generating valid results.

4.4.1. Sampling controls

There are three methods for sampling controls in case-control studies (represented pictorially in Figure 1).[128]

- *Cumulative sampling:* Traditionally employed by case-control studies, where non-cases are selected at the end of follow-up from "survivors" or those who are disease free.
- *Case-cohort sampling:* Where controls are selected from the entire cohort at baseline, in other words the base population. This method is also known as case-base sampling and is the least common method.
- *Incidence density sampling*: where controls are selected from the "risk set" of persons at risk at the time that each case occurs. Also called concurrent sampling.

Figure 1: Pictorial guide to the three different sampling methods used in case-control studies.



Note: the horizontal lines represents individual patients and their follow-up ends when the line stops.[129]

The matched case-control study in this chapter utilises incidence density sampling to match cases to controls; so for each case, controls were selected from all those "at risk" of zoster on the day the zoster case was diagnosed. It can be shown that when this method of control sampling is used, the resultant odds ratios (ORs) will estimate rate ratios for the outcome.[128,130]

Please note that although this method does provide rate ratio estimates, ORs were reported in the paper, as this is still technically correct and reporting rate ratios may have led to confusion.

In incidence density sampling, a single control could be matched to more than one case.[131] In other words, even after being selected as a control, individuals should remain eligible to be controls for other cases. Furthermore, cases can be controls prior to their zoster diagnosis.[131] These features ensure that the resulting OR will provide an unbiased estimate of the underlying rate ratio, by sampling controls from *all* those at risk of zoster at the time of sampling.

This sampling method was chosen as it is seen as the gold-standard sampling method for case-control studies and provides usefully interpretable effect estimates. The key disadvantages of *cumulative* sampling are: 1) cases cannot be in the control group, therefore the control group will not truly represent the entire base population at risk; and 2) by sampling controls at the end of follow-up, factors influencing loss to follow-up will influence the selection of controls. Finally, time-window bias, where the observation time during which exposures could have been recorded differs between cases and controls, is less of a problem if incidence density sampling is used.[132] By selecting controls from the all person-moments instead of the end of follow-up (as in cumulative sampling), the resulting exposure measurement for controls and cases are based on a more similar time span.

4.4.2. Matching cases and controls

Individual-level matching in case-control studies is the process of selecting a specified number of controls for each case, who are similar in terms of certain pre-specified characteristics, in order to reduce the confounding effects of those characteristics.[131] If the matching characteristic is a very strong confounder, then matching increases the efficiency of the study. Without matching, adjusting for these confounders could lead to multiple strata with few data. Forcing the cases and controls to have a similar distribution of the matching variables results in gains in precision and narrower confidence intervals (CIs).[133] Matching may also control for unmeasured confounders.

4.4.2.1. Matching factors

The matching factors were; age (within 1 year), gender and general practice. Calendar time is matched on by default when using incidence density sampling, as the controls have to be "active" (in this case, currently registered) when the case was diagnosed with zoster.

Age is a very strong risk factor for zoster, therefore an important confounder to control for as tightly as possible. Gender is another well-reported risk factor for zoster, and associated with a number of the potential risk factors. Matching on practice controlled for practice level SES helping to account for some unmeasured socioeconomic differences as well as allow heterogeneity between patterns of prescribing or recording to be accounted for.

4.4.2.2. Ratio of cases to controls

Cases were matched to up to four controls, as any more controls is not deemed to increase efficiency.[134]

4.4.3. Matching programme

With the help of a statistician, an algorithm was developed to individually match cases to controls, as follows:

1. All potential controls for each case were identified: as cases were eligible to be controls up until their zoster diagnosis, they were included in the pool of potential controls, with their end date redefined as their zoster date, minus one day.
2. Up to four controls were randomly selected for each case at random without replacement. Priority was given to potential controls closest in age to the case.

This produced matched sets; that is, one case and up to four controls.

4.5. Additional results: body mass index, smoking and alcohol status

BMI category, smoking status and alcohol use were investigated as potential confounders in the published zoster case-control study (section 4.2). As these factors were not pre-specified exposures of interest, their effect on zoster risk was not reported in the published paper. Table 7 below describes the relative risk of zoster by BMI, smoking and alcohol status. Please note BMI was not included in the fully adjusted models.

Table 7: Relative risk of zoster by BMI category, smoking status and alcohol use

	No (%)		OR (95% CI)		
	Cases (n=144959)	**Controls (n=549336)**	**Model 1***	**Model 2†**	**Model 3‡**
Risk factor					
BMI category					
Underweight	2,776 (2.1)	10,549 (2.2)	0.98 (0.92-1.04)	-	-
Normal weight	50,530 (38.6)	188,060 (38.7)	1.00	-	-
Overweight	47,886 (36.6)	177,603 (36.6)	1.00 (0.99-1.02)	-	-
Obese	29,581 (22.6)	109,440 (22.5)	1.01 (0.99-1.04)	-	-
Smoking					
Non-smoker	54,751 (38.2)	208,436 (38.8)	1.00	1.00	1.00
Current smoker	36,107 (25.2)	141,826 (26.4)	0.95 (0.93-0.97)	0.93 (0.91-0.95)	0.93 (0.91-0.95)
Ex-smoker	52,353 (36.6)	186,373 (34.7)	1.10 (1.08-1.12)	1.06 (1.04-1.08)	1.06 (1.04-1.09)
Alcohol use					
Non-drinker	14,481 (11.1)	56,774 (11.7)	1.00	1.00	1.00
Current drinker	103,113 (79.1)	383,976 (79.0)	1.05 (1.02-1.08)	1.05 (1.02-1.08)	1.05 (1.02-1.08)
Ex-drinker	12,786 (9.8)	45,242 (9.3)	1.13 (1.09-1.17)	1.11 (1.07-1.15)	1.11 (1.07-1.15)

*Adjusted for matching factors only.
†Adjusted for HIV, leukaemia, lymphoma, myeloma, haematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, RA, SLE, IBD, COPD, asthma, CKD, depression, diabetes, smoking, and alcohol.
‡Additionally adjusted for oral corticosteroids, other immunosuppressive treatment, and ICS.

BMI: results and interpretation

There appeared to be no evidence that BMI category was associated with zoster risk, after adjusting for matching factors (age within one year, gender and practice). BMI category was therefore not included in the fully adjusted models (that is, model 2 and model 3 in table 7 above). This null association is in line with a previous Australian cohort study.[51]

Smoking: results and interpretation

From table 7 there is good evidence that current smokers have a small but significant reduction in the risk of zoster (Model 3: OR:0.93, 95%CI 0.91-0.95), compared to non-smokers. By contrast, ex-smokers have 1.06 times the odds of zoster than non-smokers (Model 3,

OR:1.06, 95%CI 1.04-1.09). These findings are in line with previous research, suggesting that current smoking may be protective against zoster and previous smoking may be a risk factor for zoster.[51,135]

Alcohol: results and interpretation

Being both a current and an ex-drinker was associated with 5% and 11% increased risk of zoster respectively. This is the first known study to report an association, albeit small, between alcohol use and zoster risk.

4.6. Additional biological evidence indicating impaired cell-mediated immunity associated with the exposures of interest

As described in the introduction, zoster reactivation occurs due to a waning of VZV-specific T cell-mediated immunity. Below is some biological evidence suggesting that the exposures of interest (specifically, RA, SLE, IBD, asthma, COPD, depression, diabetes, and CKD) investigated as risk factors for zoster in this thesis, are associated with impaired cell-mediated immune function.

4.6.1. Autoimmune conditions

Autoimmune conditions are associated with increased risk of infections,[136] indicating poor immune function. Cell-mediated immunity may be suppressed in patients with autoimmune conditions, due to the routine use of immunosuppressive medications, or the underlying disease itself.[136] RA patients have been shown to experience accelerated immune senescence of T cells and reduced T cell diversity.[137] A study of 38 SLE patients and 51 healthy controls, found decreased cellular immune responses and VZV-specific immunity in the SLE patients compared to healthy controls, and this was not influenced by immunosuppressive medication use.[138] This finding suggests that SLE, as a disease, may be driving impaired cell-mediated immune function. The other autoimmune condition assessed in this thesis is IBD. Little research exists exploring VZV-specific immunity among IBD patients, however IBD is reported to be associated with abnormalities in cell-mediated immunity.[58,139]

4.6.2. Asthma and chronic obstructive pulmonary disorder

Authors have suggested that asthma might play a role in waning cell-mediated immunity, as evidenced by reduced immune response to measles, mumps and rubella vaccination in asthmatic compared to non-asthmatic children.[140] It is currently unclear whether COPD as a disease itself alters cell-mediated immunity; however, some authors have suggested that COPD leads to systemic immune disturbances.[141] As asthma and COPD are both treated with corticosteroids, patients may experience drug-induced alterations in cell-mediated immunity from use of ICS[142-146] and oral corticosteroids.[104]

4.6.3. Depression

Depression may also lead to poorer cell-mediated immune function. Recent virology studies indirectly support the hypothesis that depression may lead to an increased risk of zoster. A

study demonstrated that 52 patients with major depressive disorder had lower VZV-specific cell-mediated immunity, compared to 52 age and sex-matched patients without depression, and the level of the immune response correlated negatively with the severity of depression.[147] Another study showed that depressed individuals had reduced VZV cell-mediated immune responses when administered the zoster vaccine.[148]

There is also evidence that stress, common in patients with depression, may also affect cell-mediated immunity. The central nervous, endocrine and immune system interact with each other, such that a dysregulation in one system can have an effect on the other systems. Stress can affect a number of neuroendocrine functions, including activating the hypothalamic–pituitary–adrenal axis which can thereby in turn affect cell-mediated immunity.[149,150] Additionally, patients experiencing stress are likely to have habits, such as reduced sleep, which may indirectly affect immune function. Virological evidence that astronauts have experienced sub-clinical VZV reactivation during space travel, suggests stress may trigger a reduced cell-meditated immune response.[151,152] Finally, evidence of a randomised controlled trial of a stress-reducing behavioural intervention, Tai Chi, found the Tai Chi group showed higher levels of VZV cell-mediated immunity than the control group (who received some health education) after 25 weeks.[153]

4.6.4. Chronic Kidney Disease

Researchers have suggested that a decline in renal function can result in reduced cell-mediated immunity. VZV-specific cell-mediated immunity has not been assessed in patients with kidney disease. However, patients with CKD demonstrate an increased susceptibility to infections (the second most common cause of death in dialysis patients is infection) and decreased serological response to vaccination, such as Hepatitis B and influenza, which points to an impaired cellular immune response.[154,155] There is also some evidence that CKD causes a diminished activation of T cells.[156] The causes of immune dysfunction in CKD are not fully understood, however uraemia (a raised level of waste products in the blood, usually eliminated by the kidneys), is thought to be the mediating factor.[157]

4.6.5. Diabetes

Patients with diabetes have more infections than patients without diabetes[158] and hyperglycaemia (too much blood sugar in the bloodstream) is believed to lead to immune suppression[159,160] and T-cell dysregulation.[161] Furthermore, a virological study found VZV-

specific cell-mediated immune responses were reduced in patients with diabetes, compared to healthy controls.[162]

4.7. Chapter summary

Quantification of risk factors for herpes zoster

- Current zoster vaccination campaigns focus on older people only.
- Recent literature has suggested that a range of clinical conditions are associated with an increased risk of zoster, raising the possibility that some younger people may be at high risk. However, large, highly powered studies investigating the association of these clinical conditions with zoster are lacking.
- A case-control study was carried out in CPRD with 144,959 zoster cases and 549,336 age, sex and practice-matched controls, and the associations between a range of potential risk factors and zoster were investigated.
- Conditions associated with increased risk of zoster included RA, SLE, IBD, COPD, asthma, CKD, type 1 diabetes and depression.
- The increased risks were generally greater among younger age groups.
- Those at highest risk of zoster remain those who have severely weakened immune systems and the current vaccine is contraindicated for these individuals. This emphasises that alternative strategies (which could include non-live vaccines and antiviral prophylaxis) are needed to reduce the risk of shingles among these patient groups.
- Further information about the risk of complications, particularly PHN, is needed to decide if it is cost-effective to vaccinate certain patients.

Chapter 5: Prescription of antiviral therapy after herpes zoster: who receives therapy?

5.1. Introduction

Antiviral medication is given to certain patients following zoster, to accelerate rash healing during an acute zoster episode and to limit the severity and duration of pain. Their effectiveness in preventing PHN is disputed. Understanding which patients receive antivirals in routine practice will be important to: 1) assess whether prescriptions guidelines are adhered to in UK general practice; and 2) inform the analysis in chapter 7, which evaluates the effect of antiviral use on the risk of PHN among zoster patients.

This research on the prescription of antiviral therapy following zoster was published in the British Journal of General Practice and is presented below. Please note at the time of publication, CPRD was called the General Practice Research Database.

5.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Harriet Forbes
Principal Supervisor	Sinead Langan
Thesis Title	Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	British Journal of General Practice		
When was the work published?	26th November 2012		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I was responsible for preparing the dataset, designing the study, and conducting the statistical analysis. I was also primarily responsible for writing this work. My co-authors supported this work in an advisory capacity, commenting on research design and

	drafts of the paper.

Student Signature: _____ **Date:** 9/5/2016

Supervisor Signature: _____ **Date:** 4/3/2016.

Harriet J Forbes, Sara L Thomas, Liam Smeeth and Sinéad M Langan

Prescription of antiviral therapy after herpes zoster in general practice:

who receives therapy?

Abstract

Background
Antivirals can accelerate rash healing during an acute zoster episode and can limit the severity and duration of pain. Their use within 7 days of rash onset is recommended among specific patient groups.

Aim
To describe antiviral prescription patterns and patient characteristics associated with antiviral receipt after zoster diagnosis.

Design and setting
Descriptive study and risk factor analysis using electronic healthcare records from UK general practice.

Method
Incident adult zoster cases occurring between 2000 and 2011 were identified in the General Practice Research Database. Therapy records were searched for antiviral prescriptions of aciclovir, famciclovir, or valaciclovir within 7 days of zoster diagnosis. The proportion of incident zoster cases receiving antivirals was calculated and multivariable logistic regression used to assess associations between patient characteristics and antiviral use.

Results
Of 142 216 incident zoster cases 58.1% received an antiviral prescription. The majority (69.0%) were aciclovir. The proportion receiving antiviral prescriptions increased with age up to 65 years, then declined to 56.8% among patients aged ≥85 years. Being female and of higher socioeconomic status were associated with higher antiviral receipt. Antivirals were more commonly prescribed to immunosuppressed patients with herpes zoster (odds ratio 1.27; 95% CI = 1.22 to 1.33), however they were not given routinely to this patient group.

Conclusion
Antiviral therapies for zoster are under-prescribed in UK general practice even among groups, such as immunosuppressed and older individuals, for whom guidelines recommend treatment. Patients may present too late to receive treatment or physicians may decide that antivirals are not essential treatment. Consideration could be given to reviewing the guidelines.

Keywords
antivirals; database; epidemiology; general practice; GPRD; herpes zoster; shingles; United Kingdom.

INTRODUCTION

Herpes zoster presents as a painful unilateral vesicular dermatomal rash[1] resulting from reactivation of latent varicella zoster virus infection. Reactivation is thought to result from waning cell-mediated immunity. Zoster is common among older people with a lifetime risk of 10–30%, rising to 50% among those living to ≥85 years.[2] Post-herpetic neuralgia develops in around 20% of individuals aged ≥50 years[3] and causes persistent severe pain for months to years after rash onset.[4]

Antivirals have been demonstrated in multiple clinical trials to accelerate rash healing and limit the severity and duration of pain during an acute zoster episode.[4] There is also some evidence suggesting they may reduce the risk of post-herpetic neuralgia,[5–7] possibly by reducing neural damage which may contribute to its development.[4] Treatment options for post-herpetic neuralgia are limited, therefore the potential use of antivirals to prevent post-herpetic neuralgia is particularly important.

Current UK guidelines advise GPs to prescribe oral antiviral drugs within 72 hours of rash onset for: people aged ≥50 years, ophthalmic zoster, other non-truncal disease, immunosuppression, or individuals with moderate to severe pain or rash.[8] Guidelines further recommend treatment up to 1 week after rash onset, particularly when characteristics for severe zoster or complications are present, such as continued vesicle formation, older age, immunosuppression, or severe pain.[8]

Research on the proportion of zoster individuals prescribed antivirals is limited[3] and previous studies have reported overall use, rather than by specific risk groups. Zoster incidence is likely to increase in the UK, due to population ageing and increasing use of immunosuppressive therapies, and it is important to understand current prescribing patterns.

This study aims to analyse antiviral prescription patterns by patient characteristics after a zoster diagnosis in UK general practice.

METHOD

This is a descriptive and risk factor analysis of UK electronic healthcare records over a study period from 1 January 2000 to 13 June 2011.

Data source

This study utilised data from the UK General Practice Research Database (GPRD), a large computerised database of anonymised patient records that contains complete prescribing and diagnostic information in primary care and feedback from hospital referrals. It is one of the largest sources of continuous patient records in the UK, containing data on approximately 7% of the UK population and is broadly representative of patient and practice characteristics in the UK.

Selecting incident zoster cases

An incident zoster case was anyone aged ≥18 years with a diagnostic code for zoster

HJ Forbes, BA, MSc, research assistant; **SL Thomas**, MBBS, MSc, PhD, clinical senior lecturer in epidemiology; **L Smeeth**, MSc, PhD, FRCGP, FFPH, professor of clinical epidemiology; **SM Langan**, BAO, MSc, PhD, MRCP, NIHR clinician scientist & honorary consultant dermatologist, Faculty of Epidemiology & Population Health, London School of Hygiene and Tropical Medicine, London.

Address for correspondence
Harriet Forbes, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK.

E-mail: Harriet.forbes@lshtm.ac.uk

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How this fits in

This article is the first to describe who receives antiviral therapy following a zoster diagnosis within the UK. It highlights that antivirals are under-prescribed in UK primary care, including among those particularly recommended for treatment, such as older individuals and those with immunosuppressive conditions. Although patients may present too late to receive therapy, under-treatment may reflect poor adherence to treatment guidelines. Consideration could be given to reviewing the guidelines.

in GPRD during the study period, without any consultations for zoster during the previous year. For patients with recurrent zoster episodes during the study period only the first episode was included. Those with zoster episodes occurring within 1 year of the start date were excluded, to remove potentially incorrectly dated prevalent cases.[9] Patients diagnosed with zoster encephalitis, zoster meningitis, or with another central nervous system complication within 7 days of the first zoster record were also excluded (n = 113) as they would typically be treated in secondary care. Read Codes indicating the anatomical site of zoster were searched for in all records within a zoster episode, defined as 1 year following first zoster record. Site of zoster was categorised into ophthalmic, other non-truncal and unspecified site; there is no existing Read Code for truncal zoster.

Sociodemographic characteristics of zoster cases

Age, sex, and geographical health region were obtained from the extracted GPRD data. Age was categorised as 18–49, 50–64, 65–74, 75–84, or ≥85 years. Socioeconomic status was analysed using quintiles of the Index of Multiple Deprivation (IMD) score, available for patients registered at English practices agreeing to link medical records with other databases. The patient's home postcode is mapped at the lower level super output level to the corresponding 2007 IMD score; a low quintile represents the least deprived. As patient-level IMD score was not available for patients from unlinked practices in England, a sensitivity analysis was run using practice-level IMD quintile when patient-level IMD quintile was unavailable.[10]

Identifying comorbidities at zoster diagnosis

As NHS guidelines recommend antiviral prescription for all immunosuppressed individuals, prescribing patterns were explored in this group. Patients were considered severely immunosuppressed if they had a diagnosis within 2 years preceding their zoster episode of leukaemia, lymphoma, or a bone marrow transplant or if they had ever had a diagnosis of HIV, a splenectomy, an organ/tissue transplant, myeloma diagnosis, or 'other immune deficiencies' (for example, immunodeficiency with predominantly antibody defects such as selective IgA immune deficiency and agammaglobulinemia, aplastic anaemias, and non-specific diagnoses of immune disorder). Patients prescribed at least one immunosuppressive medication, including oral corticosteroids, ≤3 months before their zoster episode were also considered severely immunosuppressed.

To explore antiviral prescribing patterns among patients with moderate immunosuppression, the following autoimmune conditions were flagged: diabetes, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.

Antiviral use

Antiviral prescriptions including aciclovir, famciclovir, or valaciclovir within 7 days of a zoster diagnosis were identified from GPRD therapy records.

Data analysis

Data were analysed using STATA/MP (version 11.2). The proportion of incident zoster cases receiving antivirals was determined, and described by various patient characteristics. The association between antiviral use and patient characteristics was assessed using multivariable logistic regression adjusting for age, sex, region, year, zoster site, and immunosuppression status. Socioeconomic status was not adjusted for as it was only available for selected English practices.

RESULTS

Between 2000 and 2011 142 216 incident zoster cases were identified. Of these 82 656 (58.1%) received an antiviral prescription within 7 days of diagnosis in GPRD. Of those prescribed antivirals 80 751 (97.7%) were given on the day of the zoster diagnosis. The most commonly prescribed antiviral was aciclovir (69.0%), followed by famciclovir (27.8%) and valaciclovir (3.5%). A small number (n = 224) of cases had two different antivirals prescribed on the same day and were included in both antiviral groups (therefore totals do not add up to 100%).

The proportion of patients prescribed antivirals increased with age up to

Table 1. Proportion of patients prescribed antiviral medication, by patient characteristics

Patient characteristic	*n*	% Treated	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*P*-value
Age group, years					
18–49	38 665	52.2	1.00	1.00	
50–64	42 631	58.6	1.30 (1.26 to 1.34)	1.29 (1.26 to 1.33)	
65–74	29 203	62.6	1.53 (1.49 to 1.58)	1.53 (1.49 to 1.58)	
75–84	23 341	62.0	1.50 (1.45 to 1.55)	1.49 (1.44 to 1.54)	
≥85	8376	56.8	1.21 (1.15 to 1.26)	1.17 (1.12 to 1.23)	<0.01
Zoster site					
Site unspecified	139 214	58.4	1.00	1.00	
Non-truncal zoster (excluding ophthalmic)	873	30.9	0.32 (0.28 to 0.37)	0.34 (0.30–0.40)	
Ophthalmic zoster	2129	49.4	0.69 (0.64 to 0.76)	0.66 (0.61 to 0.72)	<0.01
Sex					
Male	57 096	56.5	1.00	1.00	
Female	85 120	59.2	1.12 (1.09 to 1.14)	1.11(1.09 to 1.13)	<0.01
Year diagnosed					
2000	8638	45.7	1.00	1.00	
2001	10 202	48.5	1.12 (1.06 to 1.18)	1.12 (1.06 to 1.19)	
2002	11 114	50.7	1.22 (1.16 to 1.29)	1.22 (1.15 to 1.29)	
2003	12 130	54.3	1.41 (1.33 to 1.49)	1.40 (1.32 to 1.48)	
2004	13 080	56.7	1.56 (1.47 to 1.65)	1.55 (1.46 to 1.63)	
2005	13 663	58.7	1.69 (1.60 to 1.78)	1.68 (1.59 to 1.77)	
2006	13 933	59.4	1.74 (1.65 to 1.84)	1.72 (1.63 to 1.81)	
2007	13 897	61.9	1.93 (1.83 to 2.04)	1.90 (1.80 to 2.01)	
2008	13 997	63.1	2.03 (1.93 to 2.15)	2.01 (1.90 to 2.13)	
2009	14 021	64.0	2.11 (2.00 to 2.23)	2.08 (1.97 to 2.20)	
2010	13 518	65.3	2.24 (2.12 to 2.37)	2.21 (2.09 to 2.33)	
2011	4023	64.2	2.13 (1.97 to 2.30)	2.07 (1.91 to 2.24)	<0.01
Region					
Yorkshire and Humber	6682	51.9	1.00	1.00	
North West	18 808	59.1	1.34 (1.27 to 1.42)	1.30 (1.23 to 1.37)	
North East	3076	52.8	1.04 (0.95 to 1.13)	1.00 (0.92 to 1.09)	
East Midlands	5789	54.6	1.11 (1.04 to 1.20)	1.10 (1.03 to 1.18)	
West Midlands	13 664	55.4	1.15 (1.09 to 1.22)	1.12 (1.06 to 1.19)	
East of England	13 274	58.2	1.29 (1.22 to 1.37)	1.25 (1.18 to 1.33)	
South West	12 056	59.4	1.36 (1.28 to 1.44)	1.29 (1.21 to 1.37)	
South Central	15 632	57.2	1.24 (1.17 to 1.31)	1.19 (1.12 to 1.26)	
London	11 551	55.4	1.15 (1.09 to 1.23)	1.10 (1.04 to 1.17)	
South East Coast	11 950	59.2	1.34 (1.27 to 1.43)	1.26 (1.19 to 1.34)	
Northern Ireland	5114	67.7	1.94 (1.80 to 2.09)	1.89 (1.75 to 2.04)	
Scotland	11 475	63.1	1.59 (1.49 to 1.69)	1.48 (1.39 to 1.57)	
Wales	13 145	58.8	1.32 (1.25 to 1.40)	1.23 (1.16 to 1.31)	<0.01
IMD quintile[c]					
(Least deprived) 0	19 762	58.4	1.00	1.00	
1	19 650	57.9	0.98 (0.94 to 1.02)	0.97 (0.93 to 1.01)	
2	16 050	57.4	0.96 (0.92 to 1.00)	0.95 (0.91 to 0.99)	
3	13 892	56.2	0.91 (0.87 to 0.95)	0.91 (0.87 to 0.95)	
(Most deprived) 4	9364	54.6	0.86 (0.81 to 0.90)	0.85 (0.81 to 0.90)	<0.01[b]

AV = antivirals. [a]Adjusted for age, sex, region, year, zoster site and immunosuppression status, based on severe immunosuppression. [b]Test for trend. [c]Analysis restricted to patients registered at English practices with IMD score available.

65–74 years, when the percentage plateaued and then reduced to 56.8% among patients aged ≥85 years (Table 1). Females were more likely to be prescribed antivirals compared to males (adjusted odds ratio [AOR] 1.11, 95% confidence interval [CI] = 1.09 to 1.13). However, the sex difference disappeared among patients aged ≥75 years (Figure 1) (in χ^2 tests $P>0.2$).

Patients with an ophthalmic zoster diagnosis were less likely to receive antivirals compared to patients with zoster at an unspecified site (AOR 0.66, 95% CI = 0.61 to 0.72) (Table 1). Similarly, patients with other non-truncal zoster were less likely to be prescribed antivirals (AOR 0.34, 95% CI = 0.30 to 0.40) (Table 1).

The percentage of patients receiving antivirals increased every year between 2000 and 2010, from 45.7% to 65.3% and this trend remained after adjusting for confounders (Table 1). Antiviral use varied by UK region. The lowest use of antivirals was in the north-east regions of England, specifically Yorkshire and Humber (51.9%) and the North East (52.8%). The highest use was in Northern Ireland (67.7%), where patients were 89% more likely to receive antivirals compared to patients in Yorkshire and Humber (AOR 1.89, 95% CI = 1.75 to 2.04). IMD score was available for 78 718/112 482 patients (70.0%) in England. The percentage of patients prescribed antivirals reduced with increasing IMD quintile, with 58.4% of patients in quintile zero and 54.6% in quintile four (most deprived) having received antiviral therapy (Table 1). Using practice-level IMD score for cases in England missing patient-level IMD, the results did not change (data not shown).

Zoster patients with immunosuppression were 27% more likely to receive antivirals compared to patients without immunosuppression (AOR 1.27, 95% CI = 1.22 to 1.33) (Table 2). Some evidence for greater antiviral use was found for all patients with severe immunosuppression, excluding myeloma (AOR 1.03, 95% CI = 0.85 to 1.24) (Table 2).

Of the selected autoimmune conditions considered to cause moderate immunosuppression, there was strong evidence that patients with rheumatoid arthritis were more likely to receive antiviral therapy, compared to patients without rheumatoid arthritis (Table 2). This effect was seen both among rheumatoid arthritis patients not taking immunosuppressive therapies (AOR 1.17, 95% CI = 1.05 to 1.29), and among rheumatoid arthritis patients on immunosuppressive therapy (AOR 1.28, 95% CI = 1.14 to 1.42). A similar pattern was seen among systemic lupus erythematosus patients (Table 2). Patients with inflammatory bowel disease were only more likely to receive therapy if they were on immunosuppressants (AOR 1.52, 95% CI

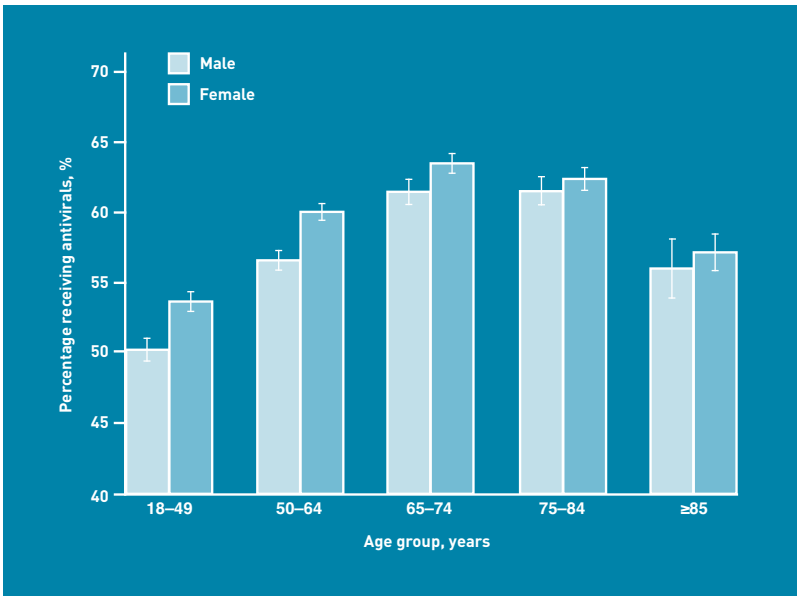

Figure 1. Percentage of patients receiving antiviral therapy, by age and sex (error bars represent 95% CIs).

= 1.24 to 1.85). Patients with diabetes were not more likely to be prescribed antivirals (Table 2).

DISCUSSION

Summary

In the UK between 2000 and 2011, the overall proportion of patients prescribed antivirals within 7 days of a zoster diagnosis was low (58.1%) though a clear increase was seen over time. Aciclovir was the most common antiviral prescribed. Antiviral prescriptions increased with age; however this trend stopped after age 65 years and prescriptions declined among patients ≥85 years. Being female, of higher socioeconomic status, and registered at a GP in Northern Ireland or Scotland was associated with higher antiviral receipt. Although antivirals were more commonly prescribed to immunosuppressed patients with herpes zoster, they were not given routinely in general practice to this patient group.

Why are antiviral prescriptions for zoster low? The finding that a low proportion of patients are prescribed antivirals for an acute episode of zoster correlates with a previous study of GPRD data reporting that 56.3% of 27 225 immunocompetent patients with herpes zoster aged ≥50 years received antivirals between 2000 and 2006.[3] These findings could suggest a lack of adherence to guidelines. Antivirals are generally safe, well tolerated,[4] and aciclovir is inexpensive, therefore neither adverse effects nor cost implications can explain their low use following zoster diagnosis. It is possible that antivirals are not seen as essential treatment, as they do not provide a cure, rather they can reduce duration of the rash and the severity of pain during the episode. Although antivirals are suggested to reduce the risk of post-herpetic neuralgia, evidence is inconclusive,[5–7] which may again deter physicians from prescribing them. This may be especially pertinent to mild cases of zoster.

An alternative explanation is patients are presenting too late to receive treatment; more than 72 hours after rash onset. This 72-hour cut-off reflects an arbitrary criterion used in clinical trials of antiviral therapy in patients with herpes zoster.[4] This may be an unrealistic time frame for patients to secure an appointment with their GP.[4] Therefore guidelines encourage GPs to 'consider' use of antivirals within 7 days of rash onset for older or immunosuppressed patients. The guidelines for treating patients presenting after 72 hours from rash onset lack clarity, and furthermore, are based on limited evidence[11–12] both of which may deter prescribing.

Patients may also present following the 7-day window when it is too late to receive antiviral therapy. Although data on time from actual rash onset to presentation to the GP is not available in this data set, two previous UK studies suggest patients present soon after rash onset: Scott *et al* reported that 50–60% of patients aged >50 years presented to GPs within 72 hours of rash onset,[13] and analyses of data from Thomas *et al* shows that 65% of adult patients with herpes zoster presented by 72 hours, with less than 7% presenting after 7 days.[14]

Additionally, a small proportion of immunosuppressed patients who get disseminated zoster will be referred, as per guidelines, to secondary care for systemic therapy and their antiviral use not recorded here. However this would not explain the low prescribing rates for the majority of patients in this study.

Why are there age, sex, regional, and socioeconomic differences? As expected the proportion of patients with herpes zoster prescribed antivirals increases with age. Explanations for why this trend plateaus at age 65 years and subsequently declines among the oldest may include; older patients being in nursing homes and presenting to GPs later, or reluctance to prescribe to older patients nearing the end of their life. Patients in Scotland and Northern Ireland were more often treated with antivirals, which may

Table 2. Proportion of patients prescribed antiviral medication, by comorbidities

Patient characteristic	*n*	% Treated	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*P*-value
Conditions causing severe immunosuppression[b]					
Severe immunosuppression	8924	64.9	1.36 (1.30 to 1.42)	1.27 (1.22 to 1.33)	<0.01
HIV	132	64.4	1.30 (0.91 to 1.86)	1.51 (1.06 to 2.17)	0.02
Leukaemia[c]	203	64.0	1.28 (0.96 to 1.71)	1.31 (0.98 to 1.76)	0.07
Lymphoma[c]	441	62.4	1.19 (0.98 to 1.45)	1.17 (0.96 to 1.43)	0.11
Myeloma	479	61.8	1.17 (0.97 to 1.40)	1.03 (0.85 to 1.24)	0.78
Organ/tissue transplant[d]	341	63.3	1.25 (1.00 to 1.55)	1.30 (1.04 to 1.62)	0.02
Splenectomy	263	63.9	1.27 (0.99 to 1.64)	1.25 (0.97 to 1.62)	0.08
Other immune deficiencies	144	67.4	1.49 (1.05 to 2.11)	1.42 (1.00 to 2.03)	0.05
Immunosuppressive therapy[e]	2174	66.8	1.46 (1.33 to 1.60)	1.37 (1.25 to 1.50)	<0.01
Oral corticosteroid therapy	6149	65.1	1.36 (1.29 to 1.44)	1.27 (1.21 to 1.34)	<0.01
Autoimmune diseases					
Diabetes	11 015	61.3	1.15 (1.11 to 1.20)	1.03 (0.99 to 1.07)	0.21
Rheumatoid Arthritis (RA)					
No RA	139 113	58.0	1.00	1.00	
RA without immunosuppressive therapy	1639	63.6	1.27 (1.14 to 1.40)	1.17 (1.05 to 1.29)	<0.01
RA with immunosuppressive therapy	1464	66.2	1.42 (1.27 to 1.58)	1.28 (1.14 to 1.42)	<0.01
Systemic lupus erythematosus (SLE)					
No SLE	141 824	58.1	1.00	1.00	
SLE without immunosuppressive therapy	223	63.2	1.24 (0.94 to 1.63)	1.20 (0.91 to 1.58)	0.20
SLE with immunosuppressive therapy	169	72.8	1.93 (1.37 to 2.71)	2.11 (1.49 to 2.97)	<0.01
Inflammatory bowel disease (IBD)					
No IBD	140 665	58.1	1.00	1.00	
IBD without immunosuppressive therapy	1083	60.4	1.10 (0.97 to 1.24)	1.05 (0.93 to 1.19)	0.43
IBD with immunosuppressive therapy	468	68.4	1.56 (1.28 to 1.90)	1.52 (1.24 to 1.85)	<0.01

[a]Adjusted for age, sex, region, year, zoster site. [b]Compared to population without specified diagnosis. [c]Diagnoses <2 years before zoster episode. [d]Bone marrow transplants included if <2years before zoster episode. [e]Excluding oral corticosteroids. Other immune deficiencies: for example immunodeficiency with predominantly antibody defects such as selective IgA immune deficiency and agammaglobulinemia, aplastic anaemias such as pancytopenia, and non-specific diagnoses of immune disorder.

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Ethical approval

Ethics approval was obtained from the GPRD Independent Scientific Advisory Committee and LSHTM Ethics Committee.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interest.

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reflect patients accessing GP services more quickly or different prescribing cultures among physicians. Reasons why males and people of lower socioeconomic status were less likely to receive antivirals may include differences in when these groups access care or physicians differentially prescribing antivirals among these groups.

Antiviral use among patients with immunosuppression. It is recommended antivirals be given routinely to patients with immunosuppression; however the proportion receiving treatment ranged between 62–68%. This may again be explained by delay in consulting GPs, some patients with severe underlying comorbidities accessing antiviral therapy through secondary care or physicians not seeing antiviral treatment as a necessity.

Antiviral use by zoster site. Ophthalmic and other non-truncal zoster cases were less commonly prescribed antivirals than zoster cases where site was unspecified, even after adjusting for age, sex, region, year, and immunosuppression status. This is a surprising finding considering guidelines suggest these groups routinely be given antiviral therapy. Patients with Ramsay Hunt Syndrome, the most common other non-truncal diagnosis, may present initially without an obvious rash and delayed diagnosis might contribute to lower prescription rates in this group. Ophthalmic zoster patients may be immediately referred to secondary care for treatment, resulting in lower prescribing rates among this group. However, misclassification of zoster site is

likely as the zoster site was seldom recorded. Despite this, it is surprising that less than 50% of cases with a definite diagnosis of ophthalmic or other non-truncal zoster received antivirals.

Strengths and limitations

The GPRD is one of the largest databases of healthcare records and has excellent capture of primary care prescriptions. However, these data may not fully capture prescriptions in secondary care. A minority of patients, particularly those with severe underlying comorbidities, may obtain antiviral prescriptions in secondary or tertiary care. Therefore this study may underestimate the prescription of antivirals following an acute zoster episode. However, as these patients received a zoster diagnosis in primary care, it is likely that most would have received any subsequent antiviral prescription from their GP. Finally, there may be misclassification of immunosuppression status as newer biologic therapies are poorly recorded in GPRD and some patients on long-term immunosuppressive therapies may be given prescriptions 6-monthly and would not have been detected; it is unclear whether receipt of antivirals among such individuals would differ from that among those identified as immunosuppressed in this study.

Comparison with existing literature

Studies from the US, Italy, and Australia report higher proportions of patients with herpes zoster receiving antiviral prescriptions. A retrospective study of healthcare records in Italy between 2003 and 2005 found 78% of 3260 immunocompetent patients with herpes zoster aged ≥50 years received antivirals.[15] In Australia analysis of healthcare records between 2000–2006 showed that 73.5% of 379 incident zoster cases aged ≥50 years received antivirals[16] and a similarly high proportion was found in the US where 71.3% of 8741 newly diagnosed zoster adults (aged ≥19) received antivirals;[17] both studies included immunosuppressed and immunocompetent individuals. In contrast, data from a large database of general practice records in the Netherlands in 2001 found 22.5% of 1129 patients with herpes zoster aged ≥44 years received antivirals.[18] Observed variation in prescribing patterns between countries may reflect differences in healthcare systems or distribution of patients with characteristics more/less likely to get antivirals in study populations, or to variations in data quality.

Implications for research and practice

The proportion of patients in the UK receiving antivirals following a diagnosis of zoster in primary care is low. This research highlights the problem of under-prescribing of antivirals for zoster in UK general practice even for groups where clear guidelines recommend treatment.

Further research is required to understand the basis for the low proportions given antivirals. This is particularly pertinent for older and immunocompromised patients. Controlled trials assessing the benefits of antivirals prescribed >72 hours after rash onset would enable more detailed guidance for physicians and may increase antiviral prescribing if delay in presenting to GPs is a factor contributing to low antiviral use. Treatment guidelines could be reviewed to clarify which patients should be treated with antivirals when it is not possible to initiate treatment within 72 hours of rash onset.

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5.3. Update of antiviral prescribing guidelines and literature:

The prescribing guidelines for use of antivirals during acute zoster have not changed since 2012, when the study was carried out and the paper published.

Regarding other literature on the use of antivirals during acute zoster in primary care, two relevant studies have been published since. Both studies are in accordance with previous literature, demonstrating that outside of the UK, a higher proportion of acute zoster patients receive antiviral prescriptions. A study within a large general practice in New Zealand between 2004 and 2009, found that of 278 incident zoster patients (≥18 years), 82% received antiviral treatment; treatment was higher among ophthalmic zoster patients (97% received antivirals) and patients presenting within 3 days of symptom onset (96%).[163] Another prospective study within 108 general practices in Italy between 2009 and 2010, found higher use of antivirals in immunocompetent patients aged ≥50 years;[164] of 413 patients, 91.5% of patients received antivirals and treatment was initiated a median of 2 days after rash onset.

5.4. Chapter summary

Antiviral use following first episode of zoster

- This chapter describes who receives antiviral therapy following a zoster diagnosis within the UK.
- A descriptive study was carried out in CPRD among 142,216 zoster patients to calculate the proportion receiving antivirals within seven days of zoster diagnosis.
- Antivirals are under-prescribed in UK primary care; 58.1% of zoster cases received an antiviral prescription within seven days of diagnosis. Even in those where guidelines recommend the use of antivirals, specifically older individuals and those with immunosuppressive conditions, treatment was not always received.
- Although patients may present too late to receive therapy, under-treatment may reflect poor adherence to treatment guidelines.
- Consideration could be given to reviewing the guidelines.

Chapter 6: Systematic review and meta-analysis of risk factors for postherpetic neuralgia

6.1. Introduction

As well as exploring risk factors for zoster, this thesis aimed to explore risk factors for PHN. Prior to conducting an original research study in CPRD, a systematic review and meta-analysis was carried out collating and presenting evidence regarding risk factors for PHN within zoster patients.

The article, published in the journal Pain, is presented below. This is followed up with the article's appendices, containing work and details that were too extensive for the main paper, specifically: further data extraction details, risk of bias assessment details and letters to authors (requesting further study details).

Following the paper and its appendices, there is an additional, shorter review of articles investigating risk factors for PHN within general population samples. The published review only included articles set within cohorts of zoster patients. In terms of vaccination policy, it is also informative to know who, within the general population, is at high risk of PHN, because such individuals could potentially be targeted for vaccination before developing zoster, therefore it was considered important to summarise this literature.

6.2. Published paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Harriet Forbes
Principal Supervisor	Sinead Langan
Thesis Title	Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Pain		
When was the work published?	January 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
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A systematic review and meta-analysis of risk factors for postherpetic neuralgia

Harriet J. Forbes*, Sara L. Thomas, Liam Smeeth, Tim Clayton, Ruth Farmer, Krishnan Bhaskaran, Sinéad M. Langan

Abstract

Patients with herpes zoster can develop persistent pain after rash healing, a complication known as postherpetic neuralgia. By preventing zoster through vaccination, the risk of this common complication is reduced. We searched MEDLINE and Embase for studies assessing risk factors for postherpetic neuralgia, with a view to informing vaccination policy. Nineteen prospective studies were identified. Meta-analysis showed significant increases in the risk of postherpetic neuralgia with clinical features of acute zoster including prodromal pain (summary rate ratio 2.29, 95% confidence interval: 1.42-3.69), severe acute pain (2.23, 1.71-2.92), severe rash (2.63, 1.89-3.66), and ophthalmic involvement (2.51, 1.29-4.86). Older age was significantly associated with postherpetic neuralgia; for individual studies, relative risk estimates per 10-year increase ranged from 1.22 to 3.11. Evidence for differences by gender was conflicting, with considerable between-study heterogeneity. A proportion of studies reported an increased risk of postherpetic neuralgia with severe immunosuppression (studies, n = 3/5) and diabetes mellitus (n = 1/4). Systemic lupus erythematosus, recent trauma, and personality disorder symptoms were associated with postherpetic neuralgia in single studies. No evidence of higher postherpetic neuralgia risk was found with depression (n = 4) or cancer (n = 5). Our review confirms a number of clinical features of acute zoster are risk factors for postherpetic neuralgia. It has also identified a range of possible vaccine-targetable risk factors for postherpetic neuralgia; yet aside from age-associated risks, evidence regarding risk factors to inform zoster vaccination policy is currently limited.

Keywords: Herpes zoster, Postherpetic neuralgia, Epidemiology, Risk factors

1. Introduction

Postherpetic neuralgia (PHN) is pain after an acute episode of herpes zoster (commonly known as shingles) continuing beyond rash healing.[16] The pain has been described as a constant burning or stabbing sensation, and some individuals experience allodynia (pain triggered from light contact with nonpainful stimuli).[47] Symptoms can persist for months or even years, and the condition can profoundly affect a patient's quality of life.[12,24] PHN is the most common complication of zoster; an estimated 12.5% of patients with zoster aged ≥50 years have PHN 3 months after zoster onset, and the proportion affected increases sharply with age.

Postherpetic neuralgia is often refractory to treatment.[10,20,40] Despite decades of research, evidence for the efficacy of administering antivirals at first appearance of the rash in reducing PHN incidence is unconvincing.[7] However, an effective live-attenuated vaccine is now available providing protection against zoster and might be used to protect those most likely to develop PHN and other complications of zoster.[30,36] Apart from age, other often reported risk factors for PHN relate largely to characteristics of the acute zoster episode, particularly, the severity of acute pain and rash at initial zoster presentation; however, the evidence has not been systematically reviewed.[14,31,32,42,48] Furthermore, as these are not vaccine-targetable, there is interest in identifying risk factors for PHN, which can be identified before the zoster episode, to inform zoster vaccination policy.

This article aims to systematically collate and summarise the epidemiological literature on risk factors for PHN including clinical features of acute zoster and those which are "vaccine-targetable."

2. Methods

2.1. Study selection

2.1.1. Search terms

We searched all published journal articles in MEDLINE and Embase between 1950 and February 3, 2014. We searched for articles containing PHN terms and risk factor analysis terms (Box 1 for full details). The search strategy used both subject heading and text word searches. Initial search terms were updated after searching the reference lists of relevant articles. To capture relevant grey literature, the New York Academy of Medicine Grey Literature Report (www.greylit.org), the Electronic Theses Online Service through the British Library (http://ethos.bl.uk), and the ISI Conference Proceedings Citation Index

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

K. Bhaskaran and S. M. Langan contributed equally to the article.

Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom

**Corresponding author. Address: London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT, United Kingdom. Tel.: 020-7927-2174; fax: 020-7580-6897. E-mail address: harriet.forbes@lshtm.ac.uk (H. J. Forbes).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

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(http://isknowledge.com) were searched for the terms: "PHN" or "postherpetic neuralgia" or "postherpetic neuralgia," within the keywords or title (Box 1).

Box 1

Search terms used.

Medline:
[{ ("Postherpetic neuralgia"[exploded MeSH] OR PHN[Title or abstract] OR "postherpetic neuralgia"[Title or abstract] OR "post herpetic neuralgia"[Title or abstract] OR post-herpetic neuralgia[Title or abstract] OR "postherpetic pain"[Title or abstract] OR "post herpetic pain"[Title or abstract] OR post-herpetic pain [Title or abstract] OR ((Neuralgia"[exploded MeSH] OR "Pain"[exploded MeSH] OR neuralgia [Title or abstract] OR pain [Title or abstract]) AND ("Herpes zoster"[exploded MeSH] OR zoster[Title or abstract] OR shingles[Title or abstract] OR zona[Title or abstract] OR VZV[Title or abstract]))
AND ("Risk factors"[exploded MeSH] OR "Epidemiologic studies"[exploded MeSH] OR "Odds ratio"[exploded MeSH] OR "Multivariate analysis"[exploded MeSH] OR "Logistic Models"[exploded MeSH] OR "Prevalence"[exploded MeSH] OR "Incidence"[exploded MeSH] OR "odds ratio"[Title or abstract] OR "risk ratio"[Title or abstract] OR "relative risk"[Title or abstract] OR "risk factor"[Title or abstract] OR risk[Title or abstract] OR predict*[Title or abstract] OR correlat*[Title or abstract] OR etiol*[Title or abstract] OR aetiol*[Title or abstract] OR prevalence[Title or abstract] OR incidence[Title or abstract] OR rate*[Title or abstract]) }
OR "Postherpetic neuralgia/etiology"[exploded MeSH]
OR (("Neuralgia/etiology"[MeSH] OR "Pain/etiology"[MeSH]) AND (herpes zoster[exploded MeSH] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))]
AND "Humans"[MeSH]; limited to articles in language: ENGLISH
Embase:
[{ ("Postherpetic neuralgia"[exploded subject heading] OR "PHN"[Title or abstract] OR "postherpetic neuralgia"[Title or abstract] OR "post herpetic neuralgia"[Title or abstract] OR "post-herpetic neuralgia"[Title or abstract] OR "postherpetic pain"[Title or abstract] OR "post herpetic pain"[Title or abstract] OR post-herpetic pain [Title or abstract] OR (("Neuralgia"[exploded subject heading] OR "Pain"[exploded subject heading] OR "neuralgia" [Title or abstract] OR "pain" [Title or abstract]) AND (herpes zoster[exploded subject heading] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))
AND ("Risk factor"[exploded subject heading] OR "Epidemiology"[exploded subject heading] OR "Odds ratio"[exploded subject heading] OR "Multivariate analysis"[exploded subject heading] OR "Statistical model"[exploded subject heading] OR "Prevalence"[exploded subject heading] OR "Incidence"[exploded subject heading] OR "odds ratio" OR "risk ratio" OR "relative risk" OR "risk factor" OR "risk" [Title or abstract] OR "risk factor"[Title or abstract] OR "predict*"[Title or abstract] OR "correlat*"[Title or abstract] OR "etiol*"[Title or abstract] OR "aetiol*"[Title or abstract] OR "prevalence"[Title or abstract] OR "incidence"[Title or abstract] OR "rate*"[Title or abstract]) }
OR "Postherpetic neuralgia/etiology"[exploded subject heading]
OR (("Neuralgia/etiology"[subject heading] OR "Pain/etiology"[subject heading]) OR (herpes zoster[exploded subject heading] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))]
AND "Humans"[subject heading]; limited to language: ENGLISH
Grey literature:
New York Academy of Medicine Grey Literature Report: PHN OR postherpetic neuralgia OR title:(postherpetic AND neuralgia) OR title:PHN
ISI Conference Proceedings Citation Index: [{TS=(PHN or "postherpetic neuralgia" or "post herpetic neuralgia") AND TS=(risk or epidem* or "odds ratio" or rate)} OR {TI=(PHN or "postherpetic neuralgia" or "post herpetic neuralgia")}] AND TI=(risk or epidem* or "odds ratio" or rate) AND LANGUAGE: (English).
Note: In both databases the subject heading terms are arranged in a hierarchy with more specific linked subheadings arranged beneath wider terms. Exploding a subject heading indicates that the search includes all results below that heading.

2.2. Inclusion and exclusion criteria

Criteria were developed in an iterative process after preliminary searches. We included studies based on original data from analytical epidemiological studies, among adults (18 years+) with zoster. Postherpetic neuralgia had to be a study outcome and an age-adjusted effect estimate was required. We included risk factors, which were either (1) clinical features of the acute zoster episode or (2) vaccine-targetable, defined as risk factors identifiable before the onset of the zoster rash. Studies assessing only age as a risk factor were required to treat age as a continuous exposure (ie, linear on a log scale) such that its effects on PHN risk could be reported per 10-year increase. Studies assessing genes as risk factors for PHN were not required to have an age-adjusted effect measure, because allele frequencies are not typically associated with age.

We omitted studies assessing antiviral therapy as a determinant of PHN as they have been recently summarised in a Cochrane Systematic Review[7]; we also omitted studies assessing other PHN treatments (such as acupuncture and corticosteroids). We excluded studies examining risk factors for PHN within a general population sample (where patients with PHN were compared with non-zoster controls) because the risk of PHN in the general population comprises 2 parts; first, the risk of zoster and second, the risk of developing PHN among those with zoster. In these studies, it is impossible to disentangle whether any identified risk factors are simply predictive of zoster itself, or whether they are specifically risk factors for getting PHN. We also excluded studies restricted to specific clinical subgroups of patients with zoster, such as individuals with HIV, because their risk factors for PHN may differ. We restricted to English articles only; however, we did not place any restriction on study location or publication status.

2.3. Selecting studies

The titles and abstracts of all identified articles were assessed. If a study was deemed to potentially fulfil the inclusion criteria, full-text versions were retrieved and assessed. Reference lists of all retrieved articles were searched. To assess how reliably the study eligibility criteria were applied, a second author (R.F.) applied the inclusion criteria to a random 10% sample of all articles, and agreement between the primary allocation and the sample allocation was tested using Cohen's kappa statistic.[29] A kappa score of 1 denotes full agreement, and kappa values greater than 0.75 indicate excellent agreement.[44]

2.4. Data extraction

Extraction tables were piloted by S. L. Thomas and H. J. Forbes and then applied to remaining studies. Data (listed in Appendix, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132) were extracted by H. J. Forbes for each study. Authors were contacted for missing information (see appendix for template e-mail to corresponding authors, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). When individual studies used multiple definitions of PHN, results classifying PHN as pain at 3 months after zoster onset (or that closest to 3 months) were extracted for the main analysis, as this is the most widely used definition of PHN.[12,17,30,36,45] Results from other PHN definitions were extracted for the Appendix (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

2.5. Assessing risk of bias

The risk of bias assessment was based on the Cochrane Collaboration approach,[1] in which each study is assessed separately for prespecified bias domains (see Appendix for further details available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

We also considered the validity of each study based on the sampling of patients with zoster, numbers declining to participate, and their characteristics, particularly the percentage developing PHN.

2.6. Data analysis

When at least 2 studies were deemed to be capturing the same risk factor within similar populations, we assessed between-study heterogeneity using the Cochrane Q statistic and the I^2 statistic, with $I^2 > 50\%$ used as a threshold indicating moderate heterogeneity. In the absence of heterogeneity, we planned to combine the estimates and produce a summary relative risk using fixed effects meta-analysis. However, for some risk factors, there was significant between-study statistical heterogeneity; therefore, we performed posthoc analysis to help ascertain the possible reasons for heterogeneity. This included rerunning the meta-analysis removing studies at high risk of bias and comparing I^2 values between clinical and methodological subgroups to evaluate potential sources of heterogeneity.[22] For this latter analysis, summary estimates from subgroups were formally compared using meta-regression; we compared subgroups according to (1) mean age of the study population (≥60 years vs <60 years), (2) definition of PHN (pain at 4 months vs pain at 3 months), (3) ascertainment of PHN (self-reported vs ascertained from medical records), (4) whether immunosuppressive patients were included or excluded, and (5) sources of study population (primary care vs other).

We also created a funnel plot to determine the risk of publication bias; gender was the only risk factor assessed in sufficient studies to be suitable for assessment (age effects were reported in different units making it unsuitable). The odds ratios (OR), representing the effect estimate of gender on PHN, were plotted against the standard error of the log odds,[41] representing the precision of the estimate, and symmetry was assessed visually (as there were too few studies to perform a formal test).[43] Statistical analyses were performed in STATA (version 13.1).

3. Results

The initial search identified 3614 articles. After removing duplicates, 2559 titles and abstracts were screened. Of these, 116 full-text articles were retrieved, 19 of which were included in the review (**Fig. 1**). Excluded studies are listed in the Appendix (Table A1), available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132.

Agreement between reviewers over the application of the inclusion criteria was very good (kappa score, 0.88). From the 10% sample of articles double screened, 1 study was not agreed on; the second reviewer initially selected this study[11] for inclusion; however, both reviewers subsequently agreed this extra article replicated a study already selected.[13]

3.1. Study characteristics and findings

Study characteristics are described in **Table 1**. There were 18 cohort studies and 1 case-base study (a modified case–control study, where the risk ratio is estimated by sampling controls from those at risk at the start of follow-up).[39] Study sizes ranged from 55 to 34,280, and 17/19 studies had less than 1000 participants at baseline. Zoster diagnoses were predominantly based on clinical opinion. Definitions of PHN were presence of pain 3 months after rash onset in 10 studies, although other definitions from 1 to 6 months were used. The percentage of patients with zoster developing PHN ranged from 2.6% to 67.3%. Mean age of study participants (available in 9 studies) ranged from 52.3 to 67.7 years. Studies were all from high-income countries.

Study findings are summarised in **Table 2** and **Figures 2 and 3**. Data were collected on clinical features of the acute episode including pain (15), rash extent and location (14), rash duration (9), sensory dysfunction (3), and other clinical features (11), and also vaccine-targetable risk factors including age and gender (18 studies), severe immunosuppression (5), other physical comorbidities such as autoimmune conditions (4), diabetes (6), cancer (5), recent physical trauma (1), psychological comorbidities (4), and other risk factors (9).

3.2. Clinical features of acute zoster episode as risk factors

3.2.1. Pain

3.2.1.1. Prodrome

Eleven cohort studies and the case-base study collected data on prodromal pain, ie, pain appearing before rash onset. Seven included prodromal pain in the final age-adjusted model and 5 reported effect estimates, with each giving a point estimate above 1. We obtained a pooled effect estimate of 2.29, 95% confidence interval (CI): 1.42 to 3.69 ($P_{heterogeneity} = 0.716$; $I^2 = 0.0\%$) in fixed effect meta-analysis. A cohort study among 533 immunocompetent patients reported a shorter prodrome (≤3 days) before rash onset was associated with reduced risk of PHN (adjOR: 0.49, 95% CI: 0.24-0.99).

3.2.1.2. Severe acute pain during zoster

Twelve cohort studies investigated severe acute pain as a risk factor for PHN. Although definitions of severe acute pain varied among studies, eg, pain scoring ≥4 using the Neuropathic Pain Questionnaire[5] and pain scoring ≥5 on the Visual Analogue Scale,[9] 8 reported it as a binary variable enabling us to pool estimates; there was good evidence that severe acute pain was associated with increased risk of PHN (rate ratio [RR]: 2.23, 95% CI: 1.71-2.92, $P_{heterogeneity} = 0.649$; $I^2 = 0.0\%$).

3.2.1.3. Allodynia

Allodynia was investigated in 3 cohort studies. One study reported a greater than 4-fold increased risk of PHN with brush (adjOR: 5.89, 95% CI: 1.50-23.1) and stretch-evoked allodynia (adjOR: 4.13, 95% CI: 0.98-17.50)[19]; however, small numbers (N = 93) led to wide CIs. A study among hospital patients treated in a pain clinic found no effect of allodynia (definition unclear; adjOR: 0.82, 95% CI: 0.24-2.81), whereas a final cohort study similarly reported no evidence of effect.[5,26] A summary estimate was not calculated because of the varying definitions of allodynia.

3.2.1.4. Pain interferes with daily functioning

Pain interfering with daily functioning at zoster onset was assessed in 3 cohort studies. The first, among 1358 individuals, reported a 1-unit increase in zoster brief pain inventory interference score was associated with 18% increase in PHN risk (adjOR: 1.18, 95% CI: 1.05-1.31).[13] Two other cohort studies reported binary (yes or

[1] *The Cochrane Collaboration have tools for assessing bias in randomized trials (Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011: 343: d5928) and non-randomised studies (Sterne JAC HJ, Reeves BC. On behalf of the development group for ACROBAT-NRSI. A Cochrane risk of bias assessment tool: for non-randomized studies of interventions (ACROBAT-NRSI). 2014 Available from: www.riskofbias.info.). Both tools pre-specify bias domains, within which there may be more than one item. Each item is assigned a judgment of risk along with a supporting comment for the judgement.*

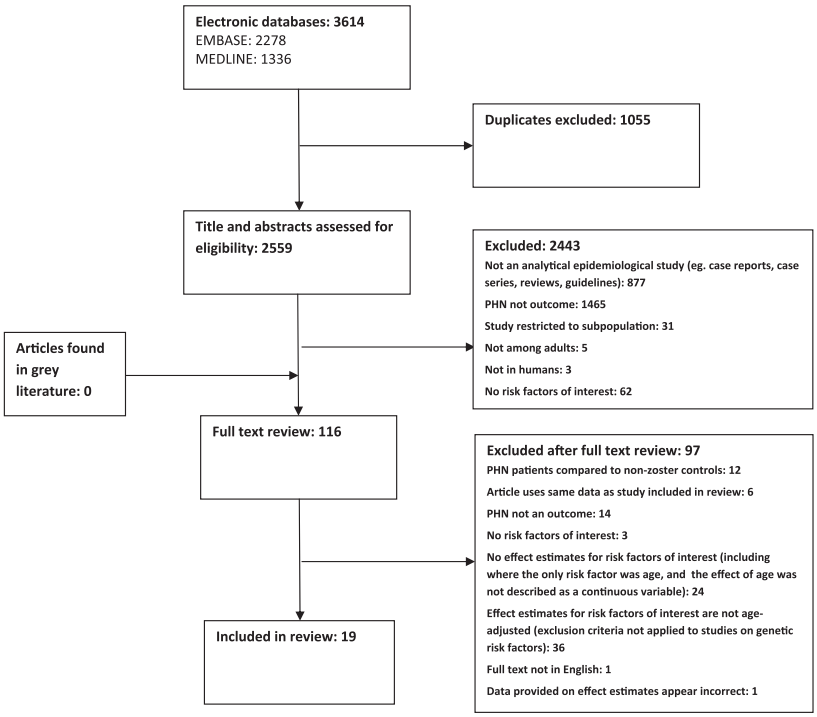

Figure 1. Flow diagram describing study selection.

no) data on pain interference. One found over 2-fold increased risk,[27] whereas the other found no evidence of association; the summary estimate of these 2 studies suggested there was strong evidence that pain interfering with daily functioning was associated with PHN (summary RR: 2.10, 95% CI: 1.27-3.48).

3.2.2. Rash severity and location

3.2.2.1. Severe rash

Rash severity data were collected in 8 studies. Five included it in their final age-adjusted model (although one did not report an OR); when combined in meta-analysis, severe rash was strongly associated with PHN risk (summary RR: 2.63, 95% CI: 1.89-3.66, $P_{heterogeneity} = 0.892$; $I^2 = 0.0\%$).

3.2.2.2. Ophthalmic involvement

A total of 13 studies recorded information on zoster location. Only 3 studies reported an effect estimate for ophthalmic involvement. Each of these 3 studies reported a point estimate above 1, yet the CIs crossed 1. When combining in a meta-analysis, there was evidence that ophthalmic zoster was associated with over twice the risk of PHN, compared with nonophthalmic zoster (summary RR: 2.51, 95% CI: 1.29-4.86, $P_{heterogeneity} = 0.782$; $I^2 = 0.0\%$).

3.2.3. Rash duration at presentation

Longer rash duration at presentation of zoster showed some evidence of being associated with reduced risk of PHN. A study on 598 immunocompetent patients showed for everyday the rash was present since presentation in primary care; there was over 20% reduced risk of PHN (adjOR: 0.78, 95% CI: 0.64-0.97).[35] Three other cohort studies estimated the risk of PHN for everyday from onset to diagnosis; point estimates were all below 1 (yet CIs were wide).[9,25,27] The summary estimate from meta-analysis showed a small reduction in PHN risk with everyday since rash onset (0.93, 95% CI: 0.86-0.99).

3.2.4. Other

One study assessed pinprick hypaesthesia (or numbness) as a risk factor for PHN: it was associated with a 7-fold increased risk of PHN (adjOR: 7.72, 95% CI: 2.00-29.90).

3.3. Vaccine-targetable risk factors

3.3.1. Age

Eighteen studies assessing the effects of age showed an increased risk of PHN with greater age. When possible, we summarised the effect of a 10-year increase in age on PHN risk (n = 9). The point estimates ranged from 1.22 to 3.11 per 10 years; the meta-analysis showed strong evidence of between-study heterogeneity ($P_{heterogeneity} = 0.029$; $I^2 = 55.1\%$). A small study (N = 249) showing an increased risk of PHN with a 10-year increase in age (adjRR: 1.22, 95% CI: 1.00-1.48) was excluded from the meta-analysis as the effect was reported as a risk ratio. In posthoc analysis, there was some weak evidence that the effect of age was associated with age of the study population (*P* value from meta-regression = 0.08; specifically the effect of age on PHN risk seemed higher in studies where the mean age was ≥60

Table 1

Studies assessing vaccine-targetable risk factors for postherpetic neuralgia nested within a population of patients with zoster: study characteristics.

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Asada et al.[2]	Japan, 2008-2010	Patients with acute zoster registered in a cohort study on VZV immunity; aged ≥50 y	258 recruited 247 analysed 11 lost to follow-up	Not reported	PHN at 3 mo after zoster	32 (13.0)	Notified during telephone follow-up and confirmed through evaluation of clinical symptoms by 3 dermatologists and PCR	Pain 3 mo after rash onset Telephone survey to ascertain pain status by secretariat members.	Survey forms and examination by dermatologists	Age, gender, history of zoster, state of VZV-specific cell-mediated immunity (using VZV skin test reaction: no oedema formation and <5 mm diameter of red skin indicated weaker VZV-specific cell-mediated immunity)	Logistic regression
Bouhassira et al.[5]	France, 2007-2008	Patients presenting to General Practitioners (GPs) years with acute zoster; aged ≥50 y	1358 recruited 1091 analysed 267 lost to follow-up	67.7 (10.7)	PHN at 3 mo after zoster	127 (11.6)	Physician diagnosis within 7 d of rash onset, no history of zoster within previous 12 mo	Pain 3 mo after rash onset Telephone interview, using question, "Do you still have pain associated with your shingles?"	Physician interview and patient completed questionnaire at zoster diagnosis	Age, gender, family situation, living arrangements, delay in diagnosis, associated disease (undefined), average pain intensity, pressure allodynia, brush-evoked allodynia, global DN4 score, NPSI score, ZBPI interference score, SF-12 physical and mental component score, HADS score, and analgesic treatment	Logistic regression
Cebrián-Cuenca et al.[6]	Spain, 2006-07	Convenience sample of patients with acute zoster from 25 general practitioners; aged >14 y	146 recruited 124 analysed 22 lost to follow-up 16 declined to participate	Median 63.5 (range: 19-94)*	PHN at 3 mo after zoster	18 (14.5)	Physician diagnosis of zoster	Pain 3 mo after rash onset. Telephone/home interview by study investigators	Interview with patients and review of medical records	Age, gender, prodromal pain, extremities localization, sacrum localization, time between symptom onset and clinical diagnosis, time between rash onset and clinical diagnosis, antiviral use	Logistic regression
Coen et al.[9]	England, 1998-2001	Patients presenting to primary care with acute zoster; any age	280 recruited 272 analysed 8 lost to follow-up	Not reported (range 0-99)	PHN at 3 mo after zoster	52/250 (20.8)	Physician diagnosis within 7 d of rash, referred to 2 investigators for clinical and PCR or IFA confirmation	VAS score ≥3.3 mo after rash onset Follow-up visit or telephone interview with research nurse	Physician interview at enrolment	Age, gender, prodromal pain, extent of rash, time from onset of rash, ophthalmic branch involvement, pain severity using VAS	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Drolet et al.[12]	Canada, 2005-2006	Immunocompetent patients presenting to general practice or specialist centres, with zoster; aged ≥50 y	249 recruited all analysed	65.6 (10.8)	PHN at 3 mo after zoster	56 (22.5)	Physician diagnosis within 14 d of rash onset. Physicians received training on zoster diagnosis and their first 3 patients were confirmed by PCR	Severe pain 3 mo after rash onset Patient completed pain questionnaire at patients home	Physician interview and patient completed questionnaire at zoster diagnosis	Age, gender, education, working, income, has other pain condition, EQ-5D health status score before and during zoster in 5 domains: mobility, self-care, usual activities, having pain/discomfort, being anxious/depressed (rated none, some, or severe problems), VAS score before and during zoster, delay between recruitment and rash onset, dermatome affected, number of lesions, worst pain, prodrome, duration of prodrome, worse prodromal pain, reported pain interference score, antiviral treatment and timing of antiviral treatment, other medications. Immune suppressed patients (using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS) included in sensitivity analysis	Log-binomial regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Haanpaa, 2000[19]	Finland, year not given	Primary care zoster patients without immunosuppression, psychiatric illness, substance abuse, systemic, or metabolic disease, neurologic disease influencing somatosensory testing; any age	113 recruited 93 analysed	58 (17.2)	PHN at 3 mo after zoster	28 (25)	Physician diagnosis	Pain 3 mo after rash onset Follow-up visit, or if nonattendance telephone interview or mail, by study investigator	Interview with patients 1-10 d after rash onset by study investigators	Age, gender, severity of zoster rash (mild: covers <quarter of affected dermatome, severe: covers >3 quarters of affected dermatome, moderate: in between above), localisation of rash, prodromal pain, acute pain (none, mild, moderate, severe), antiviral use, analgesic use, allodynia (brush, stretch, and compression evoked), and pin-prick hypaesthesia	Logistic regression
Helgason et al.[21]	Iceland, 1990-1995	Patients presenting to participating GPs with first ever zoster diagnosis, without cognitive impairment; any age	421 recruited 391 analysed 30 lost to follow-up	Not available	PHN at 3 mo after zoster	28 (7.2)	Physician diagnosis and further confirmation by study investigators using clinical information from GPs and patients	Pain 3 mo after rash onset Telephone interview/home visit by principal investigator	Researcher interview, supplemented by data from GP practice records	Age and gender	Logistic regression
Jih, 2009[23]	Taiwan, 2000-2006	Patients with zoster in nationally representative 1 million claims data sample, with primary care and inpatient data linked; any age	34,280	Not reported (1->80)	PHN at 3 mo after zoster	Exact number not given (8.6)	*ICD-9* codes for zoster in inpatient or outpatient service claim	Pain >90 d after rash onset *ICD-9* zoster code and neuralgia treatment >90 d after first onset	*ICD-9* codes: timing of records with respect to zoster or PHN is unclear	Age, gender, diabetes, systemic lupus erythematosus, HIV/AIDs, breast cancer, liver cancer, and lymphoma/ leukaemia	Poisson regression
Jung et al.[25]	Europe, US, Canada, Australia, 1990-1991	Patients with immunocompetent zoster recruited into 2 clinical trials; aged ≥15 y	965 recruited 855 analysed 110 lost to follow-up	52.3 (range 15-93)*	PHN at 4 mo after zoster	114 (13.3)	Physician diagnosis of zoster within 72 h of rash onset	Pain 4 mo after rash onset Patient reported at follow-up visit	Physician interview at zoster diagnosis	Age, gender, rash severity, rash duration, prodrome, pain severity, primary involvement of the trigeminal dermatome, number of affected dermatomes, presence of affected nonadjacent dermatomes, clinical trial sample	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Kanbayashi et al.[26]	Japan, 2008-2010	Patients treated at a hospital pain clinic, with zoster (unclear if acute/persistent); age unspecified	73 recruited all analysed	Median 69 (range 27-90)	Ordered categorical: no PHN, PHN 3-6 mo, PHN 6 mo+	PHN 3-6 mo: 13 (18) PHN 6 mo+: 25 (34)	Unclear	Pain 3-6 or 6 mo+ after rash onset Medical records of pain (unclear how pain defined)	Extraction of variables from clinical records at initial visit	Age, gender, comorbidities (hypertension, angina, diabetes, malignant tumour, autoimmune diseases) sleep disorder, rash location, period of onset, type and extent of pain, VAS, prodrome, allodynia	Ordered logistic regression
Katz et al.[27]	United States, mid 1990s	Patients presenting to hospital and community physicians with acute zoster; aged ≥18 y	129 recruited 102 analysed 8 lost to follow-up 19 excluded (initial assessment >30 d after rash onset)	Patients with PHN: 63.2 (15.1) Patients without PHN 59.2 (14.5)	PHN at 4 mo after zoster	20 (19.6)	Physician diagnosis with no more than 1 previous episode of zoster, +5 y ago	Pain ~4 mo after rash onset Telephone interview by research assistant or psychologist	Psychologist administered interview within 30 d of rash onset	Age, gender, race, education, marital status, physical health, immune compromise (definition unclear, yet includes HIV, currently treated for cancer and high-dose corticosteroids), presence of a prodrome, zoster location, zoster duration acute pain intensity, premorbid physical, role, and social functioning (1 wk before and after rash onset), symptoms of depression and anxiety, emotional well-being, personality disorder symptoms, health locus of control, disease conviction, hypochondriasis, somatosensory amplification, somatic symptoms, current major depression or dysthymia	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Kotani et al.[28]	Japan, year not given	Patients presenting to hospitals with acute zoster, excluding patients recently on immunosuppressive therapy, or with serious neurologic disorders; aged ≥50	170 recruited all analysed	65 (9)	PHN at 2 mo after zoster	52 (30.4)	Physician diagnosis of painful nontrigeminal zoster (exc. disseminated) within 4 d of rash onset, and serological confirmation	Any pain 6 mo after rash onset Assessed 24 h after coming off analgesics, unclear how pain was ascertained	Measured at zoster diagnosis: method of ascertainment unclear	Age, gender, comorbid conditions (diabetes, malignancy, immune disorders, autoimmune disease), prodromal pain, localization, severity of zoster rash, number of skin lesions, degree of acute pain, cerebrospinal fluid interleukin 8 concentrations during and at healing of herpetic rash	Logistic regression
Opstelten et al.[33]	Netherlands, 1994-1999	Patients with zoster identified from EHRs from primary care; any age	837 identified all analysed	Not available	PHN at 3 mo after zoster	22 (2.6)	Medical code or zoster mentioned in the free text: confirmed after review of full medical records	Pain at 3 mo after rash onset Any evidence of pain in EHR; pain record/analgesic prescription	From previously recorded medical records at zoster diagnosis	Age, gender, localization, comorbidity (diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, psychological problem at zoster diagnosis), medication at zoster diagnosis (corticosteroids within previous 14 d and psycho-pharmaceuticals within previous 3 mo), painful prodrome, consultation frequency, chronic analgesics use	Logistic regression
Opstelten[35]	Netherlands, 2001-2004	Immunocompetent patients presenting to GPs with acute zoster and recruited into a trial; aged >50 y	598 recruited all analysed 651 not included: 470 refused consent, 98 physician declined to participate, 83 unknown†	66.2 (9.8)	PHN at 3 mo after zoster	46 (7.7)	Physician diagnosis within 7 d of rash onset, dermatome below C6	Pain ≥30 on VAS scale 3 mo after study inclusion. Patient filled in postal survey	Measured at baseline—questionnaire and data from GP	Age, gender, rash duration (in d) and severity, prodromal pain, pain severity, use of antivirals, VZV antibodies (IgM, IgA, IgG), VZV viremia, and seven psychological predictors: negative self-efficacy, pain catastrophizing, positive expectation, resignation, and trust in health care, anxiety state and anxiety disposition	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Park et al.[37]	South Korea, 2008-2010	Patients presenting to hospital with acute zoster; any age	55 recruited all analysed	PHN patients: 63.3 (15.9) Non-PHN: 48.2 (16.8)	PHN at 1 mo after zoster	15 (27.3)	Physician diagnosis within 7 d of rash onset	Pain persisting or appearing 30 d after rash onset Method unclear	Collected at baseline—method unclear	Age, sex, affected area, pain intensity, and interval between onset of rash and hospital visit. Also, maximal temperature difference between lesional and contralateral normal skin, and size of body surface area showing thermal asymmetry	Logistic regression
Parruti et al.[38]	Italy, 2006-2008	Consecutive patients presenting to primary care or hospital with acute zoster; age unspecified	469 recruited 441 analysed 28 lost to follow-up	58.1 (20.4)	PHN 1-3 mo after zoster	130 (29.5)	Physician diagnosis any time after rash onset, with laboratory investigation of uncertain cases	Any pain between 1-3 mo after enrolment Recorded at follow-up visit or by telephone	Patient completed electronic forms at enrolment	Age, gender, familial status, educational level, hypertension, diabetes, HCV and/or HIV infection, alcohol abuse smoking status, familial history of major cardiovascular events, malignancies, neurological diseases, major depression, psychiatric illness, allergy, trauma at site of lesion (in 6 mo pre-enrolment), surgical intervention at site of lesions, zoster dermatomeric district, pain intensity at presentation, rash severity, prescribed NSAIDs, antiviral use	Logistic regression
Volpi et al.[46]	Italy, 2001-2002	Patients with immunocompetent zoster presenting to private dermatologists, aged ≥18 y	533 recruited 219 analysed	Median age: 58 (18-82)	PHN 6 mo after zoster	70 (32)	Physician diagnosis	Pain 6 mo after rash onset, with pain rating 3 or higher (on scale from 0 [no pain] to 10) Physician diagnosis using patient reported pain at follow-up	Physician interview and patient completed questionnaire at zoster diagnosis	At baseline: age, gender, years of education, presence and duration of prodromal pain, intensity of pain, localization of rash, extent of rash, abnormal sensations (itch, tingle, allodynia), systemic antiviral therapy	Logistic regression

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Table 1 (*continued*)

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Woznaik et al.[50]	United Kingdom, 1998-2001	Patients presenting to primary care with acute zoster; any age	280 recruited 104 analysed reasons for noninclusion not available	59 (range: 19-91)	PHN at 4 mo after zoster	70 (67.3)	Physician diagnosis plus confirmation by PCR for VZV	Pain/abnormal symptoms ≥120 d Follow-up visit or phone interview with study nurse	DNA preparation and APOE genotyping	APOE genotypes	ORs and 95% CI generated

Prospective case-base studies (where the controls are a sample of the base population)

First author publication year	Country year of study	Base population	Cases and controls	Study size	Mean age in years (SD)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Choo et al.[8]	United States, 1990-1992	Acute zoster patients in HMO's EHRs, with continuous membership at least 180 d before and at least 90 d after zoster; age unspecified	Cases: patients developing PHN	37 cases	Cases: 67.6 (14.5)	*ICD-9* code for incident zoster (no zoster record before 6 mo). Medical records of all patients with a code screened by 2 reviewers	Symptoms in zoster area >60 d from rash onset	Screening of previously recorded medical records at the time of zoster diagnosis	Age, gender, health care utilization, location of zoster, prodromal symptoms, time to crusting of rash, interference of zoster with daily living, comorbidities recorded 180 d before zoster (diabetes, cancer, connective tissue disease, HIV, organ transplant), complications (superinfection, motor neuropathy, keratitis, uveitis, oticus, transient ischaemic attack, from vasculitis) cytotoxic chemotherapy 180 d before zoster, antiviral treatment, corticosteroids 180 d before and 30 d after zoster	Logistic regression with a correction

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Table 1 (*continued*)

Prospective case-base studies (where the controls are a sample of the base population)									
First author publication year	**Country year of study**	**Base population**	**Cases and controls**	**Study size**	**Mean age in years (SD)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
			Controls: random sample of base population (PHN cases and noncases)	179 base population (controls sampled on a ratio of 3:1)	Controls 42.4 (17.5)		Patients with diagnoses, symptoms, meds indicating PHN screened by 2 reviewers			

* Excludes patients lost to follow-up. d, days; mo, months; SD, standard deviation.
† van Wijck AJ, Opstelten W, Moons KG, van Essen GA, Stolker RJ, Kalkman CJ, and Verheij TJ. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet 2006;367:219–24.
APOE, alipoprotein E; C^, sixth cervical dermatome; DN4, neuropathic pain questionnaire with 4 questions; EQ-5D: questionnaire on zoster pain and health-related quality of life; EHR, electronic health care record; HADS, hospital anxiety and depression scale; HCV, hepatitis C virus; HMO, health maintenance organisation; *ICD-9*, International Classification of Diseases version 9; IFA, immunofluorescence of antigen; NPSI, neuropathic pain symptom inventory score; NSAIDS, Nonsteroidal antiinflammatory drugs; PCR, polymerase chain reaction; SF-12, short-form 12; VAS, visual analogue scale ranging from 0 (no pain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; ZBPI, zoster brief pain inventory interference score.

years) (Appendix Table A2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). There was no evidence that the effect of age on PHN risk varied by definition of PHN ($P = 0.52$), ascertainment of PHN ($P = 0.14$), immunosuppression status ($P = 0.23$), or sources of study population ($P = 0.18$).

3.3.2. Gender

Of 9 studies reporting the age-adjusted association between gender and PHN, some suggested an increased risk of PHN among females,[9,25,38] others a decreased risk,[2,5] whereas others found no evidence of an association.[2,6,8,23,33,37] These conflicting results were supported by strong evidence of between-study heterogeneity ($P_{heterogeneity} < 0.001$; $I^2 = 73.9\%$). In posthoc analysis, the effect of female gender seemed protective in studies in which the mean age was ≥60 years, compared with among studies with mean age <60 years, for which female gender increased the risk of PHN; heterogeneity was reduced within these subgroups (<1% in both) (Appendix Table A2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). There was no evidence that the effect of gender on PHN risk varied by definition of PHN ($P = 0.45$), ascertainment of PHN ($P = 0.83$), immunosuppression status ($P = 0.25$), or sources of study population ($P = 0.97$). These analyses were limited by 4/7 studies in meta-analysis of gender having at least 1 bias domain assigned high-risk.

3.3.3. Severe immunosuppression

A cohort study among patients with zoster≥18 years found immunosuppression (including HIV, currently treated for cancer, or exposed to high-dose corticosteroids) was more common in patients with PHN (15%, n = 3/20) than without (7.3%, n = 6/82); but the sample size was too small to be conclusive.[27] Another cohort study among patients ≥50 years of age reintroduced 12 patients with immunosuppression excluded from the main analysis (defined as using high-dose oral corticosteroids/other immunosuppressive drugs, having invasive cancer or HIV/AIDS); these patients had an increased risk of PHN after adjustment for confounders (adjRR: 1.98, 95% CI: 1.14-3.45).[13] Finally, the case-base study in the United States found connective tissue disease, HIV, or organ allograft was associated with 10-fold increased risk of PHN, although the CI was wide (adjOR: 9.5, 95% CI: 2.0-45.0).[8] Two studies specifically assessed HIV: one excluded HIV from the final multivariable analyses,[38] whereas another found over 50% decreased risk of PHN among patients with HIV (antiretroviral treatment status not reported) (adjRR: 0.48, 95% CI: 0.26-0.86).[23] The latter study also reported strong evidence of an increased risk of PHN with lymphoma/leukaemia (adjRR: 1.74, 95% CI: 1.32-2.28).

3.3.4. Other physical comorbidities

3.3.4.1. Overall physical health

One study measured overall health status at zoster presentation using the physical component summary score and found a decreased risk of PHN with better physical health.[5] The second study summed total number of reported medical conditions and found no evidence of association with PHN.[27]

3.3.4.2. Autoimmune conditions

A large cohort study among 34,280 patients with zoster identified in Taiwanese electronic health insurance records identified 284 patients with systemic lupus erythematosus (0.83%), who were

Table 2

Association between PHN and various risk factors (defined as either vaccine-targetable or clinical features of the acute zoster episode): risk factors, adjusted effect measure and 95% confidence interval (CI) by study.

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	Severe immune suppression	Other physical or psychological comorbidities	Other risk factors	Pain (including prodrome)	Rash extent and location	Rash duration	Other
Cohort studies—risk factor: OR (95% CI) unless specified								
Asada et al.[2]	50 s: 1.20 (0.33-4.44) 60 s: 0.73 (0.19-2.79) 70 s: 1.72 (0.57-5.14) Reference ≥80 y F vs M: 0.48 (0.22-1.05)	—	—	Current smoker: OR not given History of zoster: 0.42 (0.09-1.88) Diameter of red skin after VZV skin test (≥5 vs <5 mm): 0.08 (0.02-0.45) Oedema after VZV skin test: 0.07 (0.01-0.62)	—	—	—	—
Bouhassira et al.[5]	≥70 vs <70 y 1.28 (1.05-1.55) F vs M 0.55 (0.34-0.90)	—	Physical health, using continuous PCS score, * per 1 unit increase (higher score = worse health): 0.72 (0.55-0.92) Mental Health, using continuous MCS score, * per one unit increase (higher score = worse health): $P = 0.59$ Associated disease (undefined), anxiety or depression not selected for final model	Family situation or living arrangements not selected for final model	Interference of pain on daily tasks, using continuous ZBPI score:1.18 (1.05-1.31) Neuropathic pain score at zoster presentation, using DN4 ≥4 vs <4: 1.78 (1.03-3.06) Intensity tactile allodynia, using continuous NPSI score: $P = 0.43$ Average pain intensity, using continuous score from 1-10 using ZBPI: $P = 0.54$ Pressure allodynia, brush-evoked allodynia not selected for final model	—	Delay in diagnosis not selected for final model	Analgesic treatment not selected for final model
Cebrián-Cuenca et al.†[6]	Per year increase: 1.04 (1.01-1.08, $P < 0.03$) Gender: OR not given $P > 0.05$	—	Other comorbidities (Unclear if in final model)	—	Prodromic pain (OR not reported: $P > 0.05$)	Zoster location (OR not reported: $P > 0.05$)	Time from symptom onset to diagnosis, time from appearance of eruption to diagnosis (OR not reported: $P > 0.05$)	Antiviral use: OR not given $P > 0.05$

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Coen et al.[9]	Age greater than 50 y: 3.91 (1.38-11.11) F vs M: 2.45 (0.96-6.23)	—	—	—	VAS >5: 3.92 (1.33-11.5) Prodrome not selected for final model	Extent of rash, score 1-5: 1 (least rash, baseline) 2: 1.01 (0.18-5.61) 3: 1.65 (0.31-8.80) 4: 1.08 (0.15-7.59) 5: 2.52 (0.45-14.0) Ophthalmic involvement: 3.20 (1.19-8.55)	Time from onset of rash (days): 0·93 (0.80-1.07)	—
Drolet et al.[12]	Per yr increase: RR: 1.02 (1.00-1.04) Gender not selected for final model	Immunosuppression (using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS): RR: 1.98 (1.14-3.45) (sensitivity analysis)	Limitation in performing usual activities before zoster: RR: 1.66 (0.99-2.79) Having another pain condition or other pre-zoster EQ-5D measures not selected for final model	Income, baseline ≥50,000 USD: $40K-49,999: RR: 2.24 (0.98-5.13) $20K-39,999: RR: 1.77 (0.87-3.63) <$20K: 1.85 (0.89-3.83) Working status or education not selected for final model	Severe acute pain at zoster: RR: 2.06 (0.98-4.35) Prodrome and its duration reported, plus pain interference score not selected for final model	Number of lesions dermatome affected not selected for final model	Delay between recruitment and rash onset not selected for final model	Antiviral treatment, timing of antiviral treatment and other medications not selected for final model
Hannpaa et al.[19]	Per year increase: 1.06 (1.00-1.09) Gender: OR not reported (no association in univariate analysis)	—	—	—	Moderate/severe acute pain: OR not reported (no association in univariate analysis) Brush-evoked allodynia: 5.89 (1.50-23.1) Stretch-evoked allodynia: 4.13 (0.98-17.50) Compression-allodynia: OR not reported Prodrome not selected for final model	Severity and localization of rash: ORs not reported (neither associated in univariate analysis)	—	Pinprick hypesthesia: 7.72 (2.00-29.90) Antiviral use, analgesic use not selected for final model

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Helgason et al.[21]	Per 10 y increase: 2.11 (1.56-2.84) Gender not selected for final model	—	—	—	—	—	—	—
Jih et al.†[23]	≤60 vs >60 y: RR: 2.34 (2.17-2.53) F vs M: RR: 0.95 (0.89-1.03)	Lymphoma/leukaemia: RR: 1.74 (1.32-2.28) HIV/AIDs: RR: 0.48 (0.26-0.86)	Diabetes: RR: 1.35 (1.25-1.47) Breast cancer: RR0: 0.75 (0.53-1.06) Liver cancer: RR: 0.86 (0.65-1.15) SLE: RR: 2.27 (1.75-2.94)	—	—	—	—	—
Jung et al.[25]	Per year increase: 1.03 (1.01-1.05) F vs M: 2.01 (1.28-3.16)	—	—	—	Presence of a prodrome: 2.75 (1.18-6.38) Severe acute pain: 2.12 (1.35-3.32)	Severe rash: 3.00 (1.88-4.81) Primary involvement of the trigeminal dermatome, number of affected dermatomes, presence of affected nonadjacent dermatomes not selected for final model	Rash duration, continuous variable 0-24 h, 24-48 h, 48-72 h: 0.84 (0.64-1.11)	Clinical trial sample: 2.53 (1.61-3.99)
Kanbayashi et al.‡[26]	Per year increase in age group (<50, 51-74, ≥75): 2.74 (1.10-6.76) Gender not selected for final model	—	Diabetes: 3.08 (0.79-11.95) Sleep disorder: 1.16 (0.42-3.17) Hypertension, angina, autoimmune disorders, malignant tumour not selected for final model	—	Prodromal pain: 1.55 (0.55-4.41) Allodynia: 0.82 (0.24-2.81) Pain reduced by bathing: 3.39 (0.79-14.60) Deep pain: 4.24 (1.11-16.16) Breakthrough pain: 1.99 (0.62-6.42)	Localization not selected for final model	Period of onset (in days) not selected for final model	—

(*continued on next page*)

Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Katz et al.[27]	Per y increase: 1.07 (1.01-1.12)	Immunosuppression (undefined, however, included HIV, currently being treated for cancer or high-dose corticosteroids): 1.59 (0.07-5.04)	Poorer physical health, continuous variable summing total number of medical conditions‡: 1.11 (0.93-1.32)	Race, education, marital status not selected for final model	Prodrome: 2.21 (0.54-9.15)	Localization not selected for final model	Zoster duration, per day: 0.97 (0.88-1.07)	—
	Gender not selected for final model		Personality disorder symptoms, per symptom increase: 1.09 (1.01-1.18)		Zoster interferes with role functioning: 2.34 (1.34-4.08)			
			Health locus of control, disease conviction, hypochondriasis, premorbid physical, role, and social functioning before zoster onset, depression, and anxiety symptoms not selected for final model		Acute pain intensity, 0-10 composite score§ continuous variable: 0.95 (0.69-1.32)			
					Somatosensory amplification and somatic symptoms not selected for final model			
Kotani et al.[28]	Per 10 y increase: 2.2 (1.1-4.5)	—	Diabetes, malignancy, or autoimmune disease not selected for final model	—	Prodrome: OR not reported	Localization not selected for final model	—	Cerebrospinal fluid interleukin 8 concentrations at healing of herpetic rash (per 20-μg/L increase: 1.8 (1.4-2.3)
	Gender not selected for final model				Acute pain: OR not reported	Severity of skin rash: OR not reported		
Opstelten et al.[33]	≤54: 1.00	—	Diabetes: 1.7 (0.5-6.2)	Consultation frequency not selected for final model	Painful prodrome: 1.2 (0.3-5.6)	Localization, ophthalmic vs not: 2.2 (0.8-6.5)	—	Chronic analgesics use not selected for final model
	55-74: 5.4 (1.1-26.5)		Psycho-pharmaceuticals uses 1.4 (0.·3-5.6)					

(*continued on next page*)

Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
	≥75: 19.7 (4.3-90.9)		Chronic obstructive pulmonary disease, rheumatoid arthritis, SLE, psychological problem or corticosteroid use at zoster diagnosis not selected for final model					
	F vs M: 1.0 (0.9-1.0)							
Opstelten[35]	Per y: 1.08 (1.04-1.12)	—	Trust in health care score, 1 unit increase from 0-100 (higher score relates to lower trust): 1.01 (1.00-1.03)	—	Severity of acute pain, per VAS unit: 1.02 (1.01-1.03)	Severe rash, ≥43 vesicles: 2.31 (1.16-4.58)	Duration of rash before consultation, in days: 0.78 (0.64-0.97)	Use of antivirals, VZV antibodies (IgM, IgA, IgG), VZV viremia not selected for final model
	Gender not selected for final model		Psychological predictors including anxiety disposition not selected for final model					
Park et al.[37]	≥60 vs <60 y: 8.50 (1.17-61.60)	—	—	—	VAS for pain, ≥5 vs <5: 4.78 (0.78-29.33)	Localization not selected for final model	Onset of rash, >3 d vs ≤3 d: 0.53 (0.08-3.28)	Temperature differences between normal and affected skin: <0.5°C (baseline) 0.5°C-1.0°C: 8.25 (1.06-64.40) >1.0°C: 30.26 (1.68-544.06) % body surface area with thermal asymmetry^2, ≥3 vs <3%: 8.25 (0.24-12.38)
	F vs M: 0.73 (0.13-4.24)							
Parruti et al.[38]	Per 10 y increase: 1.01 (0.99-1.02)	HIV not selected for final model	Trauma at site of lesion:2.53 (1.37-4.65)	Current/former smoking: 2.08 (1.22-3.55)	Intense/very intense pain at presentation: 2.19 (1.32-3.65)	Site of lesions and severity of rash not selected for final model	—	Antiviral use and NSAIDs not selected for final model
	F vs M: 1.39 (0.84-2.30)		Surgical intervention at site of lesion: 1.33 (0.79-2.25)	Alcohol abuse, familial status, educational level not selected for final model				

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
			HCV infection, hypertension, diabetes, neoplasm, neurological disorders, psychiatric illness, allergy, or family history of major cardiovascular events, malignancies, neurological diseases, major depression not selected for final model					
Volpi et al.[46]	>50 y vs ≤50: 2.58 (1.33-4.98)	—	—	Years of education not selected for final model	Duration of prodromal pain (≤3 vs >3 d): 0.49 (0.24-0.99)	Extent of rash: (>1 vs 1 dermatome): 2.27 (1.16-4.55)	—	Antiviral therapy: 0.51 (0.10-2.50)
	Gender not selected for final model				Intensity of pain using the Short Italian questionnaire, from 0-10 continuous variable: 1.17 (1.02-1.34)	Localization of rash not selected for final model		Abnormal sensations: 1.11 (1.02-1.34)
					Presence of prodromal pain not selected for final model			
Wozniak et al.[50]	—	—	—	APOE-ε3: 4.98 (1·88-13.23) APOE-ε4:0.25 (0.09-0.7) (females only—no effect among males)		—	—	—
Case-base studies—risk factor: prevalence ratio (95% CI)								
Choo et al.‖[8]	Per y: 1.12 (1.06-1.18)	Connective tissue disease, HIV infection or organ allograft: 9.5 (2.0-45.9)	Diabetes: 2.7 (0.4-17.·9)	Number of encounters previous 180 d: 0-2 (reference)	Prodromal symptoms: 3.4 (1.3-9.1)	Thoracic (reference), Cranial nerve V: 1.7 (0.3-9.3), Cervical: 1.1 (0.3-4.5), Lumbar/sacral: 0.6 (0.2-2.0)	—	Acyclovir exposure after rash onset, days (baseline is no exposure): 0-3: 1.0 (0.4-2.6)
	F vs M: 0.9 (0·4-2.3)		Cancer: 0.1 (0.02-0.9)	3-4: 0.3 (0.1-0.9)	Interference of pain on activities on daily living: 1.3 (0.4-4.2)	Complications (baseline is none): Superinfection: 1.9 (0.5-7.6), Ocular: 2.1 (0.7-6.3), Oticus/TIA from vasculitis/motor neuropathy: 0.6 (0.2-2.0)		4-30: 1.0 (0.3-4.0)

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Table 2 (*continued*)

Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
Age and gender	Severe immune suppression	Other physical or psychological comorbidities	Other risk factors	Pain (including prodrome)	Rash extent and location	Rash duration	Other
		Corticosteroid exposure before zoster: 1.4 (0.3-6.0)	5-7: 0.4 (0.1-1.4) >7:0.9 (0.4-2.3)				Corticosteroid exposure after zoster, 0-30 d vs none: 0.7 (0.2-2.6) Cytotoxic chemotherapy 180 d pre-zoster not selected for final model

Please note: reference category listed last.
All risk factors included in the final multivariable model are listed, unless otherwise specified.
*Adjusted for age and gender only.
†Thermal aysnmmetry index measures impairment of thermal sensation of affected vs unaffected side, vibratory asymmetry index measures impairment of vibration perception of affected vs unaffected side.
‡ Physical Health measured using the Life Stressors and Social Resources Inventory, which sums the total number of patient reported medical conditions.
§composite score ranges from 0-100 numerical pain ratings and McGill Pain Questionaire Present Pain Intensity ratings of average and worst shingles pain.
‖ Adjusted for age (continuous variable), presence (yes or no) of prodromal symptoms, severe pain, or comorbid conditions; and number of health care encounters.
APOE, alipoprotein E; DN4, Neuropathic pain questionnaire with 4 questions; EQ-5D, questionnaire on zoster pain and health-related quality of life; HCV, Hepatitis C virus; NPSI, neuropathic pain symptom inventory score; RR, rate ratio; SF-12, short-form 12; SLE, systemic lupus erythematosus; VAS, visual analogue scale, ranging from 0 (nonpain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; y, year; ZBPI, zoster brief pain inventory interference score.
¶ PCS, physical component summary score, MCS, mental component summary score (a patient reported survey of physical/mental health using short form 12 (SF-12); score <50 represented below-average health status).
#Study used ordered logistic regression, therefore the parameters represent the exposure ORs for being the highest outcome categories, compared with the lowest outcome categories: it is assumed the effect of exposure is the same for all splits of the outcome categories.

more than twice as likely to develop PHN (adjRR: 2.27, 95% CI: 1.75-2.94).[23] Another smaller study (N = 837) using electronic medical records from the Netherlands collected data on lupus and rheumatoid arthritis; however, they were not included in the final model (numbers not reported).[33]

3.3.4.3. Diabetes

Three cohort studies reported point estimates for the association between diabetes and PHN ≥1 in multivariable analyses; however, there was insufficient evidence to confirm an association.[8,26,33] A larger cohort study among 34,280 patients with zoster did find evidence of an increased risk (adjRR: 1.35, 95% CI: 1.25-1.47).[23] There was no evidence of between-study heterogeneity for studies reporting age-adjusted diabetes effects ($P_{heterogeneity}$ = 0.564; I^2 = 0.0%); the pooled effect estimate was 1.36 (95% CI: 1.25-1.47) in the fixed effect meta-analysis; however, the large study (N = 34,280) dominated the pooled relative risk (contributing 99.1% to the model).

3.3.4.4. Cancer

Five studies investigated cancer and its relationship with PHN; 3 excluded it from the final model.[26,28,38] Breast and liver cancer were investigated in a single study, but were not associated with PHN in the final adjusted model.[23] The case-base study found 13.5% of PHN cases and 4.7% of non-PHN controls had a cancer diagnosis 180 days before zoster[8]; after adjustment, cancer was associated with a reduced risk of PHN (adjOR: 0.1, 95% CI: 0.02-0.9); however, the CIs were wide. A meta-analysis for cancer effect estimates was not conducted as they involved different cancer sites.

3.3.4.5. Recent physical trauma

The only study to investigate this risk factor reported over 2-fold increased risk of PHN associated with experiencing trauma at the zoster site (contusions, burnings, wounds, and multiple traumas) within 6 months before study enrolment.[38]

3.3.4.6. Other

Other physical conditions investigated as predictors of PHN, but not included in the age-adjusted models included surgical intervention,[38] hepatitis-C virus infection,[38] hypertension,[26,38] neurological disorders,[38] allergy,[38] family history of coronary heart disease,[38] angina,[26] and chronic obstructive pulmonary disorder.[33]

3.3.5. Psychological comorbidities

These were assessed as risk factors for PHN in 4 studies. Two cohort studies assessed a range of psychological comorbidities; only personality disorder symptoms (adjOR: 1.09, 95% CI: 1.01-1.18),[27] and lower levels of trust in health care (adjOR: 1.01, 95% CI: 1.00-1.03)[35] showed a small association with PHN in multivariable analyses. Neither depression nor anxiety was included in multivariable analyses.[5,27,35,38]

3.3.6. Other risk factors

A cohort study found alipoprotein E-ε3 was more common and alipoprotein E-ε4 less common among female patients with zoster and PHN, suggesting that this host genetic factor may influence the risk of PHN.[50] One study found evidence that current/former smoking was associated with greater risk of PHN (adjOR: 2.08, 95% CI: 1.22-3.55)[38] whereas another included it in their final model, but did not report the association.[2] One study suggested a low state of varicella zoster virus (VZV)-specific

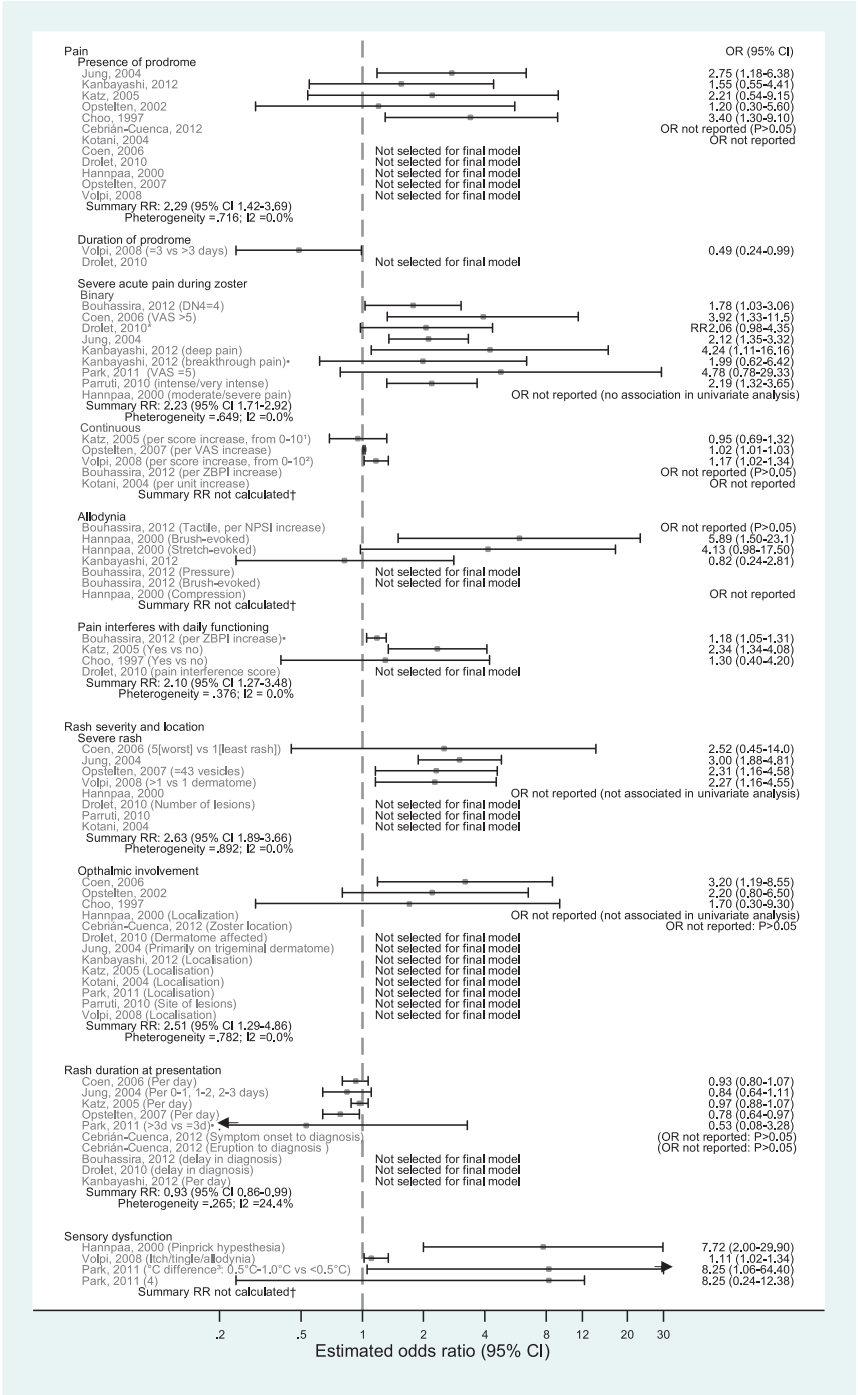

Figure 2. Summary of associations between postherpetic neuralgia and clinical features of acute zoster. [1]Composite score ranges from 0-100 numerical pain ratings and McGill Pain Questionnaire Present Pain [2]Intensity ratings of average and worst shingles pain. Intensity of pain using the Short Italian questionnaire, from 0-10. [3]Temperature differences are between normal and affected skin. [4]Percentage of body surface area thermal asymmetry (≥3 vs <3%). †Risk factors too varied to combine in meta-analyses. •Not included in summary RR (either because study has already contributed to meta-analysis, or exposure definition is not in-keeping with other studies). *Studies reporting RR (rather than OR) are not included in meta-analysis. CI, confidence interval; DN4, Neuropathic pain questionnaire with 4 questions; NPSI, Neuropathic pain symptom inventory score; OR, odds ratio; RR, rate ratio; SF-12, short-form 12; VAS, visual analogue scale ranging from 0 (non pain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; ZBPI, Zoster brief pain inventory interference score.

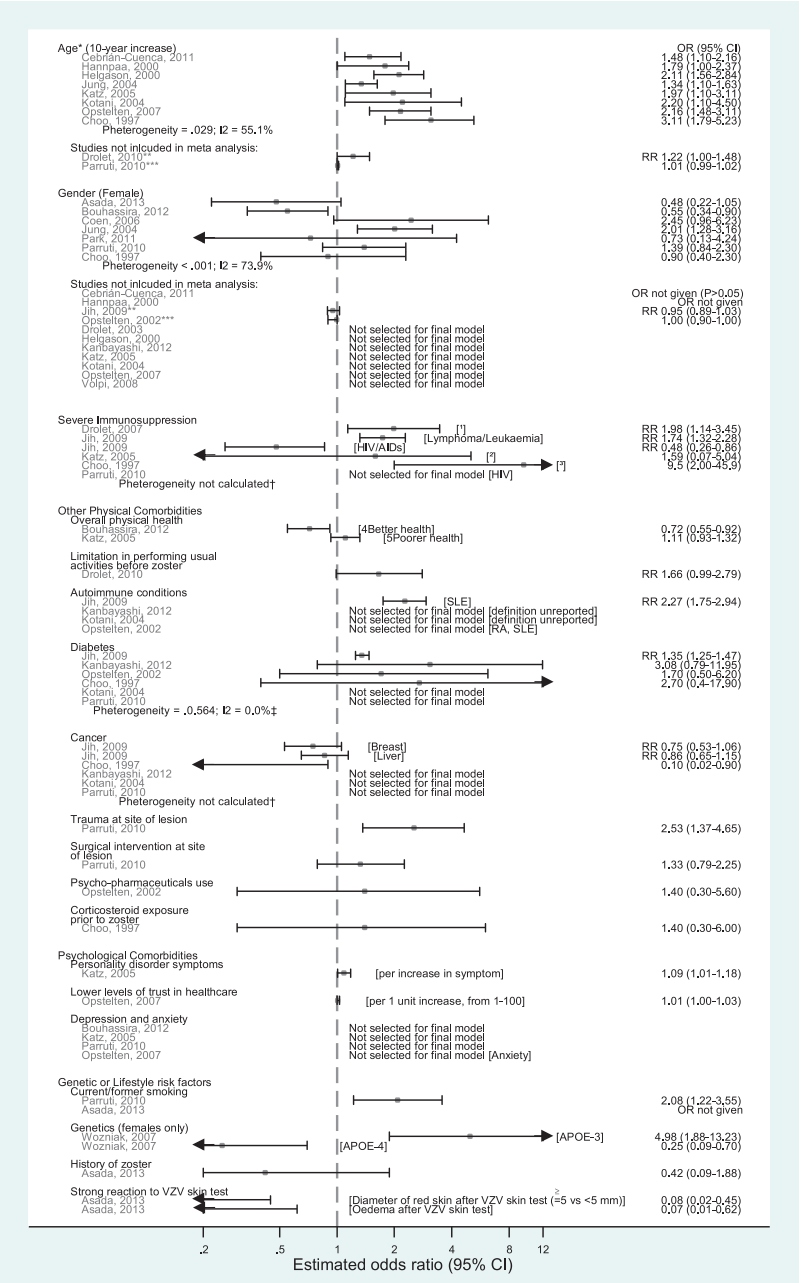

Figure 3. Summary of associations between postherpetic neuralgia and vaccine-targetable risk factors from identified studies. *Only 10/20 studies reported age such that the effect estimate could be converted into 10-year increases. Of the remaining 10 studies; 8 reported an increased risk of PHN with greater age, 1 showed no effect all, and 1 did not report an age-effect. **Studies reporting RRs rather than ORs not included in meta-analysis as RR can underestimate OR when outcome becomes common. ***Effect estimate from study may be erroneous therefore the study is not included in the meta-analysis: Parruti 2010 CIs are too narrow, and Opstelten 2002 confidence also too narrow. [1]Using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS. [2]Undefined, however included HIV or currently being treated for cancer. [3]Connective tissue disease, HIV infection or organ allograft. [4]Better health: measured using continuous physical component summary score (higher scorer score reflects worse health). [5]Poorer health: measured using continuous variable of total number of medical conditions. †Risk factors too varied to combine in meta-analyses. ‡The large study by Jih et al. (N = 34,280) dominated the pooled relative risk contributing to 99·1% of the model. Other risk factors investigated as predictors of PHN, but not included in the final model, included; surgical intervention, hepatitis-C virus infection, hypertension, neurological disorders, allergy, family history of CHD, angina, chronic obstructive pulmonary disorder, education, alcohol abuse, familial status, years of education and race. APOE, alipoprotien E; CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; RR, rate ratio; SLE, systemic lupus erythematosus.

Table 3

Assessment of bias for individual studies (◆= High risk, ■= Medium risk, O=Low /no risk or ?=Unclear risk).

Type of bias	Confounding	Selection bias	Exposure information bias	Outcome (PHN) information bias		Bias due to missing data
	Residual confounding by age	Loss to follow-up	Nondifferential misclassification	Reporting bias	Nondifferential misclassification	Missing exposure data
Asada et al.[2]	O	O	O	O	?	◆
Bouhassira et al.[5]	◆	■	O	O	?	?
Cebrián-Cuenca et al.[6]	O	■	O	O	?	O
Coen et al.[9]	◆	O	?	O	?	?
Drolet et al.[12]	O	O	O	O	?	■
Haanpaa et al.[19]	O	■	O	■	?	?
Helgason et al.[21]	O	O	O	O	?	O
Jih et al.[23]	◆	?	?	◆	◆	?
Jung et al.[25]	O	■	O	O	?	O
Kanbayashi et al.[26]	◆	O	◆	?	◆	O
Katz et al.[27]	O	O	■	■	?	O
Kotani et al.[28]	O	O	?	?	?	?
Opstelten et al.[33]	◆	O	O	◆	◆	■
Opstelten[35]	O	O	O	O	?	■
Park et al.[37]	◆	O	?	?	?	?
Parruti et al.[38]	O	O	O	O	?	■
Volpi et al.[46]	◆	◆	O	O	?	■
Wozniak et al.[50]	O	?	O	?	?	O
Choo, 1997[8]	O	O	O	■	■	■

PHN, Postherpetic neuralgia.

cell-mediated immunity, evidenced from reduced response to VZV skin-test, was associated with greater risk of PHN.[2] Studies investigating education,[13,27,38,46] race,[27] being married,[5,27,38] being in work,[13] consultation rate,[8,33] or alcohol abuse[38] did not select these risk factors in their final model.

Nine of the 19 studies had 2 or more definitions of PHN. Briefly, studies additionally defined PHN as pain at 1[6,8,13,21,33,35,38] (n = 7) and 6 months[9,21,28] (n = 3) after zoster onset; there were no major differences in study findings using these alternative definitions, except older age was a stronger risk factor for pain persisting 6 months, compared with 2 or 3 months, after zoster (Appendix Table A3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132), indicating older age may be a risk factor for long-term PHN.

3.4. Assessment of bias

Our assessment of bias found 8/19 studies with at least 1 prespecified domain with a high risk of bias, 8 studies with at least 1 domain of medium risk, and 3 studies with only low or unclear risk of bias. Residual confounding by age was the most common source of potential bias, affecting 7/19 studies requiring age-adjustment (**Table 3**). Studies using electronic health care records were at greatest risk of reporting bias; specifically ascertainment bias, where outcome ascertainment relies on patients returning to their GP and higher general practice (GP) attendance could have increased the chance of PHN diagnosis.[8,23,26,33] Of the cohort studies, 5 experienced loss to follow-up of greater than 10% (**Table 3**). See Appendix Table A4 for detailed note on the bias assessment (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

The funnel plot gave a relatively symmetric pattern, suggesting that there was little indication of publication bias (**Fig. 4**). The distribution did not suggest that more extreme findings were being selectively published.

The sampling methods and patient characteristics of some studies suggest their external validity may be limited; characteristics of included patients indicate a nonrepresentative sample in some studies (Coen et al. reported that 20% of the study population was immunosuppressed[8] and in 3 studies over 30% of the cohort developed PHN[28,46,50]); 1 study used convenience sampling,[6] thus not all population members had an equal probability of being selected; and the number or characteristics of eligible patients refusing to participate were unclear in most studies.

4. Discussion

4.1. Summary of evidence

Our systematic review identified 19 prospective studies investigating risk factors for PHN. There was good evidence that clinical features of acute zoster including prodromal pain, severe

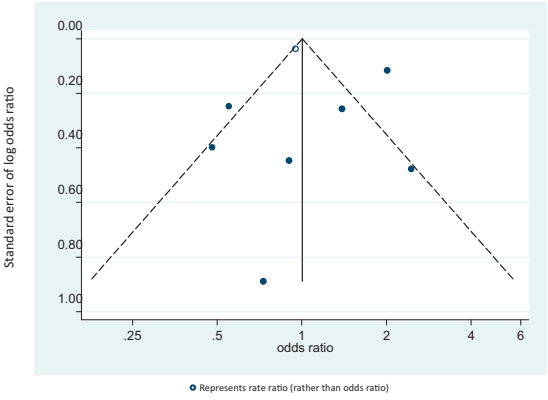

Figure 4. Assessment of publication bias for gender as a risk factor for postherpetic neuralgia. Funnel plot of the log odds ratio plotted against the standard error of the log odds ratio for seven studies reporting the effect of female gender on PHN risk (dotted line represents pseudo 95% confidence limits).

acute pain, severe rash, and ophthalmic involvement were associated with increased risk of PHN. Rash duration at zoster presentation was less strongly associated with PHN. Regarding vaccine-targetable risk factors, older age was consistently associated with PHN. The evidence for gender as a risk factor was conflicting. Immunosuppression and diabetes were significantly associated with PHN in a few, but not all studies. Systemic lupus erythematosus, recent trauma, and personality disorder symptoms were associated with PHN; however, evidence came from single studies only. No studies found evidence suggesting that depression or cancer was associated with increased risk of PHN. Most studies had small sample sizes reducing their power to detect associations. Our review highlights that we have a good understanding of which clinical features of zoster predict PHN, yet there is a need for better evidence on common and potentially easily vaccine-targetable risk factors for PHN prevention.

4.2. Interpreting the findings

It is believed that several pathophysiological mechanisms may contribute to the development of PHN. Acute zoster infection undoubtedly results in nerve damage to both the peripheral and central nervous system, yet the nature of the damage and specific mechanism resulting in persistent pain are not fully understood.[4] There are 2 (nonmutually exclusive) hypotheses for its development; the first is that persistence of VZV after acute zoster, at higher levels than during latency, causes continued pain; and the second, that after acute zoster infection, there is increased neuronal excitability and alteration of pain perception caused by neural damage.[1,20]

The variety of possible risk factors for PHN identified in the review may reflect these different mechanisms.[3] The finding that greater rash severity and greater acute pain are associated with increased risk of PHN supports the notion that greater neural damage caused by more severe infection contributes to the development of PHN.[15] That longer rash duration was associated with reduced risk of PHN initially seems inconsistent with the finding that more severe zoster rash is associated with PHN. However, late presentation might indicate patients had milder zoster not immediately demanding medical attention. Either way, this finding is unlikely to be due to the duration of the rash itself. Patients with ophthalmic zoster seem at greater risk of PHN, although it is not clear whether concerns about eye complications cause them to react differently, rather than the increased risk being driven by a biological mechanism.[20] Ageing undoubtedly causes a waning of cell-mediated immunity and may cause increased levels of the virus after zoster reactivation, potentially causing PHN. Other risk factors for PHN identified here are also associated with reduced cell-mediated immunity, including severe immunosuppression, systemic lupus erythematosus, and smoking. Trauma at the site of the rash may induce local changes facilitating reactivation of herpes zoster (HZ) and greater nerve damage leading to increased risk of PHN. However, the aetiological mechanism(s) by which these risk factors affect the development of PHN remains largely unknown.

4.3. Limitations of the selected studies

The included studies had some limitations. Many had small sample sizes, and we were unable to combine some results in a meta-analysis. Furthermore, many tested a number of risk factors; the associations observed may occur by chance due to testing multiple exposures. Most studies based zoster diagnosis on clinical opinion rather than serological or virological testing; this may have led to misclassification of patients with zoster; however, clinical diagnosis is typically reliable.[34]

Some studies may have been affected by specific biases. Age is a very strong predictor of PHN and yet 7/18 studies assessing age adjusted for it as a binary or categorical variable with wide age intervals, potentially causing residual confounding by age. Loss to follow-up affected 5/19 studies, and if loss to follow-up is associated with both PHN and the risk factor, bias could have been introduced.[18] Patients with PHN may be more likely to return for follow-up as they require continued care, and patients with particular risk factors may also return to their GP more commonly, making bias due to loss to follow-up likely. Ascertainment bias may have affected studies using routinely collected health care data. Here, spurious associations between PHN and medical conditions requiring regular contact with health care professionals may arise. One such study adjusted for health care utilisation[8] and still found a positive association with PHN and certain immunosuppressive disorders, suggesting the effect cannot be driven solely by ascertainment bias. Finally, not all studies adjusted for clinical features of the acute zoster episode,[2,21,23] and results may be subject to residual confounding.

4.4. Strengths and limitations of the review

This is the first study to systematically review the literature on risk factors for PHN; although clinical features of acute zoster have been acknowledged as risk factors for PHN, this is the first to summarise age-adjusted results and pool them in a meta-analysis. We undertook a comprehensive search of several databases using multiple keywords and indexed subject headings. The reliability of study selection criteria was confirmed by double screening of 10% of the articles.

There are some important limitations to this review. There is no consensus over the exact definition of PHN; in this review, PHN definitions ranged from pain persisting 1 to 6 months after rash onset, with some studies assessing *any* pain, whereas others required severe pain. A full assessment of risk factors by different PHN classifications was not possible here because of too few studies.

Between-study variability prevented us from pooling the effects of age and gender on PHN; there was some evidence that age of the study population contributed to the observed heterogeneity. However, these analyses were limited by the small number of studies and may have reduced our power to detect associations. Variability may be due to different adjustment for confounders or some studies reporting biased effect estimates, eg, due to PHN measurement error or loss to follow-up. Studies also used different definitions for certain clinical features of acute zoster, such as severe acute pain and severe rash, potentially giving some heterogeneity to the results.

Our search strategy may have missed some studies; however, we used multiple databases (including grey literature) and searched reference lists of selected articles, to minimise this issue. As with any literature review, studies finding no effects may have gone unpublished. Our funnel plot did not demonstrate any evidence of publication bias with respect to assessing gender as a risk factor for PHN. However, publication bias may affect other risk factors differently, and there were not enough studies per risk factor to assess this for other exposures. Finally, non–English-language articles were excluded because of resource limitations; however, the authors believe it is unlikely to have led to the omission of any major articles in the area.

4.5. Implications

Zoster vaccination offers a way of preventing this debilitating complication by preventing zoster itself, but is currently

expensive; therefore, targeting the vaccine toward groups at high-risk of PHN may be beneficial. The vaccine is currently licensed in certain countries in the European Union, United States, and Australia.[49] It is targeted at older age groups and contraindicated in patients with severe immunosuppression. As older age is the only indisputable risk factor that vaccination policies can use, this approach seems reasonable. If patients with severe immunosuppression are at increased risk of PHN as suggested by this review, in addition to being at greater risk of zoster itself, there is even more need to identify alternative strategies to prevent zoster in these groups.

This review has highlighted our lack of understanding of vaccine-targetable risk factors for PHN, and the need to perform studies exploring suggested associations. Such studies would need to be generalizable to a wide group, by recruiting patients aged 18 and over and including immunosuppressed patients, to examine the risk of PHN by age and immunosuppression status. Other desirable features would include recruiting a large number of individuals to achieve greater power to help detect small effects, collecting data on all known and possible risk factors for PHN, actively following up patients with zoster to allow persistent pain to be identified for the entire cohort at the same time and reducing loss to follow-up to avoid differential ascertainment of PHN. Finally, at the analysis stage, detailed adjustment for age using either a continuous or finely categorised age variable would reduce residual confounding by age.

5. Conclusions

This study confirms that features of the acute zoster episode, including prodromal pain, severe rash, severe acute pain, and ophthalmic involvement are risk factors for PHN. Our current understanding of vaccine-targetable risk factors for PHN is however limited. There are some suggestions that immunosuppression, systemic lupus erythematosus, diabetes, and recent trauma may be associated with greater risk of PHN. Increasing age is the only established risk factor for PHN that has been quantified with sufficient rigour as to usefully inform vaccine policy. Larger studies with greater power to detect associations, and studies addressing the limitations of previous research, may elucidate some of the unknown risk factors for PHN.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The funding source had no role in the study design; data collection, analysis, or interpretation of the data or writing of the report. H. J. Forbes has access to all studies identified from the initial search. The corresponding author has full access to all the data in the study and had final responsibility for the decision to submit for publication.

The authors do not have a commercial or other association that might pose a conflict of interest.

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Appendix A. Supplemental Digital Content

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6.3. Published appendices

Data extraction details

The following data were extracted for the selected studies by HF; study characteristics including, study design, country and year(s) of study, study size, study population (including mean age and range), definition and method of ascertaining zoster cases, risk factors assessed and how they were ascertained, definition and method of ascertaining PHN, % with PHN, and statistical analysis. We extracted all study results from the final age-adjusted model, including the multivariable effect estimates when available (e.g. adjusted relative risks (RR), or odds ratios (OR) with 95% confidence intervals (CI)) and any other relevant analysis (such as sub-group analysis or investigation of effect modification).

Risk of bias assessment details

The risk of bias was assessed separately for each study using the following pre-specified domains; residual confounding by age, selection bias, exposure and outcome information bias and bias due to missing data. We formulated our assessment based on the Cochrane Collaborations approach, where domains are categorised as having; “High risk” (bias may alter the results seriously), “Medium risk” (bias may alter the results moderately), “Low/No risk” (bias, if present, is unlikely to alter the results seriously) or “Unclear risk” (a risk of bias that raises some doubt about the results). Support for each judgement of risk is provided in the appendix (Table A3).

Letter to authors

Dear *[author name]*

I am carrying out a systematic review of studies investigating risk factors for postherpetic neuralgia (PHN). This is part of my PhD on zoster epidemiology, and we also aim to publish the review as a paper. I have identified the studies to be included in the review, one of which is the following study in which you are listed as corresponding author:
[*Reference*]

I am now extracting data from study reports to summarise in the review. I would be most grateful if you could clarify a few points (listed below) regarding your methods and results?
[Specific questions]

Your help would be greatly appreciated as I am keen to summarise your study as accurately and completely as possible.

Many thanks
Harriet

Table A1: Table of 97 studies excluded after full-text review.

Reason for exclusion	Author	Year	Title	Journal
PHN patients compared to non-zoster controls	G. H. G. Ashrafi, E.:Montague, P.:Forster, T.:Ross, A.:Ghazal, P.:Scott, F.:Breuer, J.:Goodwin, R.:Kennedy, P. G. E.	2010	Assessment of transcriptomal analysis of varicella-zoster-virus gene expression in patients with and without post-herpetic neuralgia	Virus Genes
	T. M. F. Battcock, R.:Barnes, R. M. R.	1990	Observations on herpes zoster: 1. Residual scarring and post-herpetic neuralgia; 2. Handedness and the risk of infection	British Journal of Clinical Practice
	D. Bosco, M. Plastino, M. De Bartolo, D. Cristiano, M. Ettore, G. Zurlo, F. Bosco, C. Colica, F. Tallarigo and A. Fava	2013	Role of impaired glucose metabolism in the postherpetic neuralgia	Clinical Journal of Pain
	J. Y. Chen, C. Y. Chang, P. H. Feng, C. C. Chu, E. C. So and M. L. Hu	2009	Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain	The Clinical journal of pain
	J. Y. Chen, C. C. Chu, Y. S. Lin, E. C. So, J. P. Shieh and M. L. Hu	2011	Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia	British Journal of Nutrition
	M. R. Clark, L. J. Heinberg, J. A. Haythornthwaite, A. L. Quatrano-Piacentini, M. Pappagallo and S. N. Raja	2000	Psychiatric symptoms and distress differ between patients with postherpetic neuralgia and peripheral vestibular disease	Journal of Psychosomatic Research
	M. E. G. Devlin, D. H.:Mahalingam, R.:Dueland, A. N.:Cohrs, R.	1992	Peripheral blood mononuclear cells of the elderly contain varicella-zoster virus DNA	Journal of Infectious Diseases
	A. Gatti, F. Pica, M. T. Y. Boccia, F. De Antoni, A. F. Sabato and A. Volpi	2010	No evidence of family history as a risk factor for herpes zoster in patients with post-herpetic neuralgia	Journal of Medical Virology
	A. Ozawa, Y. Sasao, K. Iwashita, M. Miyahara, J. Sugai, M. Iizuka, Y. Kawakubo, M. Ohkido, T. Naruse, T. Anzai, N. Takashige, A. Ando and H. Inoko	1999	HLA-A33 and -B44 and susceptibility to postherpetic neuralgia (PHN)	Tissue Antigens
	M. Sato, J. Ohashi, N. Tsuchiya, K. Kashiwase, Y. Ishikawa, H. Arita, K. Hanaoka, K. Tokunaga and T. Yabe	2002	Association of HLA-A*3303-B*4403-DRB1*1302 haplotype, but not of TNFA promoter and NKp30 polymorphism, with postherpetic neuralgia (PHN) in the Japanese population	Genes and Immunity
	D. Weitzman, O. Shavit, M. Stein, R. Cohen, G. Chodick and V. Shalev	2013	A population based study of the epidemiology of Herpes Zoster and its complications	Journal of Infection
	D. S. Weitzman, O.:Cohen, R.:Chodick, G.:Shalev, V.	2012	Epidemiology of herpes zoster and its complication: A population based study in Israel	Pharmacoepidemiology and Drug Safety

Table A1: (continued)

Article uses same data as study included in review	M. Bigby	2001	A population-based estimate of the prevalence of postherpetic neuralgia after herpes zoster	Archives of Dermatology
	D. Bouhassira, O. Chassany, J. Gaillat, G. Gavazzi, T. Hanslik, O. Launay, C. Mann, C. Rabaud, O. Rogeaux and C. Strady	2010	Increased burden of zoster and its complications in elderly people	European Geriatric Medicine
	M. B. Drolet, M.:Levin, M. J.:Schmader, K. E.:Oxman, M. N.:Johnson, R. W.:Camden, S.:Mansi, J. A.	2010	A prospective study of the herpes zoster severity of Illness	Clinical Journal of Pain
	M. L. Haanpaa, P. A. Laippala and T. J. Nurmikko	1999	Thermal and tactile perception thresholds in acute herpes zoster	Eur J Pain
	S. P. Helgason, G.:Gudmundsson, S.	2001	Post-herpetic neuralgia was not frequent or severe after a first episode of herpes zoster	Evidence-Based Medicine
	C. Rabaud, O. Rogeaux, O. Launay, C. Strady, C. Mann, O. Chassany, D. Bouhassira and J. Gaillat	2013	Early antiviral treatment fails to completely prevent herpes-related pain	Medecine et Maladies Infectieuses
PHN not an outcome	K. S. Ammer, T.:Melnizky, P.	2001	Thermal imaging in acute herpes zoster or post-zoster neuralgia	Skin Research and Technology
	K. R. F. Beutner, D. J.:Forszpaniak, C.:Andersen, P. L.:Wood, M. J.	1995	Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults	Antimicrobial Agents and Chemotherapy
	D. Bowsher	1992	Acute herpes zoster and postherpetic neuralgia: Effects of acyclovir and outcome of treatment with amitriptyline	British Journal of General Practice
	A. M. Cebrian-Cuenca, J. Diez-Domingo, M. S. Rodriguez, J. Puig-Barbera, J. Navarro-Perez and C. Herpes Zoster Research Group of the Valencian	2010	Epidemiology of herpes zoster infection among patients treated in primary care centres in the Valencian community (Spain)	BMC Family Practice
	U. Di Luzio Paparatti, F. Arpinelli and G. Visona	1999	Herpes zoster and its complications in Italy: An observational survey	Journal of Infection
	K. Galil, P. W. Choo, J. G. Donahue and R. Platt	1997	The sequelae of herpes zoster	Archives of Internal Medicine
	N. Haas, E. Holle, B. Hermes and B. M. Henz	2001	Acute herpes zoster neuralgia: Retrospective analysis of clinical aspects and therapeutic responsiveness	Dermatology
	K. M. Higa, M.:Hirata, K.:Hori, K.:Manabe, H.:Dan, K.	1997	Severity of skin lesions of herpes zoster at the worst phase rather than age and involved region most influences the duration of acute herpetic pain	Pain
	K. N. Higa, B.:Manabe, H.:Sato, S.:Dan, K.	1992	T-lymphocyte subsets in otherwise healthy patients with herpes zoster and relationships to the duration of acute herpetic pain	Pain
	H. Manabe, K. Dan and K. Higa	1995	Continuous epidural infusion of local anesthetics and shorter duration of acute zoster-associated pain	Clinical Journal of Pain

Table A1: (continued)

	D. Moulin	2006	Does acute pain associated with herpes zoster respond to treatment with gabapentin?	Nature Clinical Practice Neurology
	E. M. J. Nagasako, R. W.:Griffin, D. R. J.:Dworkin, R. H.	2002	Rash severity in herpes zoster: Correlates and relationship to postherpetic neuralgia	Journal of the American Academy of Dermatology
	M. L. A. Quinlivan, K. L.:Kelly, P. J.:Parker, S. P.:Scott, F. T.:Johnson, R. W.:Maple, C.:Breuer, J.	2011	Persistence of varicella-zoster virus viraemia in patients with herpes zoster	Journal of Clinical Virology
	M. J. W. Zaal, H. J. Volker-Dieben and J. D'Amaro	2000	Risk and prognostic factors of postherpetic neuralgia and focal sensory denervation: A prospective evaluation in acute herpes zoster ophthalmicus	Clinical Journal of Pain
No risk factors of interest	P. G. M. Kennedy, P.:Scott, F.:Grinfeld, E.:Ashrafi, G. H.:Breuer, J.:Rowan, E. G.	2013	Varicella-zoster viruses associated with post-herpetic neuralgia induce sodium current density increases in the ND7-23 Nav-1.8 neuroblastoma cell line	PLoS ONE [Electronic Resource]
	A. Srebrnik, R. Brandsen and S. Brenner	1991	Corticosteroid treatment in the prevention of postherpetic neuralgia	Journal of Dermatological Treatment
	A. P. Winnie and P. W. Hartwell	1993	Relationship between time of treatment of acute herpes zoster with sympathetic blockade and prevention of post-herpetic neuralgia: Clinical support for a new theory of the mechanism by which sympathetic blockade provides therapeutic benefit	Regional Anesthesia
No effect estimates for risk factors of interest (including where the only risk factor was age, and the effect of age was not described as a continuous variable)	J. Bruxelle	1995	Prospective epidemiologic study of painful and neurologic sequelae induced by herpes zoster in patients treated early with oral acyclovir	Neurology
	A. Colding	1973	Treatment of pain: organization of a pain clinic: treatment of acute herpes zoster	Proceedings of the Royal Society of Medicine
	E. Epstein	1981	Treatment of herpes zoster and postzoster neuralgia by subcutaneous injection of triamcinolone	International Journal of Dermatology
	H. M. L. Oh, A. Y. L. Ho, S. K. Chew and E. H. Monteiro	1997	Clinical presentation of herpes zoster in a Singapore hospital	Singapore Medical Journal
	J. G. J. Pierik, P. D. Gumbs, S. A. C. Fortanier, P. C. E. Van Steenwijk and M. J. Postma	2012	Epidemiological characteristics and societal burden of varicella zoster virus in the Netherlands	BMC Infectious Diseases
	B. P. Yawn, P. Saddier, P. C. Wollan, J. L. St. Sauver, M. J. Kurland and L. S. Sy	2007	A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction	Mayo Clinic Proceedings
	R. Baron, G. Haendler and H. Schulte	1997	Afferent large fiber polyneuropathy predicts the development of postherpetic neuralgia	Pain

Table A1: (continued)

	H. Bricout, E. Perinetti, P. Marchettini, P. Ragni, C. Zotti, G. Gabutti, A. Volpi and E. Franco	2013	Predictor factors for the presence of post herpetic neuralgia at 3 months in herpes zoster patients aged 50 and over in Italy: Results from a gp-based observational prospective multicenter study	Value in Health
	G. R. Brown	1976	Herpes zoster: correlation of age, sex, distribution, neuralgia, and associated disorders	Southern Medical Journal
	R. H. Dworkin	2000	Prediction and prevention of postherpetic neuralgia	Pain Clinic
	E. Franco, E. Perinetti, P. Marchettini, P. Ragni, C. Zotti, G. Gabutti, A. Volpi and H. Bricout	2013	Proportion of post herpetic neuralgia among patients with herpes zoster in Italy-A multicenter prospective observational study	European Geriatric Medicine
	E. H. Garbe, K.:Kemper, L.:Reinhard, M.:Behr, S.:Schink, T.:Bricout, H.	2013	Incidence of herpes zoster herpes zoster related manifestations and complications in Germany-A retrospective cohort database study from 2005 to 2009	European Geriatric Medicine
	E. G. Granell, M.:Nunez, F.:Rius, C.:Catala, E.:De Juan Delago, M.:Gomez-Anson, B.	2013	Glial dysfunction may occur early in the brain of patients with neuropathic pain: A 1H-MRS study	Neuroradiology
	S. S. Han, C. H. Jung, S. C. Lee, H. J. Jung and Y. H. Kim	2010	Does skin temperature difference as measured by infrared thermography within 6 months of acute herpes zoster infection correlate with pain level?	Skin Research & Technology
	S. Imafuku, J. Nakayama, K. Higa, M. Furue, M. Takahara, I. Katayama and M. Tani	2013	One-year follow-up of zoster-associated pain in 764 patients with acute herpes zoster treated using famciclovir	Journal of Investigative Dermatology
	J. I. McGill and J. E. White	1994	Acyclovir and post-herpetic neuralgia and ocular involvement	BMJ
	W. Meister, A. Neiss, G. Gross, H. W. Doerr, W. Hobel, J. P. Malin, J. Von Essen, B. Y. Reimann, C. Witke and P. Wutzler	1998	A prognostic score for postherpetic neuralgia in ambulatory patients	Infection
	Z. R. Mok and H. H. Tan	2013	Herpes zoster: A review of cases seen at the National Skin Center, Singapore (2008-2010)	Journal of the American Academy of Dermatology
	C. Mondelli, S. Romano, P. Passerv, A. Delia Porta and P. Rossi	1996	Effects of acyclovir on sensory axonal neuropathy, segmental motor paresis and postherpetic neuralgia in herpes zoster patients	European Neurology
	S. D. Nithyanandam, S.:Stephen, J.:Joseph, M.	2009	Eruption severity and characteristics in herpes zoster ophthalmicus: Correlation with visual outcome, ocular complications, and postherpetic neuralgia	International Journal of Dermatology
	M. L. A. Quinlivan, K.:Ran, H.:McElwaine, S.:Leedham-Green, M.:Scott, F. T.:Johnson, R. W.:Breuer, J.	2007	Effect of viral load on the outcome of herpes zoster	Journal of Clinical Microbiology

Table A1: (continued)

	J. M. Riopelle, M. Naraghi and K. P. Grush	1984	Chronic neuralgia incidence following local anesthetic therapy for herpes zoster	Archives of Dermatology
	R. S. Rogers, 3rd and J. P. Tindall	1971	Geriatric herpes zoster	J Am Geriatr Soc
	H. Yanagida, K. Suwa and G. Corssen	1987	No prophylactic effect of early sympathetic blockade on postherpetic neuralgia	Anesthesiology
Effect estimates for risk factors of interest are not age-adjusted (exclusion criteria not applied to studies on genetic risk factors)	D. S. Borkar, V. M. Tham, E. Esterberg, K. J. Ray, A. C. Vinoya, J. V. Parker, A. Uchida and N. R. Acharya	2013	Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study	Ophthalmology
	D. Bowsher	1999	The lifetime occurrence of Herpes zoster and prevalence of post-herpetic neuralgia: A retrospective survey in an elderly population	European Journal of Pain
	J. Decroix, H. Partsch, R. Gonzalez, H. Mobacken, C. L. Goh, J. B. Walsh, S. Shukla and B. Naisbett	2000	Factors influencing pain outcome in herpes zoster: An observational study with valaciclovir	Journal of the European Academy of Dermatology and Venereology
	R. H. Dworkin, R. J. Boon, D. R. G. Griffin and D. Phung	1998	Postherpetic neuralgia: Impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients	Journal of Infectious Diseases
	R. H. Dworkin, G. Hartstein, H. L. Rosner, R. R. Walther, E. W. Sweeney and L. Brand	1992	A high-risk method for studying psychosocial antecedents of chronic pain: The prospective investigation of herpes zoster	Journal of Abnormal Psychology
	I. B. Engberg, G. B. Grondahl and K. Thibom	1995	Patients' experiences of herpes zoster and postherpetic neuralgia	Journal of advanced nursing
	A. Gauthier, J. Breuer, D. Carrington, M. Martin and V. Remy	2009	Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom	Epidemiology and Infection
	L. E. Gialloreti, M. Merito, P. Pezzotti, L. Naldi, A. Gatti, M. Beillat, L. Serradell, R. di Marzo and A. Volpi	2009	Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: A retrospective, population-based study	BMC Infectious Diseases
	C. L. Goh and L. Khoo	1997	A retrospective study of the clinical presentation and outcome of herpes zoster in a tertiary dermatology outpatient referral clinic	International Journal of Dermatology
	M. Haanpaa, P. Dastidar, A. Weinberg, M. Levin, A. Miettinen, A. Lapinlampi, P. Laippala and T. Nurmikko	1998	CSF and MRI findings in patients with acute herpes zoster	Neurology
	M. H. Haanpaa, V.:Nurmikko, T.	1997	Motor involvement in acute herpes zoster	Muscle and Nerve
	M. Hadi Aziz Jalali, H. Ansarin and R. Soltani-Arabshahi	2006	Broad-band ultraviolet B phototherapy in zoster patients may reduce the incidence and severity of postherpetic neuralgia	Photodermatology Photoimmunology and Photomedicine
	S. P. Harding, J. R. Lipton and J. C. Wells	1987	Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement	Br J Ophthalmol

Table A1: (continued)

	K. Hillebrand, L. Kemper, R. Schulze-Rath, T. Schink and E. Garbe	2013	Incidences of herpes zoster, its manifestations and complications for 2005-2009 in Germany-a retrospective cohort study	Pharmacoepidemiology and Drug Safety
	R. E. Hope-Simpson	1975	Postherpetic neuralgia	The Journal of the Royal College of General Practitioners
	M. Kolsek	2012	TENS - an alternative to antiviral drugs for acute herpes zoster treatment and postherpetic neuralgia prevention	Swiss Medical Weekly
	J. S. H. A. Koopman, J. P. Dieleman, F. J. Huygen, M. de Mos, C. G. M. Martin and M. C. J. M. Sturkenboom	2009	Incidence of facial pain in the general population	Pain
	I. Kurokawa, K. Kumano and K. Murakawa	2002	Clinical correlates of prolonged pain in Japanese patients with acute herpes zoster	Journal of International Medical Research
	I. Kurokawa, K. Murakawa and K. Kumano	2007	The change in zoster-associated pain treated with oral valaciclovir in immunocompetent patients with acute herpes zoster	International Journal of Clinical Practice
	W. Lapolla, C. DiGiorgio, K. Haitz, G. Magel, N. Mendoza, J. Grady, W. Lu and S. Tyring	2011	Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: Open-label study	Archives of Dermatology
	J. P. Malin	1993	A retrospective and an observational study with acyclovir	Journal of medical virology
	S. C. Martin, V.:Gabriele, W.:Jennifer, L.:Andreas, B.:Birgitt, G.:Karin, K.	2012	Intravenous vitamin C in the treatment of shingles	European Journal of Integrative Medicine
	S. Ogawa, H. Suzuki, H. Saitoh, S. Saeki, J. Katoh, Y. Noda, T. Nakamura, K. Noda and T. Suzuki	1993	Risk factors for developing post-herpetic neuralgia: A retrograde analysis of 232 patients	Pain Clinic
	Petersen, K. L.:Rowbotham, M. C.	2010	Natural history of sensory function after herpes zoster	Pain
	M. W. Ragozzino, L. J. Melton, 3rd, L. T. Kurland, C. P. Chu and H. O. Perry	1982	Population-based study of herpes zoster and its sequelae	Medicine
	V. S. Schafer, T. A. Kermani, C. S. Crowson, G. G. Hunder, S. E. Gabriel, S. R. Ytterberg, E. L. Matteson and K. J. Warrington	2010	Incidence of herpes zoster in patients with giant cell arteritis: A population-based cohort study	Rheumatology
	M. Schencking, C. Vollbracht, G. Weiss, J. Lebert, A. Biller, B. Goyvaerts and K. Kraft	2012	Intravenous vitamin C in the treatment of shingles: Results of a multicenter prospective cohort study	Medical Science Monitor
	F. T. Scott, M. E. Leedham-Green, W. Y. Barrett-Muir, K. Hawrami, W. J. Gallagher, R. Johnson and J. Breuer	2003	A study of shingles and the development of postherpetic neuralgia in east London	Journal of Medical Virology
	H. G. R. Thyregod, M. C.:Peters, M.:Possehn, J.:Berro, M.:Petersen, K. L.	2007	Natural history of pain following herpes zoster	Pain

Table A1: (continued)

	B. M. A. Veetil, E. L. Matteson, S. E. Gabriel and C. S. Crowson	2011	Incidence and time trends of herpes zoster in rheumatoid arthritis: A population based cohort study	Arthritis and Rheumatism
	B. M. A. Veetil, E. Myasoedova, E. L. Matteson, S. E. Gabriel, A. B. Green and C. S. Crowson	2013	Incidence and time trends of herpes zoster in rheumatoid arthritis: A population-based cohort study	Arthritis Care and Research
	R. J. Whitley, S. Shukla and R. J. Crooks	1998	The identification of risk factors associated with persistent pain following herpes zoster	J Infect Dis
	R. J. Whitley, H. L. Weiss, S. J. Soong and J. W. Gnann	1999	Herpes zoster: risk categories for persistent pain	Journal of Infectious Diseases
	Q. Xing, D. Hu, F. Shi and F. Chen	2013	Role of regulatory T cells in patients with acute herpes zoster and relationship to postherpetic neuralgia	Arch Dermatol Res
	M. M. Zak-Prelich, R. C.:Sysa-Jedrzejowska, A.:Norval, M.	2003	Local immune responses and systemic cytokine responses in zoster: Relationship to the development of postherpetic neuralgia	Clinical and Experimental Immunology
	S. M. L. Zhu, Y. M.:An, E. D.:Chen, Q. L.	2009	Influence of systemic immune and cytokine responses during the acute phase of zoster on the development of postherpetic neuralgia	Journal of Zhejiang University: Science B
Full text not in English	Y. W. Yamasaki, K.:Kitagawa, K.:Fukuda, T.	1990	Treatment of herpes virus infection using antiviral agents 2. Treatment of herpes zoster with intravenous administration of Ara A	IRYO - Japanese Journal of National Medical Services
Data provided on effect estimates appear incorrect	Nurmikko, T. J.:Rasanen, A.:Hakkinen, V.	1990	Clinical and neurophysiological observations on acute herpes zoster	Clinical Journal of Pain

Table A2: Sub group meta-analyses to identify causes of heterogeneity for effect of age and gender on PHN.

	No. of studies	Summary RR (95% CI)	Pheterogeneity; I^2	P-value from meta-regression (univariate)
Age				
All studies	8	-	P=0.029; 55.1%	-
Mean age of study population				
≥60 years	3	2.39 (1.81-3.16)	P=0.533; 0.0%	
<60 years	3	1.46 (1.24-1.73)	P=0.242; 29.4%	0.08
Definition of PHN				
Pain at 4 months	3	1.45 (1.21-1.73)	P=0.195; 38.9%	
Pain at 3 months	3	1.80 (1.48-2.20)	P=0.305; 15.8%	0.52
Ascertainment of PHN				
Self-reported	6	1.63 (1.44-1.85)	P=0.079; 49.3%	
Medical records	1	3.11 (1.82-5.31)	-	0.14
Excluded immunosuppressed				
Yes	2	1.41 (1.18-1.68)	P=0.235; 29.1%	
No	4	1.96 (1.62-2.37)	P=0.126; 47.6%	0.23
Source population from primary care				
Yes	5	1.97 (1.67-2.33)	P=0.188; 35.0%	
No	2	1.39 (1.15-1.68)	P=0.186; 42.8%	0.18
Gender				
All studies	7	-	P=0.01; 73.9%	-
Mean age of study population				
≥60 years	2	0.62 (0.40-0.95)	P=0.335; 0.0%	
<60 years	3	1.65 (1.19-2.30)	P=0.364; 1.0%	0.04
Definition of PHN				
Pain at 4 months	1	2.01 (1.28-3.16)	-	
Pain at 3 months	3	0.68 (0.47-0.99)	P=0.013; 77.0%	0.45
Ascertainment of PHN				
Self-reported	6	1.13 (0.88-1.44)	P=0.000; 78.1%	
Medical records	1	0.90 (0.38-2.16)	-	0.83
Excluded immunosuppressed				
Yes	1	2.01 (1.28-3.16)	-	
No	6	0.88 (0.66-1.16)	P=0.018; 63.5%	0.25
Source population from primary care				
Yes	3	0.78 (0.53-1.15)	P=0.020; 74.5%	
No	3	1.36 (0.93-1.99)	P=0.006; 80.4%	0.97

Table A3: Association between PHN and various risk factors: risk factors, adjusted effect measure and 95% confidence interval by study. All risk factors included in the final multivariate model are listed, unless otherwise specified

	PHN definition	Age (in years)	Gender	Severe immune suppression	Other physical or psychological comorbidities	Genetic or lifestyle risk factors	Other "non-vaccine targetable" risk factors in final model
Cohort studies - risk factor: odds ratio (95% CI) unless specified							
Cebrián-Cuenca 2011[2]	3m (main results)	Per yr increase: 1.04 (CI 1.01-1.08, P<0.03)	Gender: OR not given P>0.05				Antiviral use: OR not reported P>0.05.
	1m	Per yr increase: 1.04 (CI not given, P<0.01)	Gender: OR not given P>0.05				Time interval (days) between symptom onset and clinical diagnosis: 1.11, P<0.01 Antiviral use: OR not reported P>0.05.
Coen 2006	3m (main results)	Age over 50 yrs: 3.91 (1.38-11.11)	F vs M: 2.45 (0.96-6.23)	-	-	-	Extent of rash score: not associated, ophthalmic branch involvement: 3.20 (1.19-8.55), VAS >5: 3.92 (1.33-11.5), VAS>5 and or age over 50: 8.51 (1.11-65.2), time from onset of rash (days): 0.93 (0.80-1.07).
	6m	Age over 50 years: 13.8 (1.74-110)	F vs M: 5.21 (1.38-19.6)	-	-	-	Extent of rash score: not associated, ophthalmic branch involvement: 5.31 (1.66-16.9), VAS >5: 3.68 (1.01-13.5), VAS>5 and or age over 50: 4.74 (1.59-38.2), time from onset of rash (days): 0.78 (0.61-1.00).
Drolet 2010	3m (main results)	Per yr increase: RR1.02 (1.00-1.04)	Not in final model: No association in univariate analyses	General immune suppression (using high dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS): RR 1.98 (1.14-3.45) (sensitivity analysis)	Limitation in performing usual activities before zoster: RR 1.09 (1.01-1.18) Not in final model: No association with having another pain condition or other pre-zoster EQ-5D measures in univariate analyses.	Income, baseline ≥50,000 USD: $40K-49,999: RR 2.24 (0.98-5.13) $20K-39,999: RR 1.77 (0.87-3.63) <$20K: 1.85 (0.89-3.83) Not in final model: No association with working status or education in univariate analyses.	Severe acute pain at zoster: RR 2.06 (0.98-4.35)
	30 days (RRs not reported)	Older age associated with PHN	-	-	-	-	Severe acute pain at zoster associated with PHN Limitation in performing usual activities at recruitment associated with PHN
Helgason 2000	3m (main results)	Per 10 yr increase: 2.11 (1.56-2.84)	Not in final model: No association in univariate analyses	-	-	-	-
	1m	1.87 (1.56 to 2.23)	Not in final model: No association in univariate analyses	-	-	-	-
	6m	2.45 (1.50-4.01)	Not in final model: No association in univariate analyses	-	-	-	-
	12m	2.33 (1.48-3.69	Not in final model: No association in univariate analyses	-	-	-	-

NB: Reference category listed last. yr=year, SLE=Systemic Lupus Erythematosus [1]PCS=physical component summary score, MCS= mental component summary score (a patient reported survey of physical/mental health using Short Form 12 (SF-12): score <50 represented below-average health status) [2]Variables included in the final model, and whether the final model was restricted to immunocompetent patients, is unclear. [3]Adjusted for age and gender only [4]Study used ordered logistic regression, therefore the parameters represent the exposure ORs for being the highest outcome categories, compared to the lowest outcome categories: it is assumed the effect of exposure is the same for all splits of the outcome categories.
[5]Physical Health measured using the Life Stressors and Social Resources Inventory, which sums the total number of patient reported medical conditions.

Table A3: (continued)

	PHN definition	Age (in years)	Sex	Severe immune suppression	Other physical or psychological comorbidities	Genetic or lifestyle risk factors	Other risk factors in final model
Cohort studies (continued)							
Kotani 2004	2m	Per 10 yr increase: 2.2 (1.1-4.5)	Not in final model (no association in univariate analyses)	-	Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses	-	-
	6m	Per 10 yr increase: 2.7 (1.2-5.7)	Not in final model (no association in univariate analyses)		Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses		
	12m	Per 10 yr increase: 2.7 (1.2-6.2)	Not in final model (no association in univariate analyses)		Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses		
Opstelten 2002	3m	≤54: 1.00 55-74: 5.4 (1.1-26.5) ≥75: 19.7(4.3-90.9)	F vs M: 1.0 (0.9-1.0)	-	Diabetes:1.7 (0.5-6.2) Psycho-pharmaceuticals use: 1.4 (0.3-5.6) Not in final model: no association with chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, psychological problem or corticosteroid use at zoster diagnosis in univariate analyses.	-	Localization, ophthalmic vs not:2.2 (0.8-6.5), Painful prodrome: 1.2 (0.3-5.6)
	1m	≤54: 1.00 55-74: 4.2 (1.8-9.7) ≥75: 10.7(4.6-25.1)	F vs M: 0.8 (0.4-1.5)	-	Diabetes:1.4 (0.6-3.8) Psycho-pharmaceuticals use: 1.4 (0.5-3.9) Not in final model: no association with chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, psychological problem or corticosteroid use at zoster diagnosis in univariate analyses.	-	Localization, ophthalmic vs not:2.3 (1.1-4.6), Painful prodrome: 2.1 (0.9-5.2)
Opstelten 2007	3m	Per y: 1.08 (1.04-1.12)	Not in final model: No association in univariate analyses	-	Trust in healthcare score, 1 unit increase from 0-100: 1.01 (1.00-1.03) Not in final model: psychological predictors not associated in univariate analyses.	-	Duration of rash prior to consultation, in d: 0.78 (0.64-0.97), Severe rash, ≥43 vesicles: 2.31 (1.16-4.58), Severity of acute pain, per vAS unit: 1.02 (1.01-1.03)
	1m (ORs not available)	Same as above, except age not associated with PHN and epidural injection was associated with PHN.					
Parruti 2010	1-3m	Per 10 y increase: 1.01 (0.99-1.02)	F vs M: 1.39 (0.84-2.30)	Not in final model: No association with HIV in univariate analyses.	Trauma at site of lesion:2.53 (1.37-4.65) Surgical Intervention at site of lesion: 1.33 (0.79-2.25) Not in final model: no association with HCV infection, hypertension, diabetes, neoplasm, neurological disorders, psychiatric illness, allergy or family history of major cardiovascular events, malignancies, neurological diseases, major depression, at univariate analysis.	Current/former smoking: 2.08 (0.22-3.55) Not in final model: no association with alcohol abuse, familial status, educational level in univariate analyses.	Intense/very intense pain at presentation:2.19 (1.32-3.65), Missed antiviral prescription: 2.28 (1.04-4.98)

Table A3: (continued)

Case base studies - risk factor: prevalence ratio (95% confidence interval)							
Choo 1997††	60 days	Per y: 1.12 (1.06-1.18)	F vs M: 0.9 (0.4-2.3)	Connective tissue disease, HIV infection or organ allograft: 9.5 (2.0-45.9)	Diabetes: 2.7 (0.4-17.9) Cancer: 0.1 (0.02-0.9) Corticosteroid exposure prior to zoster: 1.4 (0.3-6.0)	-	Prodromal symptoms: 3.4 (1.3-9.1). [In final model, but no evidence of association with PHN in multivariate analysis (confidence intervals overlapped the null): number of encounters previous 180d, dermatome affected, interference with activities on daily living, complications including superinfection and ocular complications and other, acyclovir exposure, corticosteroid exposure after zoster]
	30 days	Per y: 1.09 (1.06-1.12)	F vs M: 1.3 (0.6-2.7)	Connective tissue disease, HIV infection or organ allograft: 3.1 (1.0-9.5)	Diabetes: 2.1 (0.6-7.7) Cancer: 0.2 (0.1-0.8) Corticosteroid exposure prior to zoster: 2.9 (0.7-11.3)	-	Prodromal symptoms: 2.1 (1.1-4.3). [In final model, but no evidence of association with PHN in multivariate analysis (confidence intervals overlapped the null): number of encounters previous 180d, dermatome affected, interference with activities on daily living, complications including superinfection and ocular complications and other, acyclovir exposure, corticosteroid exposure after zoster]

NB: Reference category listed last. Yr=year, HCV=Hepatitis C virus, APOE=alipoprotien E. ††Adjusted for age (continuous variable), presence (yes or no) of prodromal symptoms, severe pain, or comorbid conditions; and number of healthcare encounters.

Table A4: Assessment of bias: detailed notes

Type of bias	Confounding Residual confounding by age	Selection Bias Loss to follow-up	Exposure information bias Non-differential misclassification	Outcome (PHN) information bias Reporting bias	 Non-differential misclassification	Bias due to missing data Missing exposure data
Cohort studies						
Asada 2013	O Age adjusted using categorical variable (50-, 60-, 70, ≥80)	O 4% of cohort lost to follow-up	O Several dermatologists collected exposure information: differences between physician recording practices may lead to different exposure ascertainment	O -Outcome assessed using a standard scale for pain -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status assessment.	? Definition of pain may vary between patients	◆ Over half patients had missing data for VZV skin test reaction tests; Impact of missing data not presented.
Bouhassira 2012	◆ Age adjusted using binary variable	■ 20% of cohort lost to follow-up: no information on non-responders	O Several risk factors assessed: some errors are possible	O -Outcome assessed using a standard question -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	? Missing data not described for all exposure variables; 36% of PHN patients and 28% non-PHN patients missing data on depression. Impact of missing data not presented.
Cebrián-Cuenca 2011	O Age adjusted using continuous variable	■ 15% of cohort lost to follow-up	O Some information from medical record review; differences between physician recording practices may lead to different exposure ascertainment	O -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	O No missing data
Coen 2006	◆ Age adjusted using binary variable	O 3% of cohort lost to follow-up	? Unclear who collected exposure data	O -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	? Missing data not reported for all exposure variables
Drolet 2010	O Age adjusted using continuous variable	O No loss to follow-up	O Several risk factors assessed: some errors are possible	O -Outcome assessed using a standard questionnaire -Unclear if patients were aware of study hypothesis	? Definition of pain may vary between patients	■ Missingness reported if exposures had 10 + missing values. Income missing for 28 patients (11%); included missing category in analyses which may cause bias.

Table A4: Assessment of bias: detailed notes (continued)

Type of bias	Confounding Residual confounding by age	Selection Bias Loss to follow-up	Exposure information bias Non-differential misclassification	Outcome (PHN) information bias Reporting bias	 Non-differential misclassification	Bias due to missing data Missing exposure data
Cohort studies						
Haanpaa 2000	O Age adjusted using continuous variable	■ 18% of cohort lost to follow-up	O Unclear how age and sex were assessed, however unlikely to be misclassified	■ -Outcome ascertained from patient reported pain symptoms -Study investigator those ascertaining outcome was aware of exposure status	? Definition of pain may vary between patients	? Missing data not reported for all exposure variables
Helgason 2000	O Not applicable: no multivariable analysis	O 7% of cohort loss to follow-up: no information on non-responders	O Unclear how age and sex were assessed, however unlikely to be misclassified	O -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	O No missing data
Jih 2009	◆ Age adjusted using binary variable	? Unclear if any zoster patients were lost to follow-up during 90d following zoster episode: e.g. patients may have moved or died.	? Based on claims data where coding has not been validated: possibility of exposure information being rule-out codes (e.g. unusually high rate of diabetes (20.6%) in the study population).	◆ -Physicians recording PHN not aware of study hypothesis -Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be ascertained in claims data, a spurious association	◆ No ICD-9 code for PHN, therefore based on zoster code plus neuralgia treatment. Physicians may have various other ways of recording PHN.	? Missing data not reported
Jung 2004	O Age adjusted using continuous variable	■ 11% of cohort lost to follow-up: generally comparable to those with complete data, except being on average 4 years younger	O Unlikely	O -Outcome ascertained from patient reported pain symptoms -Patients originally recruited into clinical trial of antiviral effectiveness thus unlikely to be influenced by these study hypotheses	? Definition of pain may vary between patients	O Missing data not available: likely to be minimal (from email correspondence)

Table A4: Assessment of bias: detailed notes (continued)

Type of bias	Confounding Residual confounding by age	Selection Bias Loss to follow-up	Exposure information bias Non-differential misclassification	Outcome (PHN) information bias Reporting bias	 Non-differential misclassification	Bias due to missing data Missing exposure data
Cohort studies						
Kanbayashi 2012	◆ Age adjusted using categorical variable (<50, 51-74, ≥75)	O No loss to follow-up	◆ Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment. Furthermore, it is unclear whether this initial visit, when exposures were defined, is for acute zoster or whether these patients already have PHN.	? -Unclear how pain defined, however ascertainment bias possible: i.e. patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be diagnosed with PHN, causing a spurious association -Physicians recording PHN not aware of study hypothesis	◆ PHN was ascertained from medical record of documented pain: clinicians may record symptoms differently	O No missing data reported
Katz 2005	O Age adjusted using continuous variable	O 8% of cohort lost to follow-up: no major differences in exposures compared to those completing follow-up	■ Several risk factors assessed: some errors are possible. Exposures recorded on average 17 days following rash onset: measures of pre-morbid functioning may be biased	■ -Outcome ascertained from patient reported pain symptoms -Some outcome assessments carried out by psychologist aware of exposure status -Unclear if patients aware of study hypotheses	? Definition of pain may vary between patients	O Missing exposure data imputed for multivariate analyses: similar results obtained with complete case analysis
Kotani 2004	O Age adjusted using categorical variable (per 10year increase)	O No loss to follow-up	? Method of ascertaining exposures is unclear	? -Unclear how pain was ascertained -Unclear if interviewers know exposure status -Unclear if patients aware of study hypotheses	? Definition of pain may vary between patients	? Missing data not reported
Opstelten 2002	◆ Age adjusted using categorical variable (≤54, 55-74, ≥75)	O No loss to follow-up	O Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment.	◆ -Physicians recording PHN not aware of study hypothesis -Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be ascertained in claims data, causing a spurious association. Under-capture of PHN likely, indicated by very low incidence of PHN in zoster patients; may be related to exposure status	◆ PHN defined as recording of pain or analgesic; clinicians may record symptoms / prescribe medicine differently	■ Certain exposures (eg prodromal symptoms) may not be routinely recorded by clinician: more likely to reduce statistical power

Table A4: Assessment of bias: detailed notes (continued)

Type of bias	Confounding Residual confounding by age	Selection Bias Loss to follow-up	Exposure information bias Non-differential misclassification	Outcome (PHN) information bias Reporting bias	 Non-differential misclassification	Bias due to missing data Missing exposure data
Cohort studies						
Opstelten 2007	O Age adjusted using continuous variable	O No loss to follow-up	O Unlikely	O -Outcome ascertained from patient-completed questionnaire -Unclear if patients aware of study hypotheses	? Definition of pain may vary between patients	■ 127 patients had missing values for ≥1 variables: details of missingness not reported. Missing data was singly imputed
Park 2011	◆ Age adjusted using binary variable	O No loss to follow-up	? Unclear how exposures assessed	? -Unclear how outcome assessed -Unclear if patients aware of study hypotheses	? Definition of pain may vary between patients	? No information on completeness of exposure data
Parruti 2010	O Age adjusted using categorical variable (per 10 year increase)	O 6% of cohort lost to follow-up: no information on non-responders	O Unlikely	O -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	■ Some missing exposure data: impact on findings unclear
Volpi 2008	◆ Age adjusted using binary variable	◆ 41% of cohort lost to follow-up: no information on non-responders	O Unlikely	O -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status	? Definition of pain may vary between patients	■ Some missing exposure data: impact on findings unclear
Wozniak 2007	O Confounding by age n/a in genetic studies: confounding by population possible, yet selected Caucasian patients	? No loss to follow-up	O Objective measures of exposure: unlikely to be biased	? -Unclear if researchers are aware of exposure status	? Definition of pain may vary between patients	O No missing data not reported

Table A4: Assessment of bias: detailed notes (continued)

Case-base study						
	Residual confounding by age	**Loss to follow-up and selection of base population**	**Non-differential misclassification**	**Reporting bias**	**Non-differential misclassification**	**Missing exposure data**
Choo 1997						
	Age adjusted as continuous variable	No loss to follow-up reported. Randomly selected non-PHN patients from all eligible zoster patients	Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment.	Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be diagnosed with PHN, causing a spurious association. However authors adjusted for healthcare utilisation.	Physicians may have various ways of recording PHN; however authors identified potential PHN cases using a broad criteria, before screening their medical records for evidence of PHN	Certain exposures (eg prodromal symptoms) may not be routinely recorded by clinician: could reduce statistical power

6.4. Review of studies assessing risk factors for postherpetic neuralgia within general population samples

6.4.1. Introduction

The risk of PHN in the general population is made up of two parts; first, the risk of zoster and second, the risk of PHN, *once you have zoster*. In general population based studies, it is not immediately clear whether any identified risk factors are simply predictive of zoster itself, and hence associated with a higher risk of PHN, or whether they are specifically risk factors for developing PHN.

However, in terms of zoster vaccine policy, understanding risk factors for PHN in the general population may be valuable. The vaccine is, after all, not useful once a patient develops zoster, therefore vaccination policies ideally need to identify groups of patients at high risk of PHN within the general population.

In this section, papers excluded from the published systematic review solely because they examined risk factors for PHN in a general population sample, were summarised.

6.4.2. Methods

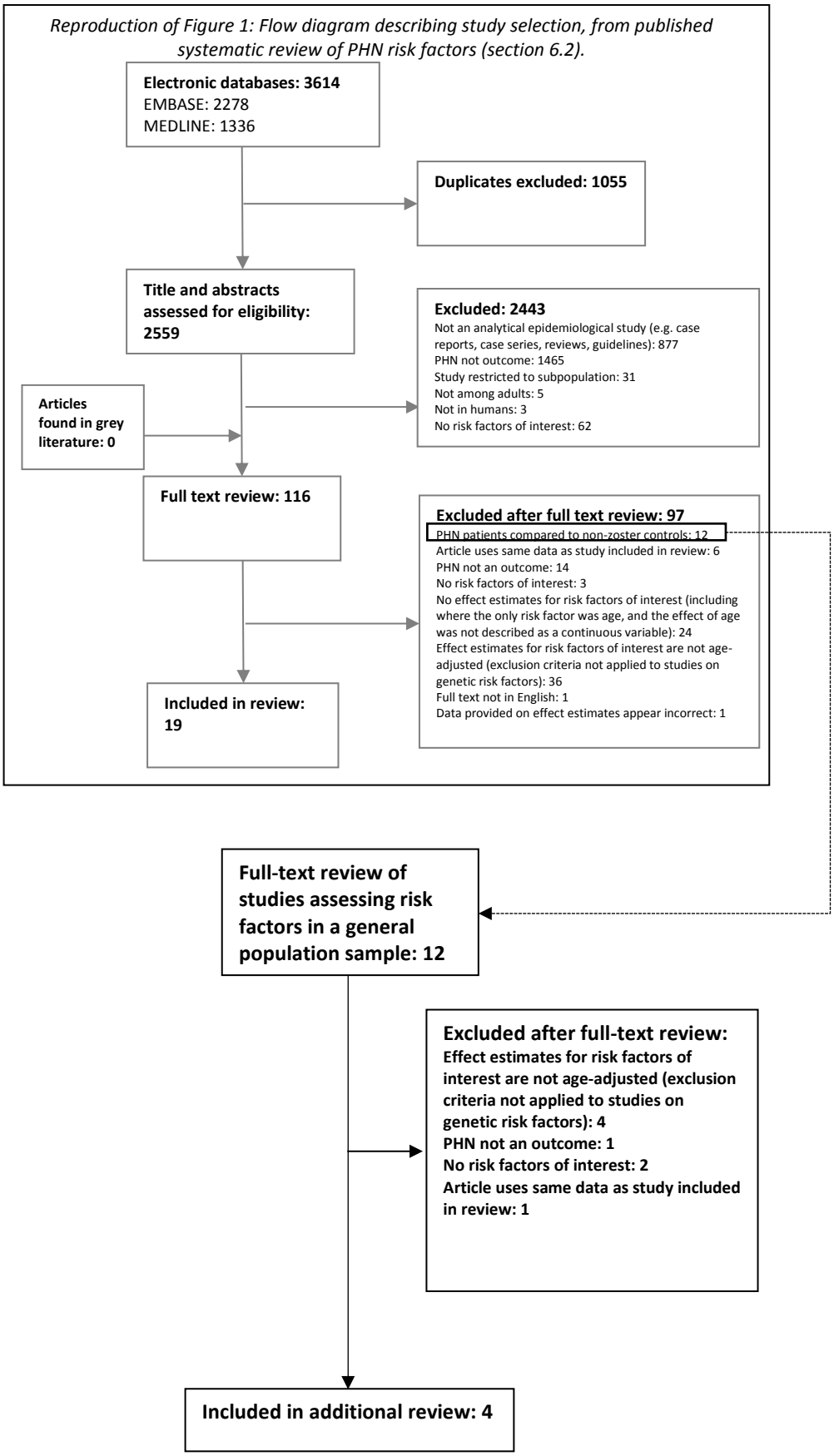
Full details of the methods are explained in the paper, "Systematic review and meta-analysis of risk factors for postherpetic neuralgia", in section 6.2. The same inclusion and exclusion criteria were applied, except that the selected studies were those that compared PHN patients to a general population sample, rather than comparing PHN patients to zoster patients without PHN. Risk of bias assessment was based on the Cochrane Collaboration approach, where each study is assessed individually for pre-specified bias domains.

6.4.3. Results

In the published systematic review of PHN risk factors (section 6.2) twelve studies were identified which were based in a general population sample, that is, they compared PHN patients to the general population (see figure 5). These 12 studies were re-reviewed to identify those meeting the inclusion criteria (see section 6.4.2. above). Four of the 12 studies were

excluded as they did not adjust for age; these studies explored the association between PHN and plasma vitamin C levels,[165]

Figure 5: Flow diagram describing study selection for additional review of studies assessing risk factors for PHN in a general population sample



nutrient deficiencies,[166] residual scarring[167] and impaired glucose metabolism.[168] Two studies used the same data, therefore only one of these reports was retained (one was a conference paper and thus excluded[169]). Two studies had no risk factors of interest (these risk factors specifically, were, VZV DNA and viral microarray-based transcriptomal measurements).[170,171] Finally, another paper was excluded because after further review, PHN was deemed to be the exposure, rather than the outcome.[172]

Four studies met the inclusion criteria. Three were case-control studies and one used a cohort study design. The characteristics of these studies are described in Table 4 and their results are outlined in Table 5.

6.4.3.1. Study findings

All three case-control studies looked at genetic susceptibility to PHN. They all recruited PHN patients from outpatient hospital clinics. Two studies assessed genes in the human leukocyte antigen (HLA) class I and II regions as predictors of genetic susceptibility for PHN in Japanese individuals, comparing individuals with PHN to patients with no history of zoster.[173,174] Both studies reported associations between alleles within the HLA region and PHN. Another study found no evidence that PHN patients were more likely to have a family history of zoster than age and gender-matched controls (with no history of zoster themselves), suggesting susceptibility to PHN may not be inherited.[175]

The cohort study used Israeli EHR data from primary and secondary care, to follow-up over one million patients during 2010 for PHN.[50] Age was the strongest risk factor for PHN, with people between 65-74 years >20 times as likely to get PHN compared to patients aged 25-34 (hazard ratio (HR) 20.9, 95%CI 11.0-39.6). Females and patients of higher SES were more likely to be diagnosed with PHN. HIV treatment and having a history of cancer in the last five years were strongly associated with PHN risk and the authors reported a borderline association between diabetes and PHN (HR 1.35, 95%CI 0.99-1.83).

6.4.3.2. Assessment of bias

Case control studies

In the genetic association study by Ozawa *et al* (n=168), it is unclear how the controls were selected. Sato et al specified that the controls were selected from the same hospital as the cases, potentially reducing the possibility of selection bias as controls are likely to come from the same source population as the cases. However, the authors did not specify the reason

controls were visiting hospital, so it is not possible to assess if controls are likely to have an association with the exposure (HLA class I and II regions).

Despite major differences in the age of the cases (68.3 years) and their controls (40.1 years) in the study by Sato *et al* (n=165), there were no associations between age and the haplotypes proposed as risk factors for PHN; thus the results are unlikely to be due to confounding by age. In the case-control study by Gatti *et al,* assessing family history as a risk factor for zoster, the researchers matched on age at the design stage. However, it is unclear how age was accounted for at the analysis stage; hence there may be residual confounding by age. The study also relied on patient recall from years (although the number of years was not specified) previously; therefore, misclassification of exposure status is likely, which may lead to underestimation of effects.

Cohort study

In the Israeli cohort study[50] PHN was defined as any patient with an ICD-9 code for PHN anytime during 2010. In practice, physicians may use general zoster or pain codes to record PHN.[102] Patients with a specified PHN code are unlikely to be systematically different to PHN patients with other codes, therefore this would cause non-differential misclassification of the outcome and reduction in the effect sizes. PHN codes were also selected without reference to the timing of acute zoster and the authors report physicians tended to use a 1-month definition of PHN. As a result, their findings may not reflect risk factors for the most commonly used definition of PHN (pain persisting for three months after zoster). There is also a possibility of ascertainment bias; that patients with risk factors of interest may seek healthcare more frequently and increase their likelihood of PHN diagnosis.

The cohort study utilised a database that is broadly representative of the Israeli population in terms of age and sex, therefore the results are likely to be generalizable to the general population of Israel.

6.4.4. Discussion

Four articles were identified which explored risk factors for PHN in the general population. Three studies investigated evidence of a genetic susceptibility to PHN, and two case-control studies found some indication that alleles within the HLA region were associated with PHN. There was a single cohort study assessing various risk factors for PHN in the general population, which reported female gender, high SES, recent cancer treatment, HIV and

diabetes were associated with increased risk of PHN. However, three of the four studies had at least one pre-specified domain with a high risk of bias, limiting the value of the evidence.

From the perspective of zoster vaccination policy understanding the risk factors for PHN in the general population may be of greater value than information on risk factors for PHN among people already with zoster. Despite this, the majority of studies focusing on risk factors for PHN are nested within zoster cohorts. Exactly why risk factor studies using general population controls, rather than zoster controls, are far less common is not clear, however two reasons have been hypothesised here: 1) population-based studies may be more challenging to conduct compared to studies within zoster cohorts, as the comparison group is less easy to identify; 2) interpretation of population-based studies is more challenging as the risk of PHN is a combination of the risk of zoster, plus the risk of PHN, having developed zoster.

HLAs regulate immune responses against viruses therefore may be involved in the pathogenesis of PHN: a study among zoster patients did not find any association between the risk of acute zoster and the HLA region, which is in contrast to the studies assessed here focussing on PHN risk.[176] However, it should be emphasised that HLA alleles and haplotypes differ between populations; therefore the findings, if replicated in larger population-based studies, may only be generalizable to Japanese populations. Confirmation of findings from different ethnic populations would be important prior to considering if the HLA region is involved in the pathogenesis of PHN. Additionally the studies were very small and need to be substantiated in larger samples.

Weitzman *et al* uniquely contributed to the literature by conducting a large cohort study within the general population. However, the definition of PHN used in Weitzman's study was pain at one month following zoster, which may limit the applicability of their findings as the more widely used definition of PHN is pain three months or greater following zoster. Furthermore, the study may be subject to residual confounding by age, as age was included in the model as a categorical variable with very wide groupings.

This brief review of studies investigating risk factors for PHN in the general population has demonstrated that there is some evidence that genes in the HLA region may be involved in PHN susceptibility, specifically among people of Japanese ethnicity. It is however not known to what extent these genetic factors reflect the risk of zoster versus risk of PHN, which is a major limitation when assessing risk factors for PHN in general population studies. One study suggested that female gender, high SES, recent cancer treatment, HIV and diabetes were

associated with increased risk of PHN in the general population. Each study had some major weaknesses, limiting the quality of the evidence.

Table 4: Studies assessing risk factors for PHN within a general population sample: study characteristics

Case control studies

First author, publication year	Country, year of study	Study population	Cases	Controls	Matching factors	Study Size	Mean age in years (SD)	Method of ascertaining PHN	Definition of PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Gatti, 2010	Italy, 2007-2008	Immunocompetent patients presenting to hospital	PHN patients	Outpatients from hypertension clinic, with no history of zoster.	Age and gender	173 cases 176 controls	Cases: 72.4 (12.4) Controls: 71.4(11.9)	Enrolled at a Pain Clinic with PHN, unclear how pain score assessed.	Pain ≥3 (on score of 1-10) at 3m after rash onset	Medically trained interviewer-administering a standardized questionnaire, blinded to case-control status.	Medical history (diabetes or other underlying diseases), zoster history (episodes, prodrome, pain intensity, clinical disease characteristics, antiviral treatments), occurrence of mechanical trauma or stressful events, family history of zoster	Chi-squared test for association of each risk factor and PHN: details of multivariate analysis unclear
Ozawa 1999	Japan, year not reported	PHN patients recruited from hospital and healthy controls without a history of zoster	Unrelated Japanese PHN patients	Unrelated Japanese healthy volunteers	Not matched	32 cases 136 controls	Cases: 74.8 (range 62-86) Controls: not reported	Visiting an outpatient dermatology clinic with PHN, unclear how pain assessed.	Not reported	Serological typing using the lymphocyte cytotoxicity test and DNA typing using PCR-PHFA	HLA class I and class II alleles	Relative risks calculated from cross-product ratio of entries in the Chi-square 2x2 table.
Sato 2002	Japan, year not reported	Immunocompetent PHN patients visiting hospital pain clinic and healthy controls without a history of zoster	Japanese PHN patients	Japanese healthy volunteers from same institution as cases	Not matched	40 cases 125 controls	Cases: 68.3 Controls: 40.1 (SDs not given)	Patients receiving medical treatment at Pain clinic.	Pain ≥50 VAS persisting 3-6 m after initial zoster presentation	Serological typing and PCR-PHFA	HLA class I, II and III regions and candidate loci (TNFA and NKp30)	Unclear

Cohort Studies

First author, publication year	Country, year of study	Study population	Follow-up	Study Size	Mean age in years (range)	Method of ascertaining PHN	Definition of PHN	Number with PHN	Method of ascertaining risk factor(s)	-	Risk factors assessed	Statistical analysis
Weitzman, 2013	Israel, 2010	Patients registered in the MHS Health Maintenance Organisation during 2010, identified from electronic healthcare records	1st Jan 2010 until earliest of PHN diagnosis, 31st Dec 2010, death date or date left HMO	1 032 413	Not reported (25-84)	Medical diagnosis codes	An ICD-9 code or internal MHS code for PHN in 2010	248	Electronic healthcare records as of 1st January 2010		Age, gender, anti-TNF-ά, ≥1 prescription in 2010, history of transplantation, SES (categorized into tertiles according to a locale-specific poverty index), cancer history, diabetes mellitus, HIV treatment.	Cox-proportional hazards regression

SD= standard deviation, PCR-PHFA =polymerase chain-reaction fragment length polymorphism method, MHS=Maccabi Healthcare services, SES=socioeconomic status, VAS=visual analogue scale, HLA=human leukocyte antigens, HMO=Health Maintenance Organisation

Table 5: Association between PHN and various risk factors within a general population sample: risk factors, adjusted effect measure and 95% confidence interval by study.

Note: All risk factors included in the final multivariate model are listed

	Age (in years)	Sex	Severe immune suppression	Other physical or psychological comorbidities	Socioeconomic status and other risk factors	Genetics	Other risk factors in final model
Studies assessing risk factors for PHN within a general population sample							
Case-control studies (OR, 95% CI unless otherwise specified)							
Gatti 2010	*(matched on age)*	*(matched on gender)*	-	-	-	Family history of zoster among first degree relatives, RR 1.03 (0.78-1.37) and all relatives RR 1.03 (0.81-1.31), compared to no family history of zoster	-
Ozawa 1999	-	-	-	-	-	HLA-A33: RR 4.79, P=0.00972, HLA-B44: RR 4.51, P=0.03499, HLA-Cw3: RR 0.07, P=0.00152	-
Sato 2002	-	-	-	-	-	HLA-A3303: 3.27, P=0.0007, HLA-B*4403: 3.10, P=0.001, HLA-DRB1*1302: 3.36, P=0.001 [95% CIs not given]	-
Cohort Studies (HR, 95% CI)							
Weitzman 2013	*65-74 vs 25-34:* 20.9 (11.0-39.6)	*F vs M:* 1.44 (1.12-1.86)	*HIV treatment:* 15.53 (2.17-111.21) *Anti-TNF drugs*: 2.95 (0.41-21.06)	*Cancer history, vs none* *<1 year:* 3.00 (1.23-7.30) 1-5 years: 1.91 (1.16-3.14) 5+ years: 1.17 (0.65-2.11) *Diabetes Mellitus:* 1.35 (0.99-1.83)	*High SES vs other:* 1.39 (1.07-1.81)	-	

Table 6: Assessment of bias in individual studies set within the general population (◆= High risk, ■= Medium risk, O=Low/No risk or ?=Unclear risk)

	Confounding	Selection Bias		Information bias						Bias due to missing data
				Exposure			*Outcome (PHN)*			
Matched case-control studies										
Type of bias	**Residual confounding**	**Selection of controls**	**Non responders bias**	**Researchers reporting bias**	**Recall bias**	**Non-differential misclassification**	**Researchers reporting bias**	**Participant reporting bias**	**Non-differential misclassification**	**Missing exposure data**
Gatti 2010	◆	◆	?	◆	◆	◆	O	O	-	?
	Handling of age in analysis is unclear	Hospital controls with no history of zoster, however recruited from hypertension clinic thus may be a different population to cases	No information on non responders	Researcher not blinded to case-control status	PHN patients may recall more family history of zoster	Exposure may have been years previously	Outcome ascertained prior to exposure	Outcome ascertained prior to exposure	N/A	Missing data not reported
Ozawa 1999	■	◆	?	O	O	O	O	O	-	?
	Confounding by age not applicable in genetic studies: confounding by population possible, however did select Caucasian patients	Very unclear how controls were selected	No information on non-responders	Objective measures of exposure: unlikely to be biased	Objective measures of exposure: unlikely to be biased	Objective measures of exposure: unlikely to have errors	Outcome ascertained prior to exposure	Outcome ascertained prior to exposure	N/A	Missing data not reported
Sato 2002	■	■	?	O	O	O	O	O	-	?
	Confounding by age not applicable in genetic studies: confounding by population possible, however did select Caucasian patients	Controls selected from the same hospital as cases	No information on non-responders	Objective measures of exposure: unlikely to be biased	Objective measures of exposure: unlikely to be biased	Objective measures of exposure: unlikely to have errors	Outcome ascertained prior to exposure	Outcome ascertained prior to exposure	N/A	Missing data not reported
Cohort studies										
	Residual confounding by age	**Loss to follow-up**		**Reporting bias**	**Non-differential misclassification**	**Reporting bias**			**Non-differential misclassification**	**Other**
Weitzman 2013	■	?		■	O	◆			◆	
	Age adjusted using categorical variable with 10 year age intervals	Unclear how many people were lost to follow-up during study period		Exposures recorded prior to record of PHN, however PHN may have been diagnosed previously	Several risk factors assessed: some coding errors are possible	Data not collected for research purposes therefore study hypothesis not known when outcome recorded: however, patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be diagnosed with PHN, causing a spurious association			Only patients with diagnostic codes for PHN classified as cases: under capture of PHN is likely	Unclear how rate ratios were calculated: no raw data on follow-up time.

6.5. Chapter summary

Systematic review of risk factors for PHN among zoster patients

- Risk factors for PHN have been posited, but the evidence has never been systematically reviewed.
- Nineteen studies were selected for review, which assessed risk factors for PHN among adult zoster patients and reported age-adjusted effect estimates.
- The risk of PHN was significantly increased with clinical features of acute zoster including prodromal pain, severe acute pain, severe rash and ophthalmic involvement. Older age was significantly associated with PHN. Evidence for a difference in PHN risk by gender was conflicting, with considerable between-study heterogeneity. A proportion of studies reported an increased risk of PHN with severe immunosuppression (n=3/5 studies) and diabetes mellitus (n=1/4).
- The review has confirmed that a number of clinical features of acute zoster are associated with PHN. It identified a range of other possible risk factors for PHN, yet aside from age-associated risks, the evidence is currently limited. Larger studies with strict definitions of exposures and outcomes and control for confounding variables may elucidate some of the unknown risk factors for PHN.

Systematic review of risk factors for PHN in the general population

- Understanding risk factors for PHN within the general population may be particularly helpful in informing vaccination policy.
- Four studies were identified investigating risk factors for PHN in the general population, however all studies had some limitations, therefore the findings must be treated cautiously.
- Three case-control studies investigated genetic susceptibility to PHN; two found evidence that alleles in the HLA region, known to be involved in immunity, were associated with PHN in Japanese populations, whilst the third study found no evidence of family history of zoster being a risk factor for PHN. The final cohort study reported female gender, high SES, recent cancer treatment, HIV and diabetes were associated with increased risk of PHN.
- Interpreting results of these studies is more difficult, as the effect reflects both the risk of zoster plus the risk of PHN, once zoster developed. This difficulty in interpreting study results may explain why the majority of studies investigating risk factors for PHN remain in zoster cohorts.

Chapter 7: Quantification of risk factors for postherpetic neuralgia in a cohort of herpes zoster patients

7.1. Introduction

As demonstrated in the systematic review in chapter 6, knowledge of the risk factors for PHN is limited, with studies often being small and yielding inconsistent results. An understanding of PHN risk factors may be helpful in informing zoster vaccination policy, as patients at high risk of PHN could be specifically targeted. A large cohort study was therefore carried out to investigate risk factors for PHN among a cohort of zoster patients in CPRD. The findings from this study were written up as an article and the paper is currently accepted for publication at Neurology.

This chapter begins with the article, and is followed by the submitted appendices which were too detailed for the article. The appendices include detailed information of how age was modelled, how missing data were dealt with and a fuller investigation of gender as a risk factor for PHN.

7.2. Accepted paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Harriet Forbes
Principal Supervisor	Sinead Langan
Thesis Title	Understanding risk factors for herpes zoster and postherpetic neuralgia in UK primary care: investigations to inform vaccine policy

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Neurology
Please list the paper's authors in the intended authorship order:	Harriet J Forbes, Krishnan Bhaskaran, Sara L Thomas, Liam Smeeth, Tim Clayton, Kathryn Mansfield, Caroline Minassian, Sinéad M Langan
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author on this paper. I was responsible for preparing the dataset, designing the study, and conducting the statistical analysis. I was also primarily responsible for writing this work. My co-authors supported this work in an advisory

	capacity, commenting on research design and drafts of the paper.

Student Signature: _____ **Date:** 26/04/2016

Supervisor Signature: _____ **Date:** 28/04/2016

7.2.1. Abstract

Objective: We aimed to investigate risk factors for postherpetic neuralgia, the neuropathic pain that commonly follows herpes zoster.

Methods: Using primary care data from the Clinical Practice Research Datalink, we fitted multivariable logistic regression models to investigate potential risk factors for postherpetic neuralgia (defined as pain ≥90 days after zoster, based on diagnostic and/or prescription codes), including demographic characteristics, co-morbidities, and characteristics of the acute zoster episode. We also assessed whether their effects were modified by antiviral use.

Results: Of 119,413 zoster patients, 6,956 (5.8%) developed postherpetic neuralgia. Postherpetic neuralgia risk rose steeply with age, most sharply between 50-79 years (adjusted odds ratio for a 10-year increase, 1.70, 99% confidence interval 1.63-1.78). Postherpetic neuralgia risk was higher in women (6.3% vs 5.1% in men: OR=1.19, 1.10-1.27); and those with severely immunosuppressive conditions, including leukaemia (13.7%: 2.07, 1.08-3.96) and lymphoma (12.7%: 2.45, 1.53-3.92); autoimmune conditions, including rheumatoid arthritis (9.1%: 1.20, 0.99-1.46); and other comorbidities including asthma and diabetes. Current and ex-smokers, as well as underweight and obese individuals were at increased risk of postherpetic neuralgia. Antiviral use was not associated with postherpetic neuralgia (OR=1.04, 0.97-1.11). However, the increased risk associated with severe immunosuppression appeared less pronounced in patients given antivirals.

Conclusions: Postherpetic neuralgia risk was increased for a number of patient characteristics and comorbidities, notably with age and among those with severe immunosuppression. As zoster vaccination is contraindicated for patients with severe immunosuppression, strategies to prevent zoster in these patients, which could include the new sub-unit zoster vaccine, are an increasing priority.

7.2.2. Introduction

Postherpetic neuralgia (PHN) is the commonest complication of herpes zoster[177] and may cause severe pain.[178] The lifetime incidence of zoster is 30% and an estimated 12·5% of zoster patients aged ≥50 years develop PHN.[23] Symptoms can persist for months or years, often profoundly affecting a patient's quality of life.[179] There are no known effective disease-modifying therapies for PHN. Treatments instead target symptom control, yet are often inadequate at relieving pain and are ineffective in almost half of PHN patients.[27,33,180]

To date, observational and trial data have provided inconsistent evidence that administering antivirals at rash onset reduces PHN risk.[31] These trials also tend to exclude immunosuppressed patients, such that the efficacy of antivirals to prevent PHN in this patient group is greatly under-researched. The only proven and available intervention to reduce PHN risk is through VZV vaccination.[19] However, the high-cost of the vaccine means many countries limit its coverage. A recent review demonstrates our incomplete understanding of PHN risk factors;[181] except for age, evidence is conflicting and studies are often underpowered to detect associations. Considering the dearth of effective treatment options for PHN, identifying PHN risk factors to inform zoster vaccination policy could have important public health benefits.[4]

This paper aims to quantify risk factors for PHN in a large prospective study among zoster patients. It also investigates whether antivirals modify the effect of these risk factors on PHN.

7.2.3. Methods

7.2.3.1. Study design and setting

We conducted a study among zoster patients using prospectively collected data from the Clinical Practice Research Datalink (CPRD), a large routinely collected UK database of anonymised primary care records. CPRD is broadly representative of UK patient and practice characteristics.[85] 60% of CPRD patients had data available in the Hospital Episode Statistics (HES) database (Version 9), a linked database of hospital attendances in England from 1997. Clinical diagnoses are coded in CPRD with Read codes and in HES with ICD-10 codes.[85]

7.2.3.2. Study population

The study cohort included patients with first ever zoster (identified previously[182]), followed-up to determine who develops PHN. Briefly, these patients were diagnosed with zoster between 01/01/2000 and 31/12/2011 in CPRD (Read code for zoster and >12 months follow-up in CPRD before zoster diagnosis [to ensure the code represented incident zoster]) or HES (ICD-10 code for zoster in the primary diagnosis field of any episode). The zoster vaccine was introduced into the UK in 2013, therefore this was an unvaccinated population.

7.2.3.3. Definition of PHN

Our underlying definition of PHN was pain persisting ≥90 days following zoster diagnosis.[27] The primary definition of PHN included patients classified as having diagnosed, probable or possible PHN, based on a validated algorithm of PHN within a US administrative database utilising diagnosis codes and prescription data.[102] See Table 1 for full definition.

Exclusions

As anticonvulsant prescriptions were part of our PHN algorithm (Table 1), patients with other indications for anticonvulsants (e.g. epilepsy) recorded pre-zoster were excluded. We also excluded patients without 365 days follow-up after zoster diagnosis; we could not know whether individuals censored before 365 days without PHN met our PHN definition, which used data to 365 days.

7.2.3.4. Risk factors of interest

Demographic risk factors included age at zoster, gender and socioeconomic status. Comorbidities included severely immunosuppressive conditions, specifically a recent history (<2 years before zoster diagnosis) of leukaemia or lymphoma, or any history of HIV, hematopoietic stem cell transplantation, myeloma or 'other unspecified cellular immune deficiencies' (e.g. pancytopenia), or ≥14-day course of high-dose (≥20 mg/day) oral corticosteroids, or exposure to other immunosuppressive therapies, in the month prior to zoster diagnosis. Other comorbidities included autoimmune conditions (systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD)), diabetes, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease (CKD), personality disorder, recent depression and recent cancer. Other characteristics included

smoking, BMI, site of acute zoster rash and antivirals given within 7 days of zoster diagnosis (appendix, section e-I).

7.2.3.5. Statistical analysis

Crude and age-adjusted odds ratios (ORs) were calculated to estimate the strength of association of each potential risk factor with PHN at 90 days (defined above), using logistic regression. The age-PHN association was non-linear, therefore age was modelled as a 5-knot restricted cubic spline. To numerically summarise the effect of non-linear age on PHN risk we also fitted piecewise linear models (appendix, section e-II).

Multivariable analyses using logistic regression were carried out on patients with complete data for all variables. All variables were included in the final model. Two models were built, first excluding then including immunosuppressive therapies, to assess whether some of the overall effects of diseases were mediated by their treatments.

Antivirals given at zoster may modify the risk of PHN. Antivirals are given to approximately 60% of patients with zoster in CPRD.[183] We calculated stratum-specific ORs for each variable in the multivariable model by whether patients received antivirals. Patients potentially receiving antivirals in hospital were excluded from this analysis (figure 1). In a *post-hoc* analysis we also calculated the adjusted OR for the effect of antivirals on PHN risk among patients with immunosuppression using logistic regression.

Finally, a potentially effect-modifying role of age was investigated by computing stratum-specific ORs for each variable in the multivariable model by age groups “<70 years" and "≥70 years” as well as “<60 years" and "≥60 years” (age groups chosen to reflect different vaccination ages, e.g. ≤60 years in the US[38] and 70, 78 or 79 years[184] in the UK).

General practice was included in all models as a random effect to account for clustering, as data might be correlated within practices.

Sensitivity analyses and bias assessments

We repeated the main risk factor analysis: 1) for PHN at 30 days following zoster; 2) restricting PHN cases to diagnosed PHN only (Table 1); 3) excluding possible misdiagnosed herpes simplex patients (appendix, section e-I). We tested for healthcare utilization bias by assessing the

association between PHN and hypothyroidism (a chronic condition requiring high-level health-care use,[185] not associated with PHN) and calculated mean yearly consultation rate pre-zoster to confirm hypothyroidism patients had the same opportunity for PHN diagnosis (i.e. via GP contact). We used multiple imputation by chained equations[127] as an alternative approach to account for missing data (9% of patients had missing data for BMI or smoking) (appendix, section e-III).

Bias may be introduced from excluding patients <365 days follow-up post-zoster if those included had a different association between our risk factors and PHN, compared to those excluded. We repeated the main analysis, restricting our outcome definition to PHN identified up to 120 and 180 days after zoster; the follow-up requirements are less, thus any selection biases due to excluding patients with insufficient follow-up is reduced.

7.2.3.6. Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by ISAC [application no.11028] and the London School of Hygiene and Tropical Medicine [application no.5930].

7.2.4. Results

Of 144,959 patients with zoster, 119,413 were eligible for inclusion (appendix, Figure e-1). Almost 60% of the sample was female (Table 2) and the median age was 61 years (IQR:48-72, range:18-101). In total, 6,956 zoster patients (5.8%) developed PHN.

The risk of PHN rose with age (appendix, Figure e-2) and the association was non-linear (P<0.001, appendix Figure e-3). Patients 50-79 years had the steepest increased risk of PHN (Table 3); a 10-year increase in age within this age-band was associated with 70% increased risk of PHN (adjusted OR (adjOR):1.70, 99%CI:1.63-1.78), whereas the effect of a 10-year increase in age was attenuated above age 80 years (adjOR:1.10, 99%CI:0.94-1.28). Women were more likely to develop PHN than men, an association which remained after adjustment (adjOR:1.19, 99%CI:1.10-1.27) (Table 3).

Conditions and therapies causing severe immunosuppression were strong risk factors for PHN (Table 2 and 3). Patients with leukaemia or lymphoma in the previous two years, myeloma or other unspecified cellular immune deficiencies ever, or recently taking high-dose oral corticosteroids had over twice the risk of developing PHN, compared to unaffected patients.

For HIV, the point estimate was also large, however only 6 of 99 HIV patients developed PHN, hence the evidence for an association was weak (adjOR:2.17, 99%CI:0.64-7.37).

Of the autoimmune conditions, SLE was most strongly associated with PHN (adjOR:1.76, 99%CI:1.04-2.98) (Table 2 and 3). RA and IBD were also associated with a higher PHN risk (9.1% and 7.5% respectively) with some evidence they were associated with between 10-20% increased risk of PHN after adjustment for confounders; the effects of these two conditions were less pronounced after adjusting for immunosuppressive drugs.

Of the other comorbidities assessed (Table 2 and 3), COPD was associated with a 53% increased risk (PHN risk 13.2%; adjOR:1.53, 99%CI:1.35-1.72) and recent depression a 40% increased risk (PHN risk 7.0%; adjOR:1.40, 99%CI:1.20-1.62). Asthma and type 2 diabetes were associated with 20% increased risk of PHN. After fully adjusting for confounders, personality disorder, CKD or recent cancer diagnosis were not associated with PHN.

The overall risk of PHN among current smokers was lower than the study sample overall (5.4% vs 5.8%), however after adjusting for age, there was around 30% increased risk of PHN in current smokers (adjOR:1.27, 99%CI:1.15-1.39) (Table 2). Being underweight or obese was also associated with PHN. PHN was more prevalent in patients with non-truncal zoster (Table 2 and 3).

The effects of the risk factors on PHN were broadly similar between those given and not given antivirals, except for individuals with leukaemia (P-value for interaction 0.045), SLE (0.026), COPD (0.043) and smoking (0.002); point estimates for their effect on PHN appeared higher in those not given antivirals (Figure 1 and appendix Table e-8). *Post-hoc* analysis found no evidence that antivirals reduced the risk of PHN in patients with immunosuppression (appendix, section e-V).

The effect of COPD (P-value for interaction 0.006), diabetes (0.004), currently smoking (0.006), or being obese (0.037) were slightly stronger in patients <70 years (appendix, Table e-1); the effect of asthma (0.068), CKD (0.018), diabetes (0.018) and being underweight or obese were slightly stronger in patients <60 years (0.031) (appendix, Table e-2). However, no clear patterns were observed.

Sensitivity analyses

We re-ran the main analysis varying the PHN definitions. Most confidence intervals included the point estimate from the main analysis (appendix, Table e-3), except for: PHN at 30 days was associated with antiviral use (adjOR:1.12, 99%CI:1.06-1.18), yet less strongly associated with ophthalmic zoster (adjOR:1.72, 99%CI:1.56-1.91); restricting the outcome to diagnosed PHN only, the effect of ophthalmic zoster (adjOR:2.67, 99%CI:2.24-3.19) and a 10-year increase in age between 50-79 years (adjOR:2.08, 99%CI:1.92-2.24) became stronger and the effect of female gender disappeared (adjOR:1.00, 99%CI:0.89-1.14).

We explored in *post-hoc* analysis this loss of an association with female gender (using the primary PHN definition). The effect of female gender on PHN was driven by cases of PHN defined using tricyclic antidepressant use, yet we found evidence suggesting prescribing practices for PHN differ by gender (appendix, section e-IV).

Of 7,416 patients with hypothyroidism, 599 (8.1%) developed PHN. The fully adjusted OR between hypothyroidism and PHN indicated no association (adjOR:1.01, 99%CI:0.90-1.14, adjusted for variables in Table 3 Model 2); furthermore, mean yearly consultation rates among patients with our risk factors of interest were very variable (appendix, Table e-6), showing no consistent pattern with PHN risk.

Accounting for missing BMI and smoking data using multiple imputation made no difference to the results (appendix, Table e-7). Restricting to shorter follow-up periods (specifically 120 and 180 days) also had no major effect on the results (appendix, Figure e-4).

7.2.5. Discussion

This study shows older age and severe immunosuppression, such as recently having lymphoma or leukaemia, are the strongest risk factors for PHN among zoster patients. Although immunosuppressed patients are not currently eligible for vaccination, promising research on a new sub-unit zoster vaccine (HZ/su) may enable vaccination within this group.[47] Other risk factors included: autoimmune conditions (RA, SLE and IBD), COPD, depression, diabetes, asthma, lower socioeconomic status, smoking, being under- or overweight and non-truncal zoster. Antivirals given at zoster were not associated with PHN risk overall, but there was some weak evidence that their use mitigated the increased risks associated with leukaemia, SLE, COPD and smoking.

This study addresses an absence in the literature of well-powered studies assessing PHN risk factors.[181] The study benefits from: being the largest study addressing this question; being population-based; using a dataset broadly representative of the UK;[85] tightly accounting for confounding by age; and using a more precise definition of PHN than earlier studies using routinely collected data.

Despite its strengths, this study has some limitations. Although we attempted to reduce misclassification of PHN by basing our definition on a validated method for administrative data,[102] PHN incidence is lower than previous studies (5.8% versus 7.2% in an Icelandic study with active follow-up of similar aged zoster cases[186]). The reported prevalence of PHN varies hugely across studies. We used a 90 (rather than 30) day definition and included patients <50 years old, which may explain the relatively low PHN prevalence. However, some PHN diagnoses could have been missed. Unidentified cases are likely those with mild pain, who used over-the-counter medications for initial pain relief or (if GP-prescribed treatments were ineffective) for follow-on pain relief. These findings are therefore likely to be generalizable to patients with severe PHN. Another explanation for the low prevalence may be that some immunocompromised patients are treated exclusively in secondary care; however, this is likely to be a few cases only, because PHN is largely treated in primary care.

Certain clinical features of zoster are accepted PHN risk factors, including prodromal pain and increased rash severity.[181] In CPRD, these data are unavailable. These features may lie on the causal pathway or be mediators between our exposures and PHN. For example, leukaemia patients may experience greater viral load, which manifests as a severe rash and increase PHN risk. It would be inappropriate to control for rash severity, as we want the total effect of leukaemia on PHN; lacking data on these clinical features is therefore unlikely to limit our findings.

In numerous studies increasing age is associated with a sharp increase in PHN risk.[23,187] Our study identified a non-linear age effect; PHN risk increased steeply between 50-79 years and attenuated after age 80. A Dutch cohort study among 837 zoster patients[13] suggested PHN incidence continues to increase in individuals >80 years; however PHN was defined as analgesic prescription three months post-zoster, potentially causing misclassification, particularly among older individuals. Other studies report PHN risk lessening around 80 years.[26,100,188] Our observed effect may arise from under-ascertainment of PHN in patients >80 years due to: frailty preventing GP attendance; or PHN-associated pain being superseded by other comorbidities.

Previous studies have not identified depression as a risk factor for PHN,[189-192] unlike our study. We acknowledge our result may be driven by patients requiring tricyclic antidepressants for depression, and being misclassified as PHN cases; when restricting PHN cases to diagnosed PHN only, the association with depression disappeared (adjOR:1.12, 99%CI:0.84-1.49). However, the wide confidence intervals suggest there may have been insufficient power to detect an effect.

The study found no evidence that antivirals protected against PHN. This is unlikely to be attributed to inadequate dosing, as 93% of treated patients received at least the recommended minimum antiviral dose. However, other limitations could explain this null finding. In primary care, patients with severe zoster are recommended to receive antivirals, yet are also more likely to develop PHN. This may introduce confounding by indication and mask a protective effect. Also, trial data has assessed the efficacy of antivirals administered within 72 hours of rash onset.[31] Although 97.5% of patients were prescribed antivirals on the day of zoster diagnosis, zoster treatment initiation may occur >72 hours after rash onset, when the effect of antivirals is unproven. Although data on time from actual rash onset to presentation at general practitioners is not available in this data set, two previous UK studies suggest 50-65% of patients present within 72 hours,[193,194] leaving a number of patients treated after 72 hours from rash onset.

Our recent systematic review of PHN risk factors concluded there was no consensus regarding immunosuppression as a risk factor for PHN.[181] The present study demonstrates that immunosuppression is associated with greater PHN risk and the study had sufficient power to assess the effect of specific immunosuppressive conditions and therapies on PHN risk. Our study is also novel in identifying autoimmune conditions as PHN risk factors; autoimmune conditions had scarcely been assessed previously, though SLE was associated with over two-fold increased risk of PHN in a large Taiwanese cohort study.[195]

Disentangling the role of diseases and their drug treatments on the PHN risk is challenging. There was little evidence that the increased risks associated with severely immunosuppressive conditions were mediated by immunosuppressive drugs. However, treatment such as chemotherapy, given in secondary care, is not captured in CPRD and probably explains at least part of the increased risk. The effects of IBD and RA on PHN were less pronounced after adjusting for immunosuppressive treatments, suggesting that the association is driven predominantly by exposure to these drugs. By contrast, the effect of SLE did not appear to be

mediated by immunosuppressive therapies, although CRPD lacks reliable data on newer biological therapies.

Establishing the role of severe immunosuppression and autoimmune conditions on PHN risk may help shed light on the underlying pathophysiological mechanisms that lead to PHN, which are poorly understood. Two key aetiological hypotheses are: that PHN is caused by a persistence of varicella-zoster virus following zoster; or by increased neuronal excitability and alteration of pain perception.[33,34] Our finding of a strong association between immunosuppression and PHN risk seems to support the former hypothesis; lower cell-mediated immunity may lead to higher levels of virus during acute infection and thus an increased risk of PHN.

Cost-effectiveness studies are needed to determine the value in vaccinating patients with identified risk factors for PHN against zoster. Those of older age and with severe immunosuppression were at the highest risk of PHN. Strategies to prevent zoster in patients with severe immunosuppression are an increasing priority as these patients are not currently eligible for zoster vaccination, although the new development of a subunit vaccine provides a promising alternative.[47]

Table 1: Postherpetic neuralgia classifications. The primary analysis included diagnosed, probable and possible postherpetic neuralgia patients

PHN classification	
Diagnosed PHN	PHN code* (90-365 days post-zoster)
Probable PHN	Zoster code and prescription consistent with PHN• on same day (90-365 days post-zoster)
	Non-specific neuralgia code (90-365 days post-zoster)
	NEW anticonvulsant or capsaicin cream or lidocaine patch prescription (90-180 days post-zoster)
	NEW tricyclic antidepressants 90-180 days post-zoster with no other indication on the day of the prescription, plus evidence of the drug being prescribed for zoster or PHN previously†
Possible PHN	**NEW** tricyclic antidepressants 90-180 days post-zoster with no other indication on the day of the prescription
	NEW strong painkiller 90-180 days following zoster with no other indication on the day of the prescription, plus evidence of the drug being prescribed for zoster or PHN previously†
	Non-specific neuropathic pain code (90-365 days post-zoster)

PHN: Postherpetic neuralgia.
*Read code for PHN in CPRD or (for those with linked data) an ICD10 PHN code in the primary diagnosis field within any episode of linked HES.
•Prescriptions included anticonvulsants, tricyclic antidepressants, capsaicin cream or lidocaine patch.
NEW prescriptions were defined as no previous prescriptions of the same medication type 12 months to two weeks prior to zoster, to increase the likelihood of the medication being prescribed for PHN (medications may have been prescribed for pain management two weeks pre-zoster, if zoster initially presented without a rash).
†Here, previously is defined as a prescription 0-89 days following zoster.
Medications indicative of zoster were only considered in the 90-180 day period after zoster diagnosis (rather than 90-365 days) to reduce the chance of misclassifying other reasons for medication use as PHN.

Table 2: Baseline characteristics of 119413 eligible zoster cases and the proportion developing PHN

	Total cohort, n (%)	No. with PHN, n (%)
Total	119413 (100)	6956 (5.8)
Demographic characteristics		
Age (in years)		
<50	33010 (27.6)	588 (1.8)
50-79	72744 (60.9)	4623 (6.4)
≥80	13659 (11.4)	1745 (12.8)
Gender		
Male	48250 (40.4)	2467 (5.1)
Female	71163 (59.6)	4489 (6.3)
Socioeconomic status (practice level)[1]		
1 (least deprived)	24058 (20.1)	1282 (5.3)
2	23653 (19.8)	1288 (5.4)
3	24568 (20.6)	1443 (5.9)
4	24994 (20.9)	1557 (6.2)
5 (most deprived)	22140 (18.5)	1386 (6.3)
Severe Immunosuppression		
HIV	99 (0.1)	6 (6.1)
Leukaemia	153 (0.1)	21 (13.7)
Lymphoma	314 (0.3)	40 (12.7)
Myeloma	312 (0.3)	53 (17.0)
Hematopoietic stem cell transplantation	17 (0.0)	5 (29.4)
Other unspecified cellular immune deficiencies	60 (0.1)	8 (13.3)
Oral corticosteroids[2]	365 (0.3)	53 (14.5)
Other immunosuppressive therapy[2]	1708 (1.4)	145 (8.5)
Autoimmune conditions		
Rheumatoid Arthritis	2474 (2.1)	225 (9.1)
Systemic Lupus Erythematosis	307 (0.3)	29 (9.4)
Inflammatory Bowel Disease	1469 (1.2)	110 (7.5)
Other comorbidities		
COPD	5060 (4.2)	669 (13.2)
Asthma	8267 (6.9)	512 (6.2)
Chronic Kidney Disease	5989 (5.0)	635 (10.6)
Depression	5459 (4.6)	380 (7.0)
Personality disorder	774 (0.6)	53 (6.8)
Diabetes	8492 (7.1)	789 (9.3)
Diabetes type		
No diabetes	110921 (92.9)	6167 (5.6)
Type 1	282 (0.2)	10 (3.5)
Type 2	7744 (6.5)	740 (9.6)
Type not specified	466 (0.4)	39 (8.4)
Recent cancer diagnosis	1203 (1.0)	97 (8.1)
Health behaviours and characteristics of zoster episode		
Smoking[3]		
Non-smoker	45775 (38.3)	2326 (5.1)
Current smoker	30756 (25.8)	1646 (5.4)
Ex-smoker	41731 (34.9)	2946 (7.1)
BMI Category[3]		
Underweight (BMI <18.5)	2150 (1.8)	188 (8.7)
Normal Weight (BMI 18.5-24.9)	42051 (35.2)	2398 (5.7)
Overweight (BMI 25-30)	39934 (33.4)	2395 (6.0)
Obese (BMI ≥30)	24249 (20.3)	1560 (6.4)
Antiviral record within 7 days of zoster	68882 (57.7)	4248 (6.2)
Anatomical site of zoster		
Site Unspecified	113000 (94.6)	6214 (5.5)
Non-Truncal (excluding ophthalmic zoster)	736 (0.6)	74 (10.1)
Ophthalmic zoster	5677 (4.8)	668 (11.8)

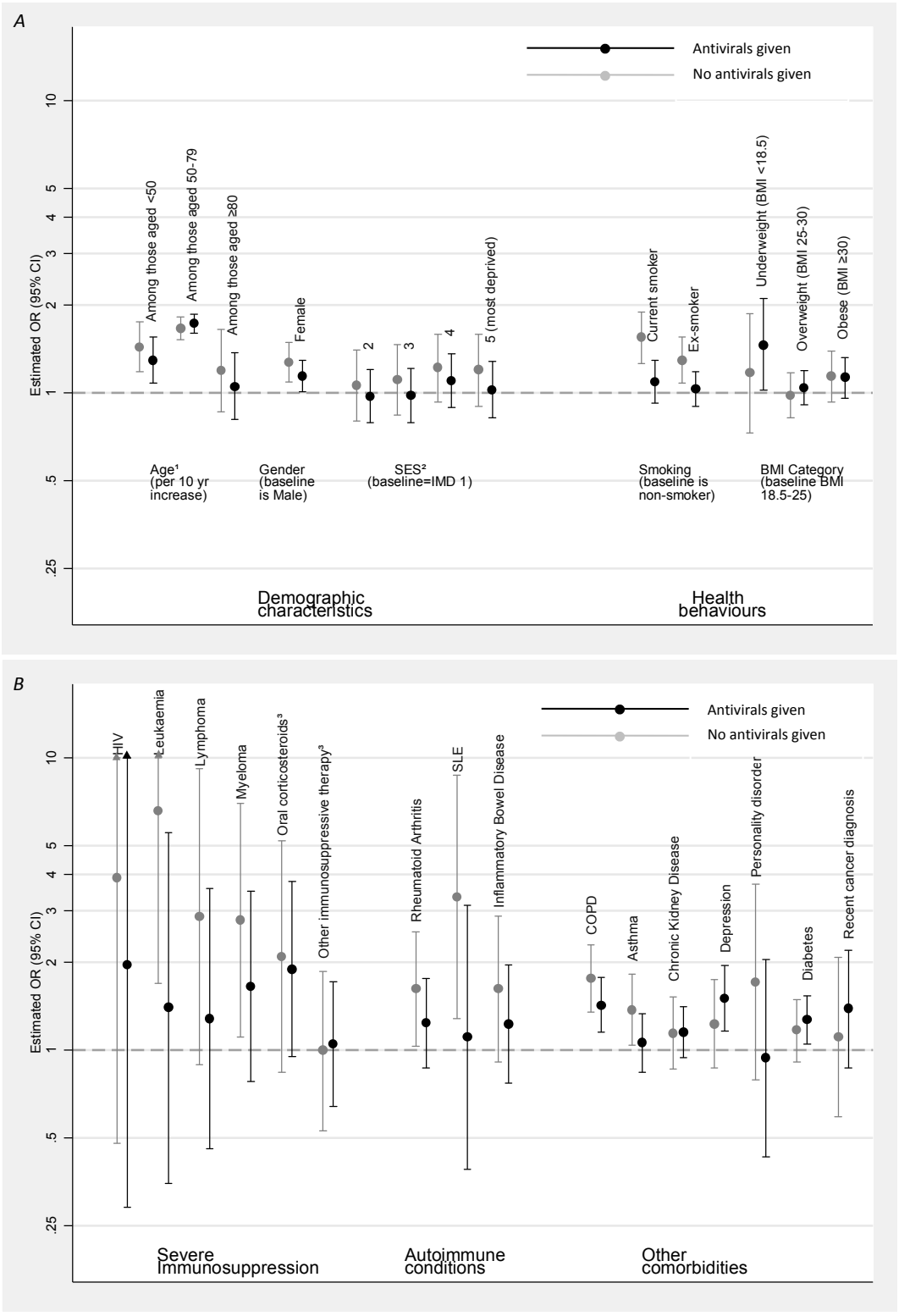
[1]Measured by Index of Multiple deprivation score. [2]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day). [3]Missing data: complete for all variables, except smoking (n=1151 (1.0%) missing) and BMI category (n=11029 (9.3%) missing).

Table 3: Unadjusted and adjusted associations between postherpetic neuralgia and demographic risk factors, comorbidities and health behaviours

	Unadjusted OR (99% CI)	Age-adjusted OR (99% CI)	Model 1: Adjusted OR† (99% CI)	Model 2: Model 1 additionally adjusted for immunosuppressive therapies, OR (99% CI)
Demographic characteristics				
Age (years) [Estimated ORs for 10 year increase in age within the specified age-band][1]				
Among those aged <50	1.48 (1.35-1.63)	-	1.42 (1.28-1.58)	1.42 (1.28-1.57)
Among those aged 50-79	1.74 (1.68-1.81)	-	1.70 (1.63-1.78)	1.70 (1.63-1.78)
Among those aged ≥80	0.99 (0.87-1.14)	-	1.09 (0.94-1.27)	1.10 (0.94-1.28)
Female	1.25 (1.17-1.34)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	1.19 (1.10-1.27)
Socioeconomic status (practice level)[2]				
1 (least deprived)	1.00	1.00	1.00	1.00
2	1.01 (0.89-1.15)	1.05 (0.92-1.19)	1.04 (0.91-1.18)	1.04 (0.91-1.18)
3	1.09 (0.96-1.24)	1.09 (0.96-1.24)	1.09 (0.96-1.24)	1.09 (0.96-1.24)
4	1.17 (1.03-1.33)	1.19 (1.05-1.35)	1.17 (1.03-1.32)	1.17 (1.03-1.32)
5 (most deprived)	1.19 (1.04-1.35)	1.26 (1.11-1.44)	1.20 (1.06-1.37)	1.20 (1.06-1.37)
Severe Immunosuppression				
HIV	1.04 (0.35-3.08)	2.40 (0.80-7.27)	2.23 (0.66-7.53)	2.17 (0.64-7.37)
Leukaemia	2.65 (1.44-4.87)	2.32 (1.25-4.33)	2.06 (1.08-3.95)	2.07 (1.08-3.96)
Lymphoma	2.38 (1.54-3.70)	2.39 (1.53-3.75)	2.44 (1.52-3.90)	2.45 (1.53-3.92)
Myeloma	3.33 (2.25-4.93)	2.36 (1.58-3.51)	2.18 (1.44-3.31)	2.17 (1.43-3.29)
Hematopoietic stem cell transplantation	6.89 (1.73-27.52)	11.25 (2.73-46.44)	5.85 (1.30-26.29)	5.91 (1.32-26.59)
Other unspecified cellular immune deficiencies	2.43 (0.91-6.52)	2.19 (0.80-6.02)	2.15 (0.78-5.97)	2.12 (0.77-5.89)
Oral corticosteroids[3]	2.76 (1.88-4.07)	2.55 (1.71-3.78)	-	2.26 (1.51-3.40)
Other immunosuppressive therapy[3]	1.52 (1.21-1.91)	1.46 (1.16-1.84)	-	1.21 (0.92-1.58)
Autoimmune conditions				
Rheumatoid Arthritis	1.64 (1.36-1.97)	1.27 (1.06-1.54)	1.20 (0.99-1.46)	1.13 (0.91-1.39)
Systemic Lupus Erythematosis	1.70 (1.03-2.82)	1.95 (1.16-3.27)	1.82 (1.08-3.08)	1.76 (1.04-2.98)
Inflammatory Bowel Disease	1.31 (1.01-1.70)	1.33 (1.03-1.74)	1.27 (0.97-1.67)	1.22 (0.93-1.60)
Other comorbidities				
COPD	2.60 (2.32-2.91)	1.66 (1.48-1.86)	1.54 (1.36-1.74)	1.53 (1.35-1.72)
Asthma	1.07 (0.95-1.21)	1.22 (1.08-1.39)	1.21 (1.07-1.38)	1.21 (1.06-1.37)
Chronic Kidney Disease	2.01 (1.79-2.25)	1.17 (1.04-1.32)	1.09 (0.96-1.23)	1.08 (0.96-1.22)
Depression	1.21 (1.05-1.40)	1.53 (1.32-1.77)	1.39 (1.20-1.62)	1.40 (1.20-1.62)
Personality disorder	1.18 (0.81-1.70)	1.37 (0.94-1.99)	1.25 (0.85-1.84)	1.25 (0.85-1.85)
Diabetes	1.74 (1.57-1.93)	1.26 (1.13-1.40)	1.19 (1.07-1.33)	1.19 (1.07-1.33)
Diabetes Type				
No diabetes	1.00	1.00	1.00	1.00
Type 1	0.62 (0.27-1.44)	1.45 (0.62-3.36)	1.53 (0.66-3.55)	1.51 (0.65-3.51)
Type 2	1.79 (1.61-1.99)	1.24 (1.12-1.38)	1.17 (1.05-1.31)	1.17 (1.05-1.31)
Type not specified	1.55 (1.00-2.39)	1.62 (1.04-2.52)	1.54 (0.99-2.41)	1.54 (0.98-2.40)
Recent cancer diagnosis	1.42 (1.08-1.88)	1.05 (0.79-1.38)	1.06 (0.79-1.41)	1.06 (0.79-1.41)
Health behaviours and characteristics of zoster episode				
Smoking				
Non-smoker	1.00	1.00	1.00	1.00
Current smoker	1.06 (0.97-1.15)	1.32 (1.21-1.45)	1.26 (1.15-1.39)	1.27 (1.15-1.39)
Ex-smoker	1.42 (1.32-1.54)	1.21 (1.12-1.30)	1.14 (1.05-1.24)	1.14 (1.05-1.24)
BMI Category				
Underweight (BMI <18.5)	1.58 (1.29-1.94)	1.38 (1.12-1.70)	1.25 (1.01-1.54)	1.25 (1.01-1.54)
Normal Weight (BMI 18.5-24.9)	1.00	1.00	1.00	1.00
Overweight (BMI 25-30)	1.05 (0.98-1.14)	0.99 (0.92-1.07)	1.01 (0.93-1.09)	1.01 (0.93-1.09)
Obese (BMI ≥30)	1.13 (1.04-1.24)	1.18 (1.08-1.29)	1.13 (1.03-1.24)	1.13 (1.03-1.24)
Antiviral record within 7 days of zoster	1.16 (1.09-1.24)	1.05 (0.98-1.12)	1.04 (0.97-1.12)	1.04 (0.97-1.11)
Anatomical site of zoster				
Site Unspecified	1.00	1.00	1.00	1.00
Non-Truncal (excluding ophthalmic zoster)	1.94 (1.41-2.67)	2.34 (1.68-3.25)	2.20 (1.54-3.12)	2.19 (1.54-3.11)
Ophthalmic zoster	2.29 (2.05-2.56)	1.93 (1.72-2.16)	1.94 (1.73-2.19)	1.95 (1.73-2.19)

†Adjusted for age, gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antivirals. [1]ORs estimate the effect of a 10-year increase in age on PHN derived, in age groups <50, 50-79 and ≥80, from piecewise linear splines. [2]Measured by Index of Multiple deprivation score. [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day). There was no evidence of collinearity between variables (indicated by a 20% increase in standard errors in the fully, versus age-adjusted, model for each risk

Figure 1 A and B: Adjusted† associations between postherpetic neuralgia and A) demographic risk factors and health behaviours and B) comorbidities, stratified by whether a patient received antivirals during acute zoster. Analyses are restricted to 69,661 patients for whom antiviral status was most likely to be available.* Full results can be found in appendix, Table e-8.



†Adjusted for age, gender, socioeconomic status (SES), HIV, leukaemia, lymphoma, myeloma, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking and BMI category. Please note hematopoietic stem cell transplantation and other unspecified cellular immune deficiencies were excluded due to too few numbers. *Patients excluded were those with zoster diagnosed in HES or having a HES visit for zoster 7 days after diagnosis (n=494), patients who were not HES-linked (n=45,418) and patients with non-truncal zoster (n= 3,840), as their antiviral use may not be recorded in CPRD.[1]ORs estimate the effect of a 10-year increase in age on PHN derived, in age groups <50, 50-79 and ≥80, from piecewise linear splines. [2]Measured by Index of Multiple deprivation score (IMD1=least deprived, IMD5=most deprived). [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day). Interaction terms between antiviral use and other risk factors were added to the model one at a time.

7.3. Accepted appendices

e-I: Further details on definitions of risk factors

Aside from the discussion below about possible misdiagnosis of herpes simplex patients as zoster patients, this section (e-I) of the appendices repeats information written in chapter 3, "Data sources and variable definitions", therefore has been placed in the thesis appendices (appendix IV).

Possible misdiagnosis of herpes simplex as herpes zoster

Of the 119,413 cohort, 1586 (1.6%) patients had a further zoster code 90-365 days after their first zoster. Of these 215 (13.6%) had a PHN medication or a PHN diagnostic code, and in the main analysis these were categorised as PHN. However, the other 1371 patients had a zoster code without medications or codes suggesting PHN. There were three possible explanations for these patients. The first is that they were recurrent zoster; however this is very rare in immunocompetent patients, who made up 96% of the group. The second is that these are poorly coded PHN patients, however it seems unlikely that no PHN prescriptions would be given. The third, and perhaps most plausible explanation is that these patients were misdiagnosed herpes simplex cases. Herpes simplex is known to recur more frequently than zoster and can, albeit rarely, present with dermatomal distribution similar to herpes zoster. [196] Further to this, half of the patients were prescribed an antiviral at their later zoster diagnosis, which may further indicate misdiagnosis of herpes simplex. Therefore as a sensitivity analysis we excluded all 1586 patients with a further zoster code following first zoster diagnosis.

e-II: Modelling age

a) Using restricted cubic splines to adjust for age

There was very good evidence that the relationship between PHN and age at zoster diagnosis was not linear (test for departure from linear trend $P<0.001$); in other words there was no evidence of a constant increase in the log odds of PHN per unit increase in age.

Categorizing age into groups was considered but not pursued as this may lead to loss of information. Splitting age into categories would assume there is a single exposure effect within that category; considering age is such a strong risk factor for PHN this may be an unrealistic assumption. Further to that, cut-points are often arbitrarily chosen potentially heavily influencing the apparent shape of the age-PHN relationship.[197] Allowing for a non-linear relationship would improve our understanding of the relationship between age and PHN,

reduce the possibility of residual confounding by age when including it as a confounder and improve the model from a statistical viewpoint.

We therefore utilised restricted cubic splines to make better use of within category information and allow for non-linearity. Splines are a type of smoothing function which provide a continuous curve rather than a step function. Cubic splines are one type of spline where the effect measure is regressed on a cubic function of exposure (here, age), across several different regions or categories of exposure and spanning the entire range of exposure. So cubic splines consist of piecewise cubic polynomials (in other words curves with up to 2 turning points) between specified "knots". The "restricted" means the relationships will be linear before the first knot and after the last knot. A single smooth curve across these regions is then produced.

As there was no obvious biological rationale for where to place the knots, they were placed at equal percentiles of age. The number of knots was chosen by assessing the Akaike information criterion (AIC) when 3 to 7 knots were included: the AIC criterion is a measure of the relative quality of a model given a set of data and thus provides a method to select the most appropriate model. AIC rewards goodness of fit of a model but includes a penalty for increasing number of parameters; this therefore discourages over-fitting (including more parameters will almost always improve the fit of the model). The model with the minimum AIC is preferred. Here, the AIC reduced from 49825 to 49758 when modelling it as a 3-knot and 5-knot respectively. The reduction in AIC beyond 5 knots was marginal (6 knots: 49753, 7 knots: 49728), therefore 5 knots were chosen (with knots at 26, 49, 61, 71, 84 years).

b) Using piecewise linear splines to estimate the effect of age on PHN

Restricted cubic splines provide a smooth curve of the age-PHN relationship and impose few constraints on that curve; however, they have the drawback of not providing interpretable parameters. Linear splines were used to estimate the relationship between age and PHN as a piecewise linear function, in other words a function composed of linear (straight line) segments between the specified knots. The points (knots) at which the linear segments join were determined by first, looking at the restricted cubic spline graph to assess where the effect of age on PHN appeared to alter. We then fitted piecewise linear models across various possible threshold values and used the one giving the lowest AIC. The knots were at 50 and 80 years.

e-III: Dealing with missing data

We used multiple imputation to account for missing data. Missing data were present for BMI and smoking. In total, 91% percent of patients had complete data for all variables. To maximise the use of the data while properly incorporating the extra uncertainty arising due to missing data, multiple imputation by chained equations [127] was used to impute missing values for BMI and smoking from multinomial models. The imputation model included all covariates from the main outcome model (Model 2 in table 2), with age included as a 5-knot restricted cubic spline. We also included extra comorbidities, identified using medical Read codes, to look for additional markers of BMI or smoking related diseases. These included: stroke, peripheral artery disease, angina (stable and unstable), acute coronary syndrome, congestive heart failure, myocardial infarction, hypertension and alcoholic liver disease (including portal hypertension) and pancreatitis. Five imputed datasets were created and combined for analysis. Distributions of imputed values were visually checked for comparability with the observed data. This was not done as the primary approach due to possible violation of the "missing at random" assumption for BMI and smoking.

e-IV: Investigating gender as a risk factor for PHN

In a sensitivity analysis which restricted the PHN definition to diagnosed PHN only (that is, patients with a Read code for PHN 90-365 days following zoster), female gender was no longer associated with an increased risk of PHN (table e-2, sensitivity analysis 2). We carried out some post-hoc analysis to investigate this further.

Gender distribution by PHN classification (diagnosed, probable and possible PHN)

The proportion of females among those with diagnosed, probable and possible PHN was 61.8%, 65.4%, 66.4% respectively. The effects of gender on PHN risk showed some variation across PHN classifications (see Table e-3); gender was not associated with diagnosed PHN, whilst females appeared to be at increased risk of probable and possible PHN. The association between gender and PHN according to the exact source of evidence for PHN was calculated (see table e-6); PHN defined from prescription of tricyclic antidepressants was driving the increased risk of probable and possible PHN in females (see table e-4, analysis A).

Three hypotheses were suggested and explored to explain this pattern:

c) *Patients with depression were being misclassified as PHN cases:* Of particular concern was that PHN cases defined from tricyclic antidepressant use were actually patients with depression, a condition widely known to be more common in females. To explore whether there may be systematic misclassification of PHN, the effects of gender on PHN risk were stratified by history of mental health problems ever in CPRD prior to zoster. These mental health problems included symptoms or diagnoses suggesting depression, anxiety, bipolar, or suicidal ideation. In both strata there appeared to be an increased risk of tricyclic antidepressant-defined PHN, suggesting the association between PHN and gender isn't driven entirely by previous mental health problems (see table e-4, analysis B and C). As a secondary check, patients with depression (using depression diagnosis and depression symptom codes) in the year prior to zoster or the year following zoster were excluded; there was still an increased risk of PHN defined by tricyclic antidepressant use among females (see table e-6; analysis D).

d) *Females with PHN are more likely to be prescribed medications than males with PHN:* Among 2156 patients with "diagnosed PHN", 33% (701/2156) did not receive any PHN medications 90-180 days following zoster. It was hypothesised that females may be more likely to receive treatment when visiting their GP; however, there was little difference in the proportion of male and females prescribed medications 90-180 days following zoster (69.8% vs 66.1% respectively, chi-squared P-value=0.07).

e) *Females with PHN are more likely to receive a tricyclic antidepressant than males with PHN:* Among patients with diagnosed PHN who received treatment 90-180 days following zoster (n=1455), females were more likely to receive tricyclic antidepressants in the 90-180 day period than males; 43.6% (384/880) females received a tricyclic, compared to 34.8% (200/575) of males (chi² P-Value=0.001). This suggests GPs may have different prescribing practices for males and females, which may explain why PHN defined through tricyclic antidepressant use is associated with gender.

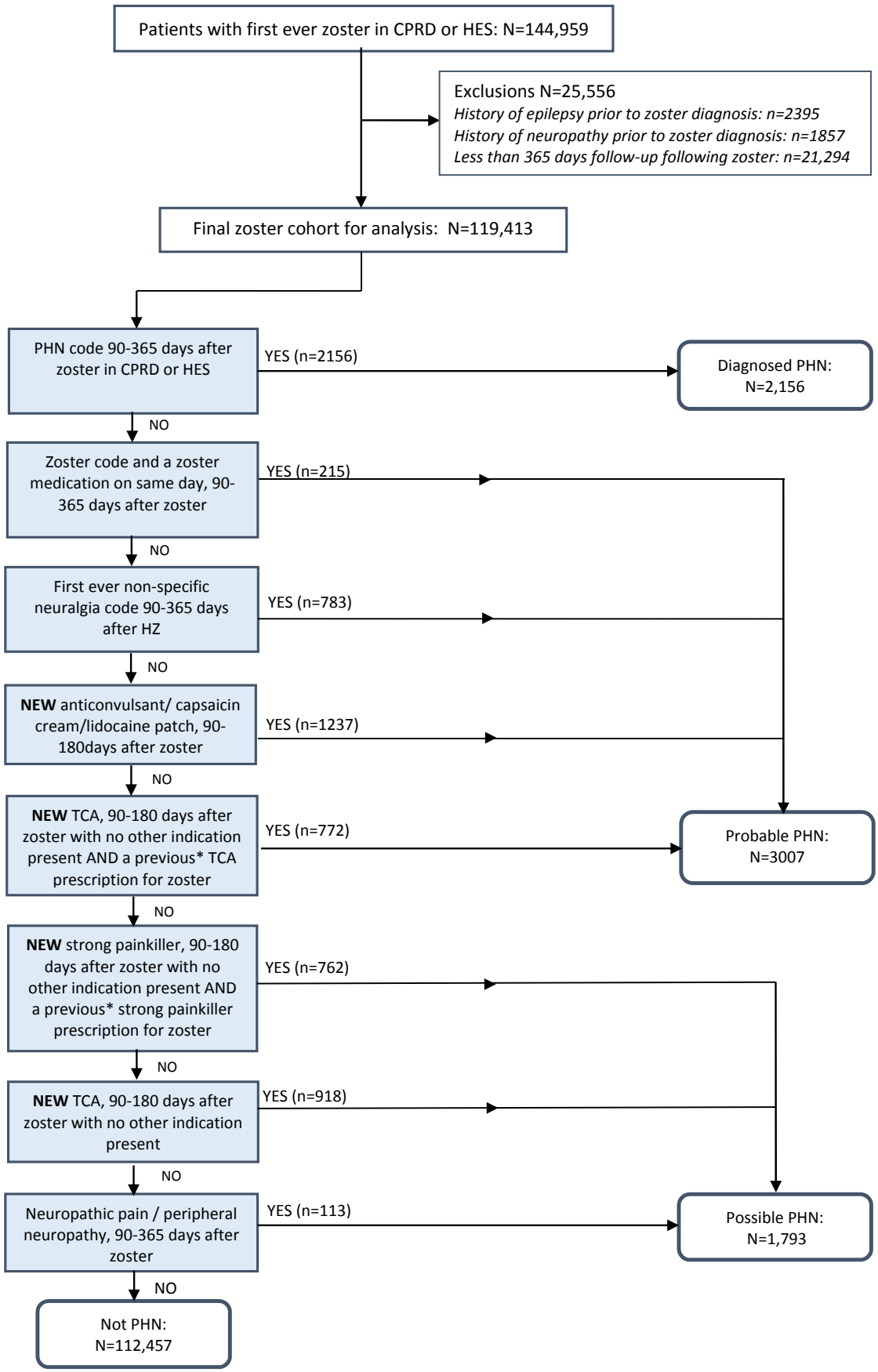
We therefore concluded that the association between gender and probable and possible PHN reflects different prescribing practices; specifically that female PHN patients are more likely to be given a tricyclic antidepressant compared to male PHN patients.

e-V: Effect of antivirals in patients with immunosuppression

Post-hoc analysis explored whether antivirals reduced the risk of PHN in patients with immunosuppression. Among patients with *any* severely immunosuppressive condition (grouped due to small numbers; n=1614), 8.3% of those given antivirals developed PHN (86/1,043), compared to 10.9% not given antivirals (62/571); however this was compatible with chance variation (OR for the effect antiviral use on PHN risk, among those with severe immunosuppression: 0.73, 99%CI:0.45-1.18, adjusted for variables in Table 2 Model 2).

Using antivirals to prevent PHN in patients with immunosuppression is under-researched; many trials exclude these patients.[31] In this *post-hoc* analysis, the rate of PHN among severely immunosuppressed patients given antivirals was lower, than those not given antivirals, but the confidence interval around the OR was wide and included one, reflecting the small numbers available. Given that *a priori* we assumed antiviral use would be associated with greater risk of PHN (due to confounding by indication; patients with severe zoster are more likely to develop PHN and receive antivirals) a lower risk of PHN in this group, albeit non-significant, suggests antiviral effectiveness in patients with severe immunosuppression should be investigated further. Capture of antiviral therapy among the more severely immunosuppressed patients may be poor, as patients could be immediately referred for intravenous antiviral therapy; therefore, differential misclassification of antiviral exposure may be driving the higher risk of PHN in the “no antivirals” group.

Figure e-1: Flow diagram describing the identification of diagnosed, probable and possible postherpetic neuralgia

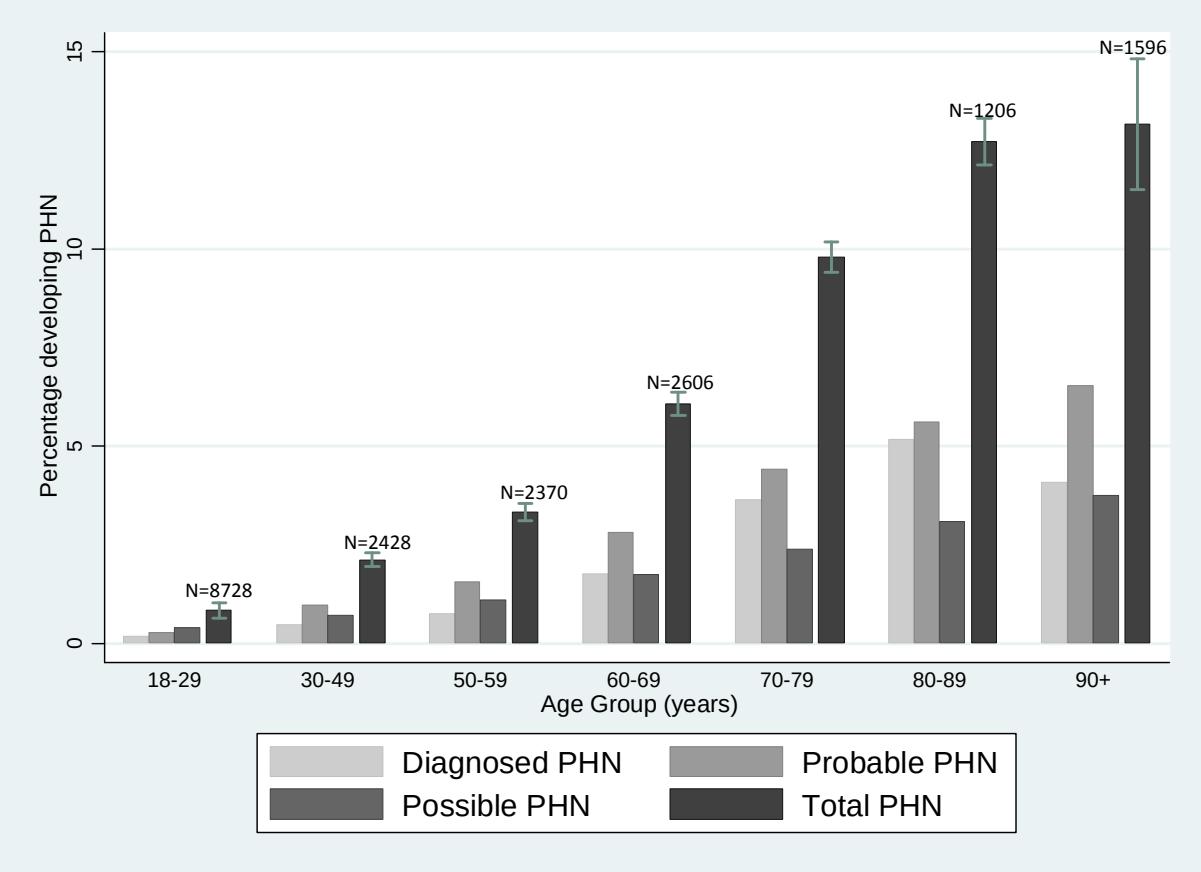


Notes

TCA: tricyclic antidepressants. **NEW** medications defined as no previous prescription of the same drug class 12 months to two weeks prior to zoster diagnosis.

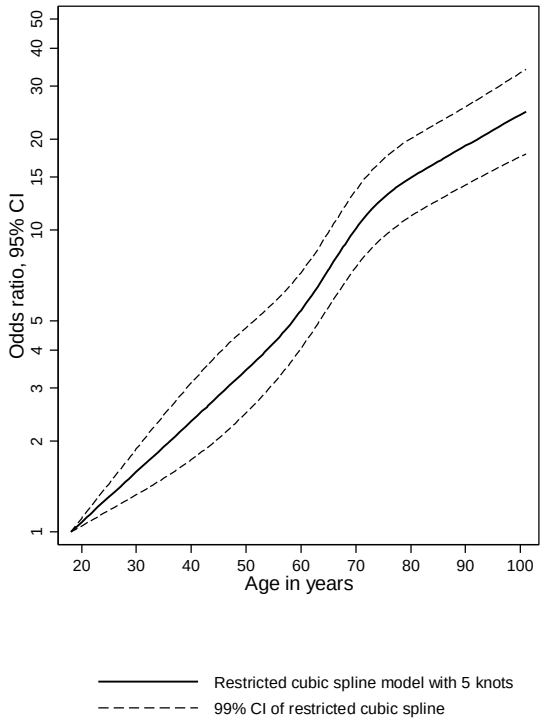
*A previous prescription for zoster is defined as zoster/PHN code and prescription (TCA or strong painkiller) on the same day, 0-89 days after zoster

Figure e-2: Prevalence of postherpetic neuralgia in the cohort of 119,413 zoster patients, by age group and postherpetic neuralgia classification (diagnosed, probable or possible postherpetic neuralgia)



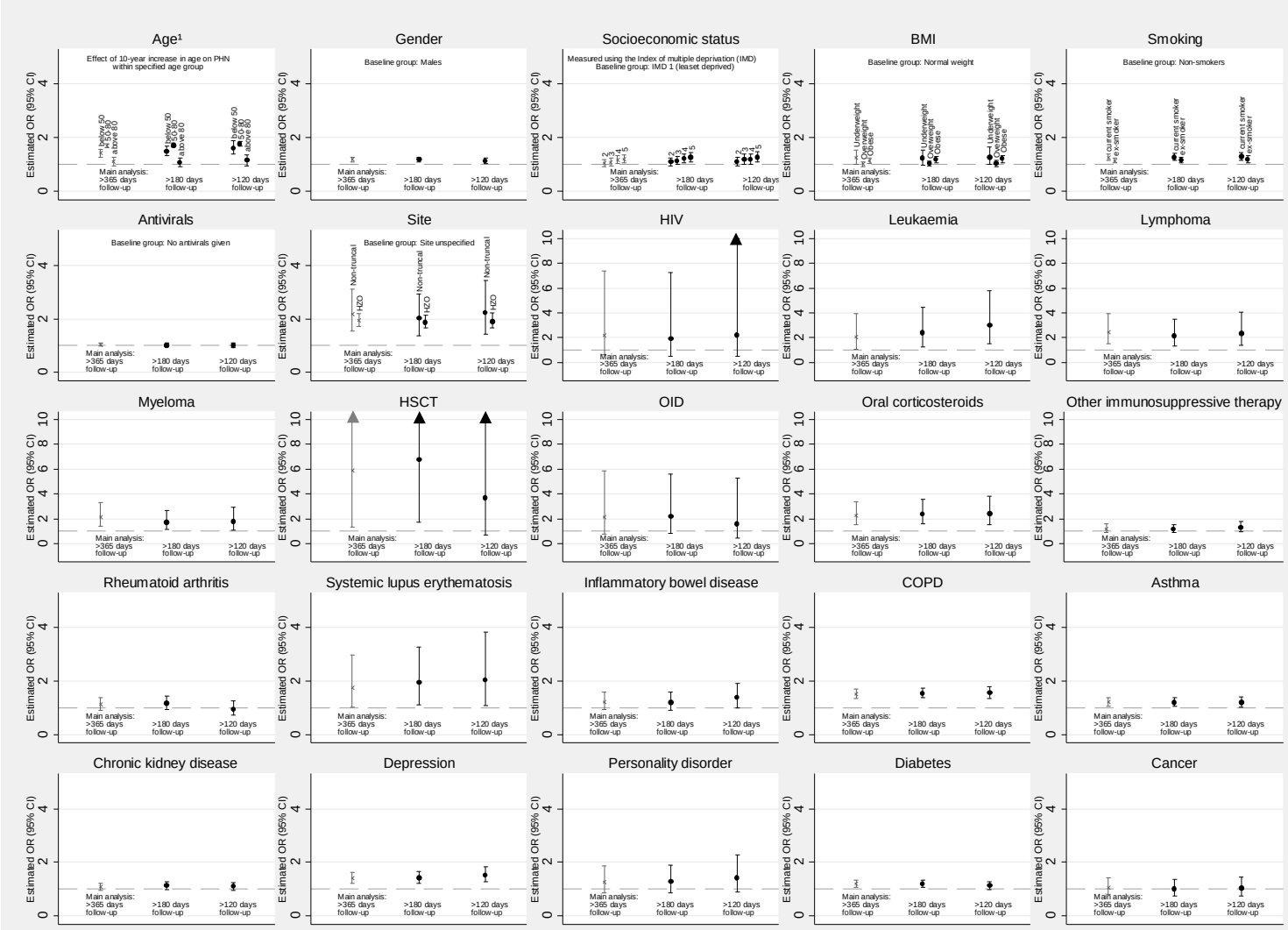
PHN: Postherpetic neuralgia. See Table 1 for description of PHN classifications.

Figure e-3: Association between postherpetic neuralgia and age at zoster diagnosis, modelled using a 5-knot restricted cubic spline



The 5-knot restricted cubic spline model is centred at 18 years. Knots were placed at equal percentiles of the data, with Akaike information criterion used to select optimal knots. Curves estimated were adjusted for gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, antiviral use and site of zoster (as in Model 2 from table 2). The data are shown on a natural-log scale. See Appendix, section A3, for more detailed explanation of modelling age using splines.

Figure e-4: Estimated associations between risk factors and PHN, with minimum number of days follow-up required lowered to reduce excluded patients



ORs are adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity unless otherwise specified[1]), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use. Note: The main analysis includes only patients followed up for at least 365 days following rash onset (Risk of PHN 5.8% (6956/119413). [1]Age not modelled as a 5-knot restricted cubic spline but included as a linear effect, with slopes changing at age 50 and 81. The two sensitivity analyses lowered the restrictions on follow-up time, so all patients followed up for 180 and 120 days were included in the analysis (Risk of PHN 4.9% (6345/129592) and 3.1% (4145/133312) respectively). Please note the y axis are not identical for all graphs. OID=other immune deficiencies. COPD=Chronic obstructive pulmonary disorder. HSCT=hematopoietic stem cell transplantation.

Table e-1: Relative risk of PHN in patients with risk factors of interest stratified by age of diagnosis

	<70 years				≥70 years				
	Total cohort, n	**Risk of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**Total cohort, n**	**Risk of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**P-value for interaction**
Total	82776 (100)	2959 (3.6)			36637 (100)	3997 (10.9)			
Demographic characteristics									
Female	48215 (58.2)	1850 (3.8)	1.20 (1.08-1.32)	1.19 (1.07-1.32)	22948 (62.6)	2639 (11.5)	1.14 (1.04-1.25)	1.18 (1.07-1.31)	0.872
Socioeconomic status (practice level)[1]									
1 (least deprived)	16525 (20.0)	528 (3.2)	1.00	1.00	7533 (20.6)	754 (10.0)	1.00	1.00	0.811
2	16625 (20.1)	563 (3.4)	1.07 (0.89-1.29)	1.08 (0.89-1.30)	7028 (19.2)	725 (10.3)	1.04 (0.89-1.20)	1.02 (0.87-1.19)	
3	16718 (20.2)	581 (3.5)	1.08 (0.90-1.30)	1.08 (0.89-1.29)	7850 (21.4)	862 (11.0)	1.10 (0.96-1.27)	1.11 (0.96-1.29)	
4	17210 (20.8)	662 (3.8)	1.22 (1.02-1.46)	1.17 (0.98-1.40)	7784 (21.2)	895 (11.5)	1.17 (1.02-1.35)	1.16 (1.00-1.34)	
5 (most deprived)	15698 (19.0)	625 (4.0)	1.31 (1.10-1.58)	1.22 (1.01-1.46)	6442 (17.6)	761 (11.8)	1.22 (1.05-1.41)	1.18 (1.01-1.38)	
Severe Immunosuppression									
HIV	95 (0.1)	4 (4.2)	1.78 (0.47-6.75)	1.73 (0.43-6.93)	4 (0.0)	2 (50.0)	9.52 (0.71-127.82)	5.09 (0.21-121.53)	0.667
Leukaemia	92 (0.1)	4 (4.3)	1.09 (0.29-4.13)	1.11 (0.29-4.27)	61 (0.2)	17 (27.9)	3.26 (1.55-6.86)	2.84 (1.31-6.16)	0.234
Lymphoma	222 (0.3)	25 (11.3)	3.10 (1.77-5.42)	3.08 (1.72-5.51)	92 (0.3)	15 (16.3)	1.67 (0.80-3.47)	1.88 (0.87-4.06)	0.407
Myeloma	149 (0.2)	21 (14.1)	3.17 (1.71-5.89)	2.95 (1.55-5.64)	163 (0.4)	32 (19.6)	1.97 (1.18-3.29)	1.96 (1.15-3.32)	0.385
Other unspecified cellular immune deficiencies	37 (0.0)	3 (8.1)	2.18 (0.45-10.62)	1.70 (0.34-8.46)	23 (0.1)	5 (21.7)	2.23 (0.60-8.28)	2.49 (0.65-9.48)	0.835
Oral corticosteroids[2]	233 (0.3)	24 (10.3)	2.76 (1.56-4.86)	2.14 (1.19-3.87)	132 (0.4)	29 (22.0)	2.32 (1.34-4.01)	2.26 (1.29-3.96)	0.866
Other immunosuppressive therapy[2]	1174 (1.4)	77 (6.6)	1.69 (1.24-2.31)	1.28 (0.89-1.84)	534 (1.5)	68 (12.7)	1.26 (0.89-1.76)	1.09 (0.73-1.62)	0.261
Autoimmune conditions									
Rheumatoid Arthritis	1380 (1.7)	98 (7.1)	1.61 (1.22-2.13)	1.29 (0.94-1.76)	1094 (3.0)	127 (11.6)	1.09 (0.85-1.40)	1.02 (0.77-1.36)	0.110
Systemic Lupus Erythematosis	226 (0.3)	16 (7.1)	2.23 (1.13-4.40)	1.74 (0.87-3.50)	81 (0.2)	13 (16.0)	1.65 (0.75-3.62)	1.68 (0.76-3.73)	0.826
Inflammatory Bowel Disease	1051 (1.3)	54 (5.1)	1.41 (0.97-2.03)	1.19 (0.80-1.76)	418 (1.1)	56 (13.4)	1.28 (0.88-1.86)	1.26 (0.86-1.85)	0.863
Other comorbidities									
COPD	1995 (2.4)	208 (10.4)	2.10 (1.72-2.57)	1.83 (1.49-2.26)	3065 (8.4)	461 (15.0)	1.51 (1.31-1.73)	1.41 (1.22-1.64)	0.006
Asthma	6206 (7.5)	276 (4.4)	1.37 (1.16-1.63)	1.33 (1.12-1.58)	2061 (5.6)	236 (11.5)	1.08 (0.89-1.29)	1.08 (0.89-1.31)	0.129
Chronic Kidney Disease	1891 (2.3)	124 (6.6)	1.39 (1.08-1.78)	1.18 (0.92-1.53)	4098 (11.2)	511 (12.5)	1.13 (0.99-1.29)	1.06 (0.93-1.22)	0.290
Depression	4283 (5.2)	204 (4.8)	1.61 (1.32-1.96)	1.42 (1.16-1.74)	1176 (3.2)	176 (15.0)	1.44 (1.16-1.79)	1.34 (1.07-1.69)	0.548
Personality disorder	609 (0.7)	33 (5.4)	1.56 (0.98-2.50)	1.34 (0.83-2.18)	165 (0.5)	20 (12.1)	1.12 (0.60-2.07)	1.07 (0.56-2.07)	0.572
Diabetes	4357 (5.3)	298 (6.8)	1.53 (1.30-1.81)	1.38 (1.16-1.65)	4135 (11.3)	491 (11.9)	1.13 (0.99-1.29)	1.09 (0.95-1.25)	0.004
Recent cancer diagnosis	625 (0.8)	43 (6.9)	1.50 (0.99-2.27)	1.40 (0.90-2.17)	578 (1.6)	54 (9.3)	0.83 (0.57-1.21)	0.88 (0.60-1.28)	0.106
Health behaviours and characteristics of zoster episode									
Smoking									
Non-smoker	31837 (38.5)	899 (2.8)	1.00	1.00	13938 (38.0)	1427 (10.2)	1.00	1.00	0.006
Current smoker	24698 (29.8)	962 (3.9)	1.48 (1.31-1.68)	1.39 (1.22-1.59)	6058 (16.5)	684 (11.3)	1.17 (1.03-1.33)	1.12 (0.97-1.28)	
Ex-smoker	25414 (30.7)	1083 (4.3)	1.28 (1.14-1.45)	1.18 (1.04-1.34)	16317 (44.5)	1863 (11.4)	1.15 (1.05-1.27)	1.10 (0.99-1.23)	
BMI Category									
Underweight (BMI <18.5)	1237 (1.5)	60 (4.9)	1.66 (1.16-2.37)	1.42 (0.99-2.05)	913 (2.5)	128 (14.0)	1.27 (0.98-1.64)	1.18 (0.91-1.53)	0.037
Normal Weight (BMI 18.5-24.9)	28856 (34.9)	960 (3.3)	1.00	1.00	13195 (36.0)	1438 (10.9)	1.00	1.00	

Table e-1: Relative risk of PHN in patients with risk factors of interest stratified by age of diagnosis (continued)

Overweight (BMI 25-30)	26905 (32.5)	979 (3.6)	0.95 (0.84-1.07)	0.97 (0.86-1.09)	13029 (35.6)	1416 (10.9)	1.02 (0.92-1.13)	1.04 (0.94-1.16)	
Obese (BMI ≥30)	17813 (21.5)	829 (4.7)	1.24 (1.10-1.41)	1.17 (1.02-1.33)	6436 (17.6)	731 (11.4)	1.11 (0.98-1.26)	1.08 (0.95-1.22)	
Antiviral record within 7 days of zoster	46332 (56.0)	1775 (3.8)	1.08 (0.97-1.19)	1.05 (0.95-1.16)	22550 (61.6)	2473 (11.0)	1.03 (0.94-1.12)	1.02 (0.93-1.12)	0.800
Anatomical site of zoster									
Site Unspecified	78915 (95.3)	2684 (3.4)	1.00	1.00	34085 (93.0)	3530 (10.4)	1.00	1.00	0.901
Non-Truncal (excluding ophthalmic zoster)	40 (1.4)	40 (7.1)	2.54 (1.64-3.92)	2.31 (1.45-3.68)	34 (0.9)	34 (19.5)	2.13 (1.29-3.51)	2.04 (1.20-3.47)	
Ophthalmic zoster	235 (7.9)	235 (7.1)	1.94 (1.61-2.33)	1.91 (1.58-2.31)	433 (10.8)	433 (18.2)	1.91 (1.65-2.21)	1.96 (1.68-2.28)	

†Adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity unless otherwise specified), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use. Interaction terms between age and other risk factors were added one at a time into the multivariable regression model. [1]Measured by Index of Multiple deprivation score. [2]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day).

Table e-2: Relative risk of PHN in patients with risk factors of interest stratified by age of diagnosis

	<60 years				≥60 years				
	Total cohort, n	**Risk of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**Total cohort, n**	**Risk of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**P-value for interaction**
Total	56711 (100)	1377 (2.4)			62702 (100)	5579 (8.9)			
Demographic characteristics									
Female	33271 (58.7)	917 (2.8)	1.35 (1.16-1.56)	1.31 (1.12-1.54)	37892 (60.4)	3572 (9.4)	1.12 (1.04-1.21)	1.16 (1.07-1.26)	0.141
Socioeconomic status (practice level)[1]									
1 (least deprived)	11204 (19.8)	236 (2.1)	1.00	1.00	12854 (20.5)	1046 (8.1)	1.00	1.00	0.898
2	11425 (20.1)	265 (2.3)	1.11 (0.86-1.44)	1.11 (0.86-1.45)	12228 (19.5)	1023 (8.4)	1.04 (0.91-1.19)	1.03 (0.89-1.18)	
3	11281 (19.9)	265 (2.3)	1.13 (0.87-1.46)	1.12 (0.86-1.45)	13287 (21.2)	1178 (8.9)	1.09 (0.95-1.24)	1.09 (0.95-1.25)	
4	11757 (20.7)	308 (2.6)	1.26 (0.98-1.62)	1.19 (0.93-1.54)	13237 (21.1)	1249 (9.4)	1.18 (1.03-1.34)	1.16 (1.01-1.33)	
5 (most deprived)	11044 (19.5)	303 (2.7)	1.37 (1.06-1.76)	1.24 (0.96-1.61)	11096 (17.7)	1083 (9.8)	1.24 (1.08-1.42)	1.19 (1.04-1.37)	
Severe Immunosuppression									
HIV	90 (0.2)	4 (4.4)	2.08 (0.55-7.88)	2.38 (0.61-9.31)	9 (0.0)	2 (22.2)	3.55 (0.44-28.86)	1.60 (0.10-26.75)	0.635
Leukaemia	55 (0.1)	2 (3.6)	1.34 (0.21-8.74)	1.29 (0.19-8.61)	98 (0.2)	19 (19.4)	2.53 (1.30-4.94)	2.21 (1.10-4.44)	0.554
Lymphoma	128 (0.2)	13 (10.2)	4.46 (2.07-9.63)	4.32 (1.95-9.54)	186 (0.3)	27 (14.5)	1.91 (1.11-3.29)	2.04 (1.15-3.62)	0.117
Myeloma	56 (0.1)	6 (10.7)	3.61 (1.17-11.18)	3.63 (1.12-11.74)	256 (0.4)	47 (18.4)	2.23 (1.46-3.41)	2.16 (1.40-3.34)	0.358
Other unspecified cellular immune deficiencies	20 (0.0)	2 (10.0)	5.21 (0.74-36.80)	4.21 (0.55-31.95)	40 (0.1)	6 (15.0)	1.80 (0.57-5.72)	1.78 (0.55-5.71)	0.410
Oral corticosteroids[2]	140 (0.2)	12 (8.6)	3.46 (1.57-7.63)	2.66 (1.17-6.02)	225 (0.4)	41 (18.2)	2.33 (1.48-3.66)	2.10 (1.32-3.36)	0.474
Other immunosuppressive therapy[2]	691 (1.2)	31 (4.5)	1.71 (1.06-2.78)	1.15 (0.65-2.02)	1017 (1.6)	114 (11.2)	1.39 (1.07-1.81)	1.18 (0.87-1.60)	0.479
Autoimmune conditions									
Rheumatoid Arthritis	659 (1.2)	33 (5.0)	1.73 (1.08-2.78)	1.37 (0.81-2.31)	1815 (2.9)	192 (10.6)	1.21 (0.99-1.48)	1.09 (0.87-1.38)	0.263
Systemic Lupus Erythematosis	170 (0.3)	8 (4.7)	1.92 (0.75-4.94)	1.41 (0.54-3.73)	137 (0.2)	21 (15.3)	1.95 (1.05-3.63)	1.86 (0.99-3.49)	0.652
Inflammatory Bowel Disease	713 (1.3)	28 (3.9)	1.56 (0.94-2.58)	1.35 (0.79-2.32)	756 (1.2)	82 (10.8)	1.27 (0.94-1.73)	1.18 (0.86-1.63)	0.559
Other comorbidities									
COPD	549 (1.0)	32 (5.8)	1.75 (1.08-2.84)	1.44 (0.88-2.35)	4511 (7.2)	637 (14.1)	1.66 (1.48-1.87)	1.54 (1.36-1.74)	0.675
Asthma	4449 (7.8)	150 (3.4)	1.52 (1.21-1.92)	1.40 (1.10-1.77)	3818 (6.1)	362 (9.5)	1.12 (0.97-1.30)	1.14 (0.97-1.32)	0.068
Chronic Kidney Disease	773 (1.4)	41 (5.3)	1.92 (1.25-2.93)	1.59 (1.02-2.48)	5216 (8.3)	594 (11.4)	1.14 (1.01-1.29)	1.06 (0.93-1.20)	0.018
Depression	3407 (6.0)	127 (3.7)	1.67 (1.31-2.14)	1.43 (1.11-1.85)	2052 (3.3)	253 (12.3)	1.47 (1.23-1.75)	1.36 (1.13-1.64)	0.427
Personality disorder	424 (0.7)	21 (5.0)	2.04 (1.13-3.67)	1.66 (0.91-3.05)	350 (0.6)	32 (9.1)	1.11 (0.68-1.79)	1.05 (0.64-1.74)	0.180
Diabetes	1949 (3.4)	98 (5.0)	1.78 (1.34-2.35)	1.47 (1.09-1.97)	6543 (10.4)	691 (10.6)	1.20 (1.08-1.35)	1.16 (1.03-1.30)	0.018
Recent cancer diagnosis	283 (0.5)	14 (4.9)	1.68 (0.82-3.43)	1.41 (0.65-3.06)	920 (1.5)	83 (9.0)	0.98 (0.72-1.32)	1.01 (0.74-1.38)	0.380
Health behaviours and characteristics of zoster episode									
Smoking									
Non-smoker	22730 (40.1)	457 (2.0)	1.00	1.00	23045 (36.8)	1869 (8.1)	1.00	1.00	0.324
Current smoker	18413 (32.5)	506 (2.7)	1.43 (1.21-1.70)	1.39 (1.16-1.67)	12343 (19.7)	1140 (9.2)	1.29 (1.16-1.43)	1.21 (1.09-1.36)	
Ex-smoker	14829 (26.1)	405 (2.7)	1.22 (1.02-1.46)	1.15 (0.95-1.38)	26902 (42.9)	2541 (9.4)	1.20 (1.10-1.31)	1.13 (1.04-1.24)	
BMI Category									
Underweight (BMI <18.5)	909 (1.6)	29 (3.2)	1.76 (1.06-2.93)	1.58 (0.95-2.64)	1241 (2.0)	159 (12.8)	1.31 (1.04-1.65)	1.19 (0.94-1.50)	0.031
Normal Weight (BMI 18.5-24.9)	20643 (36.4)	457 (2.2)	1.00	1.00	21408 (34.1)	1941 (9.1)	1.00	1.00	
Overweight (BMI 25-30)	16932 (29.9)	419 (2.5)	1.00 (0.84-1.19)	1.03 (0.86-1.23)	23002 (36.7)	1976 (8.6)	0.99 (0.90-1.08)	1.01 (0.92-1.10)	
Obese (BMI ≥30)	11506 (20.3)	396 (3.4)	1.39 (1.16-1.66)	1.29 (1.07-1.56)	12743 (20.3)	1164 (9.1)	1.12 (1.01-1.24)	1.08 (0.97-1.20)	

Table e-2: Relative risk of PHN in patients with risk factors of interest stratified by age of diagnosis (continued)

Antiviral record within 7 days of zoster	30510 (53.8)	796 (2.6)	1.10 (0.96-1.28)	1.06 (0.91-1.23)	38372 (61.2)	3452 (9.0)	1.03 (0.96-1.11)	1.03 (0.95-1.11)	0.548
Anatomical site of zoster									
Site Unspecified	54309 (95.8)	1262 (2.3)	1.00	1.00	58691 (93.6)	4952 (8.4)	1.00	1.00	0.789
Non-Truncal (excluding ophthalmic zoster)	425 (0.7)	21 (4.9)	2.38 (1.32-4.29)	1.94 (1.01-3.73)	311 (0.5)	53 (17.0)	2.31 (1.56-3.44)	2.27 (1.49-3.46)	
Ophthalmic zoster	1977 (3.5)	94 (4.8)	1.94 (1.46-2.57)	1.92 (1.43-2.59)	3700 (5.9)	574 (15.5)	1.92 (1.69-2.17)	1.94 (1.71-2.21)	

†Adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity unless otherwise specified), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use. Interaction terms between age and other risk factors were added one at a time into the multivariable regression model. [1]Measured by Index of Multiple deprivation score. [2]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day).

Table e-3: Sensitivity analysis using alternative definitions of PHN

	PRIMARY PHN definition (results from Model 2)	PHN defined as pain at 30 days after zoster*		PHN restricted to diagnosed cases only		Excluding patients possible herpes simplex patients (n=1586)	
	Fully adjusted OR† (99% CI)	Risk of PHN, n (%)	Fully adjusted OR† (99% CI)	Risk of PHN, n (%)	Fully adjusted OR† (99% CI)	Risk of PHN, n (%)	Fully adjusted OR† (99% CI)
Total	-	11755/119413 (9.8)	-	2156/11943 (1.8)		6810/117827 (5.8)	
Demographic characteristics							
Age (years) [Estimated ORs for 10 year increase in age within the specified age-band][1]							
<50	1.42 (1.28-1.57)	922 (2.8)	1.54 (1.42-1.67)	127 (0.4)	1.36 (1.10-1.68)	569 (1.8)	1.41 (1.27-1.56)
50-79	1.70 (1.63-1.78)	8104 (11.1)	1.73 (1.67-1.78)	1396 (1.9)	2.08 (1.92-2.24)	4530 (6.3)	1.71 (1.64-1.79)
≥80	1.10 (0.94-1.28)	2729 (20.0)	0.96 (0.85-1.09)	633 (4.6)	0.89 (0.69-1.15)	1711 (12.7)	1.10 (0.95-1.28)
Female	1.19 (1.10-1.27)	7467 (10.5)	1.15 (1.09-1.22)	1332 (1.9)	1.00 (0.89-1.14)	4382 (6.3))	1.18 (1.10-1.27)
Socioeconomic status (practice level)[2]							
1 (least deprived)	1.00	2208 (9.2)	1.00	461 (1.9)	1.00	1259 (5.3)	1.00
2	1.04 (0.91-1.18)	2217 (9.4)	1.04 (0.93-1.15)	401 (1.7)	0.94 (0.70-1.25)	1257 (5.4)	1.03 (0.91-1.18)
3	1.09 (0.96-1.24)	2461 (10.0)	1.09 (0.98-1.21)	430 (1.8)	0.89 (0.67-1.19)	1415 (5.8)	1.09 (0.96-1.24)
4	1.17 (1.03-1.32)	2560 (10.2)	1.13 (1.02-1.25)	477 (1.9)	0.99 (0.75-1.32)	1529 (6.2)	1.17 (1.03-1.33)
5 (most deprived)	1.20 (1.06-1.37)	2309 (10.4)	1.18 (1.06-1.31)	387 (1.7)	0.98 (0.74-1.32)	1350 (6.2)	1.19 (1.04-1.36)
Severe Immunosuppression							
HIV	2.17 (0.64-7.37)	11 (11.1)	2.86 (1.16-7.07)	2 (2.0)	1.71(0.12-24.01)	6 (6.2)	2.22 (0.65-7.56)
Leukaemia	2.07 (1.08-3.96)	34 (22.2)	2.11 (1.22-3.64)	7 (4.6)	2.07 (0.73-5.87)	21 (14.4)	2.27 (1.18-4.36)
Lymphoma	2.45 (1.53-3.92)	61 (19.4)	2.27 (1.52-3.40)	10 (3.2)	1.94 (0.79-4.75)	37 (12.1)	2.34 (1.43-3.82)
Myeloma	2.17 (1.43-3.29)	79 (25.3)	2.06 (1.44-2.95)	19 (6.1)	2.33 (1.21-4.46)	52 (17.2)	2.20 (1.44-3.36)
Hematopoietic stem cell transplantation	5.91 (1.32-26.59)	6 (35.3)	4.72 (1.12-19.77)	0 (0.0)	-	5 (31.3)	6.89 (1.48-32.02)
Other unspecified cellular immune deficiencies	2.12 (0.77-5.89)	11 (18.3)	1.79 (0.72-4.43)	0 (0.0)	-	8 (13.6)	2.14 (0.77-5.92)
Oral corticosteroids[3]	2.26 (1.51-3.40)	79 (21.6)	2.08 (1.46-2.96))	20 (5.5)	2.83 (1.50-5.33)	53 (14.6)	2.31 (1.54-3.47)
Other immunosuppressive therapy[3]	1.21 (0.92-1.58)	239 (14.0)	1.24 (1.00-1.54)	40 (2.3)	1.14 (0.70-1.86)	144 (8.6)	1.23 (0.94-1.61)
Autoimmune conditions							
Rheumatoid Arthritis	1.13 (0.91-1.39)	363 (14.7)	1.09 (0.92-1.29)	66 (2.7)	1.04 (0.71-1.52)	223 (9.1)	1.14 (0.92-1.41)
Systemic Lupus Erythematosis	1.76 (1.04-2.98)	40 (13.0)	1.32 (0.82-2.12)	12 (3.9)	2.66 (1.20-5.88)	29 (9.6)	1.80 (1.07-3.05)
Inflammatory Bowel Disease	1.22 (0.93-1.60)	173 (11.8)	1.13 (0.90-1.42)	26 (1.8)	0.91 (0.53-1.56)	108 (7.5)	1.22 (0.92-1.61)

Table e-3: Sensitivity analysis using alternative definitions of PHN (continued)

	Final analysis for PRIMARY definition	PHN defined as pain at 30 days after zoster*		PHN restricted to diagnosed		Excluding patients with zoster code following first zoster diagnosis (possible herpes simplex)	
	Fully adjusted OR (99% CI)[2]	Risk of PHN 30, n (%)	Fully adjusted OR[2] (99% CI)	Risk of PHN, n (%)	Risk of PHN, n (%)	Risk of PHN, n (%)	Fully adjusted OR[2] (99% CI)
Other comorbidities							
COPD	1.53 (1.35-1.72)	1054 (20.8)	1.49 (1.35-1.65)	219 (4.3)	1.43 (1.17-1.76)	654 (13.1)	1.52 (1.34-1.72)
Asthma	1.21 (1.06-1.37)	866 (10.5)	1.24 (1.12-1.37)	147 (1.8)	1.17 (0.93-1.48)	503 (6.2)	1.22 (1.07-1.38)
Chronic Kidney Disease	1.08 (0.96-1.22)	1006 (16.8)	1.05 (0.95-1.16)	176 (2.9)	0.91 (0.73-1.13)	621 (10.5)	1.07 (0.95-1.21)
Depression	1.40 (1.20-1.62)	575 (10.5)	1.27 (1.12-1.45)	93 (1.7)	1.12 (0.84-1.49)	372 (7.0)	1.41 (1.21-1.64)
Personality disorder	1.25 (0.85-1.85)	76 (9.8)	1.04 (0.74-1.46)	17 (2.2)	1.48 (0.77-2.84)	52 (6.8)	1.28 (0.87-1.90)
Diabetes	1.19 (1.07-1.33)	1300 (15.3)	1.19 (1.09-1.29)	205 (2.4)	0.94 (0.77-1.15)	773 (9.2)	1.18 (1.06-1.32)
Recent cancer diagnosis	1.06 (0.79-1.41)	156 (13.0)	0.98 (0.78-1.25)	26 (2.2)	0.89 (0.53-1.51)	93 (7.9)	1.03 (0.77-1.39)
Health behaviours and characteristics of zoster episode							
Smoking							
Non-smoker	1.00	3978 (8.7)	1.00	743 (1.6)	1.00	2274 (5.0)	1.00
Current smoker	1.27 (1.15-1.39)	2800 (9.1)	1.26 (1.17-1.36)	491 (1.6)	1.19 (1.00-1.40)	1610 (5.3)	1.27 (1.15-1.39)
Ex-smoker	1.14 (1.05-1.24)	4907 (11.8)	1.11 (1.04-1.19)	915 (2.2)	1.09 (0.94-1.25)	2891 (7.0)	1.15 (1.06-1.24)
BMI Category							
Underweight (BMI <18.5)	1.25 (1.01-1.54)	282 (13.1)	1.15 (0.96-1.38)	77 (3.6)	1.56 (1.13-2.17)	187 (8.8)	1.27 (1.03-1.57)
Normal Weight (BMI 18.5-24.9)	1.00	4026 (9.6)	1.00	771 (1.8)	1.00	2345 (5.7)	1.00
Overweight (BMI 25-30)	1.01 (0.93-1.09)	4131 (10.3)	1.03 (0.97-1.10)	749 (1.9)	0.99 (0.86-1.14)	2338 (5.9)	1.01 (0.93-1.09)
Obese (BMI ≥30)	1.13 (1.03-1.24)	2570 (10.6)	1.11 (1.03-1.19)	425 (1.8)	1.03 (0.87-1.21)	1536 (6.4)	1.14 (1.04-1.25)
Antiviral record within 7 days of zoster	1.04 (0.97-1.11)	7345 (10.7)	1.12 (1.06-1.18)	1355 (2.0)	1.08 (0.96-1.22)	4151 (6.1)	1.04 (0.97-1.11)
Anatomical site of zoster							
Site Unspecified	1.00	10648 (9.4)	1.00	1854 (1.6)	1.00	6097 (5.5)	1.00
Non-Truncal (excluding ophthalmic zoster)	2.19 (1.54-3.11)	110 (15.0)	2.00 (1.49-2.70)	15 (2.0)	1.77 (0.88-3.53)	74 (10.5)	2.34 (1.65-3.34)
Ophthalmic zoster	1.95 (1.73-2.19)	997 (17.6)	1.72 (1.56-1.91)	287 (5.1)	2.67 (2.24-3.19)	639 (11.6)	1.94 (1.72-2.18)

*PHN at 30 days: same definition as PHN at 90 days, but gathering evidence from 30-365 days following zoster. †Adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity unless otherwise specified), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use.[1]ORs estimate the effect of a 10-year increase in age on PHN derived, in age groups <50, 50-79 and ≥80, from piecewise linear splines. [2]Measured by Index of Multiple deprivation score. [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day).

Table e-4: Relative risk of diagnosed, probable or possible PHN by gender (N=119,413)

	Diagnosed PHN		Probable PHN		Possible PHN	
	n (%)	Adjusted OR* (99% CI)	n (%)	Adjusted OR* (99% CI)	n (%)	Adjusted OR* (99% CI)
Total	2156 (1.8)		3007 (2.5)		1793 (1.5)	
Male	824 (1.7)	1.00	1041 (2.2)	1.00	602 (1.3)	1.00
Female	1332 (1.9)	1.01 (0.90-1.13)	1966 (2.8)	1.21 (1.09-1.33)	1191 (1.7)	1.27 (1.12-1.45)

*Association between gender and PHN is age-adjusted (with age modelled as a 5 knot-restricted cubic spline).

Table e-5: Association between female gender and PHN, according to different PHN outcome definitions

PHN evidence category		*ANALYSIS A: Whole study cohort (N=119413)*			*ANALYSIS B: Patients with a history of mental health problems (N=37451)*	*ANALYSIS C: Patients with NO history of mental health problems (N= 81962)*	*ANALYSIS D: Patients with no evidence of depression one year before or after zoster (N= 110,730)*
		Risk of specific PHN diagnosis (%)	Risk of specific PHN diagnosis in females n (%)	Age-adjusted OR (99% CI)	Age-adjusted OR (99% CI)	Age-adjusted OR (99% CI)	Age-adjusted OR (99% CI)
PHN							
Diagnosed	PHN code*	2156 (1.9)	1332 (2.0)	1.02 (0.91-1.15)	1.02 (0.82-1.27)	0.95 (0.82-1.10)	1.01 (0.90-1.15)
Presumed	Zoster code and prescription same day*	215 (0.2)	146 (0.2)	1.35 (0.92-1.97)	1.41 (0.65-3.08)	1.32 (0.85-2.06)	1.33 (0.90-1.96)
	Non-specific neuralgia code*	783 (0.7)	511 (0.7)	1.21 (1.00-1.48)	1.16 (0.80-1.67)	1.19 (0.94-1.51)	1.22 (1.00-1.50)
	NEW anticonvulsant**	1120 (0.9)	699 (1.0)	1.04 (0.89-1.23)	0.87 (0.66-1.13)	1.02 (0.83-1.26)	1.04 (0.88-1.24)
	NEW capsaicin cream/lidocaine patch**	117 (0.1)	75 (0.1)	1.11 (0.67-1.84)	1.58 (0.57-4.41)	1.02 (0.83-1.26)	1.11 (0.67-1.84)
	NEW TCA ** with PHN/zoster code and zoster medication on the same day, 0-89 days after zoster	772 (0.7)	535 (0.8)	1.43 (1.16-1.75)	1.36 (0.95-1.96)	1.34 (1.04-1.72)	1.39 (1.13-1.72)
Possible	**NEW** TCA**	918 (0.8)	653 (0.9)	1.55 (1.28-1.88)	1.45 (1.04-2.01)	1.42 (1.12-1.81)	1.50 (1.23-1.84)
	NEW strong PK ** with PHN/zoster code and zoster medication on the same day, 0-89 days after zoster	762 (0.6)	457 (0.6)	0.98 (0.81-1.18)	0.86 (0.60-1.24)	1.00 (0.79-1.26)	0.96 (0.79-1.17)
	Non-specific neuropathy code*	113 (0.09)	81 (0.11)	1.71 (1.00-2.93)	1.55 (0.62-3.88)	1.63 (0.83-3.21)	1.84 (1.04-3.27)

TCA: tricyclic antidepressant. PK: Painkiller. *90-365d post-zoster ** 90-180d post-zoster

Table e-6: Estimated mean number of consultations per year during follow-up prior to zoster, for patients with each risk factor.

Exposure	Estimated mean number of consultations per year during follow-up, for patients with each exposure[1]	Adjusted OR† (95% CI)PRIMARY PHN definition (results from Model 2)
Overall	7.3	-
Demographic characteristics		
Gender		
Female	8.1	1.19 (1.10-1.27)
Male	6.0	1.00
Socioeconomic status (practice level)[2]		
1 (least deprived)	7.1	1.00
2	7.1	1.04 (0.91-1.18)
3	7.2	1.09 (0.96-1.24)
4	7.4	1.17 (1.03-1.32)
5 (most deprived)	7.5	1.20 (1.06-1.37)
Severe Immunosuppression		
HIV	7.5	2.17 (0.64-7.37)
Leukaemia	8.8	2.07 (1.08-3.96)
Lymphoma	8.5	2.45 (1.53-3.92)
Myeloma	10.7	2.17 (1.43-3.29)
Hematopoietic stem cell transplantation	9.6	5.91 (1.32-26.59)
Other unspecified cellular immune deficiencies	12.5	2.12 (0.77-5.89)
Oral corticosteroids[3]	13.3	2.26 (1.51-3.40)
Other immunosuppressive therapy[3]	13.0	1.21 (0.92-1.58)
Autoimmune conditions		
Rheumatoid Arthritis	12.2	1.13 (0.91-1.39)
Systemic Lupus Erythematosis	11.4	1.76 (1.04-2.98)
Inflammatory Bowel Disease	10.6	1.22 (0.93-1.60)
Other comorbidities		
COPD	12.4	1.53 (1.35-1.72)
Asthma	10.0	1.21 (1.06-1.37)
Chronic Kidney Disease	11.4	1.08 (0.96-1.22)
Depression	10.8	1.40 (1.20-1.62)
Personality disorder	11.6	1.25 (0.85-1.85)
Diabetes	12.2	1.19 (1.07-1.33)
Recent cancer diagnosis	9.3	1.06 (0.79-1.41)
Health behaviours and characteristics of zoster episode		
Smoking		
Non-smoker	6.6	1.00
Current smoker	6.8	1.27 (1.15-1.39)
Ex-smoker	8.3	1.14 (1.05-1.24)
BMI Category		
Underweight (BMI <18.5)	8.0	1.25 (1.01-1.54)
Normal Weight (BMI 18.5-24.9)	6.9	1.00
Overweight (BMI 25-30)	7.3	1.01 (0.93-1.09)
Obese (BMI ≥30)	8.8	1.13 (1.03-1.24)
Antiviral record within 7 days of zoster	7.4	1.04 (0.97-1.11)
Anatomical site of zoster		
Site Unspecified	7.2	1.00
Non-Truncal (excluding ophthalmic zoster)	8.9	2.19 (1.54-3.11)
Ophthalmic zoster	7.9	1.95 (1.73-2.19)
CONTROL RISK FACTOR: Hypothyroidism	10.9	1.01 (0.90-1.14)

†Adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use. [1]Calculated by dividing the total number of face-to-face or telephone consultations, by the total years of follow-up prior to zoster diagnosis for each patient and calculating the mean number of consultations per year for patients with each risk factor. [2]Measured by Index of Multiple deprivation score. [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day).

Table e-7: Relative risk of PHN in patients with various risk factors, using a multiply imputed dataset

Exposure	**Adjusted OR† (95% CI) from multiply imputed dataset**	**Adjusted OR† (95% CI) PRIMARY PHN definition (results from Model 2)**
Demographic characteristics		
Age (years) [Estimated ORs for 10 year increase in age within the specified age-band][1]		
<50	1.45 (1.32-1.60)	1.42 (1.28-1.57)
50-79	1.71 (1.64-1.78)	1.70 (1.63-1.78)
≥80	1.04 (0.90-1.19)	1.10 (0.94-1.28)
Female	1.19 (1.11-1.28)	1.19 (1.10-1.27)
Socioeconomic status (practice level)[2]		
1 (least deprived)		1.00
2	1.04 (0.91-1.18)	1.04 (0.91-1.18)
3	1.07 (0.95-1.22)	1.09 (0.96-1.24)
4	1.16 (1.03-1.32)	1.17 (1.03-1.32)
5 (most deprived)	1.20 (1.05-1.36)	1.20 (1.06-1.37)
Severe Immunosuppression		
HIV	2.39 (0.78-7.33)	2.17 (0.64-7.37)
Leukaemia	2.11 (1.12-3.98)	2.07 (1.08-3.96)
Lymphoma	2.32 (1.47-3.66)	2.45 (1.53-3.92)
Myeloma	2.20 (1.46-3.30)	2.17 (1.43-3.29)
Hematopoietic stem cell transplantation	6.14 (1.36-27.66)	5.91 (1.32-26.59)
Other unspecified cellular immune deficiencies	1.93 (0.70-5.29)	2.12 (0.77-5.89)
Oral corticosteroids[3]	2.25 (1.51-3.35)	2.26 (1.51-3.40)
Other immunosuppressive therapy[3]	1.26 (0.97-1.63)	1.21 (0.92-1.58)
Autoimmune conditions		
Rheumatoid Arthritis	1.10 (0.89-1.35)	1.13 (0.91-1.39)
Systemic Lupus Erythematosis	1.66 (0.99-2.80)	1.76 (1.04-2.98)
Inflammatory Bowel Disease	1.24 (0.95-1.62)	1.22 (0.93-1.60)
Other comorbidities		
COPD	1.56 (1.39-1.76)	1.53 (1.35-1.72)
Asthma	1.23 (1.08-1.39)	1.21 (1.06-1.37)
Chronic Kidney Disease	1.10 (0.97-1.24)	1.08 (0.96-1.22)
Depression	1.41 (1.22-1.63)	1.40 (1.20-1.62)
Personality disorder	1.26 (0.86-1.83)	1.25 (0.85-1.85)
Diabetes	1.20 (1.08-1.34)	1.19 (1.07-1.33)
Recent cancer diagnosis	1.04 (0.78-1.37)	1.06 (0.79-1.41)
Health behaviours and characteristics of zoster episode		
Smoking		
Non-smoker	1.00	1.00
Current smoker	1.27 (1.16-1.39)	1.27 (1.15-1.39)
Ex-smoker	1.16 (1.07-1.25)	1.14 (1.05-1.24)
BMI Category		
Underweight (BMI <18.5)	1.24 (0.99-1.56)	1.25 (1.01-1.54)
Normal Weight (BMI 18.5-24.9)	1.00	1.00
Overweight (BMI 25-30)	1.01 (0.94-1.10)	1.01 (0.93-1.09)
Obese (BMI ≥30)	1.14 (1.04-1.25)	1.13 (1.03-1.24)
Antiviral record within 7 days of zoster	1.04 (0.97-1.11)	1.04 (0.97-1.11)
Anatomical site of zoster		
Site Unspecified	1.00	1.00
Non-Truncal (excluding ophthalmic zoster)	2.36 (1.69-3.28)	2.19 (1.54-3.11)
Ophthalmic zoster	1.93 (1.72-2.17)	1.95 (1.73-2.19)

†Adjusted for age (modelled as a 5-knot restricted cubic spline to allow for non-linearity unless otherwise specified), gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking, BMI category, site of zoster and antiviral use. [1]ORs estimate the effect of a 10-year increase in age on PHN derived, in age groups <50, 50-79 and ≥80, from piecewise linear splines. [2]Measured by Index of Multiple deprivation score. [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day).

Table e-8: Associations between postherpetic neuralgia and demographic risk factors, comorbidities and health behaviours, stratified by whether a patient received antivirals during acute zoster. Analyses are restricted to 69,661 patients for whom antiviral status was most likely to be available*

	Not prescribed antivirals				Prescribed antivirals				
	Total cohort, n	**Prevalence of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**Total cohort, n**	**Prevalence of PHN, n (%)**	**Age-adjusted OR (99% CI)**	**Fully adjusted† OR (99% CI)**	**P-value††**
Total	30302 (100)	1416 (4.7)	-	-	39359 (100)	2250 (5.7)	-	-	
Demographic characteristics									
Age (years) [Estimated ORs for 10 year increase in age within the specified age-band][1]									
Among those aged <50	9785 (32.3)	152 (1.6)	1.52 (1.26-1.83)	1.43 (1.18-1.75)	9738 (24.8)	179 (1.8)	1.32 (1.12-1.56)	1.30 (1.08-1.55)	0.401
Among those aged 50-79	17273 (57.1)	901 (5.2)	1.71 (1.57-1.87)	1.66 (1.52-1.82)	24863 (63.3)	1467 (5.9)	1.77 (1.65-1.90)	1.73 (1.60-1.86)	0.465
Among those aged ≥80	3200 (10.6)	329 (10.3)	1.05 (0.79-1.40)	1.18 (0.86-1.64)	4698 (12.0)	563 (12.0)	1.01 (0.80-1.28)	1.05 (0.81-1.37)	0.880
Female	17526 (57.8)	919 (5.2)	1.25 (1.07-1.45)	1.24 (1.05-1.46)	23851 (60.6)	1453 (6.1)	1.14 (1.01-1.28)	1.14 (1.00-1.29)	0.288
Socioeconomic status (practice level)[2]									
1 (least deprived)	5017 (16.6)	205 (4.1)	1.00	1.00	6773 (17.2)	382 (5.6)	1.00	1.00	0.636
2	6785 (22.4)	291 (4.3)	1.08 (0.83-1.42)	1.07 (0.81-1.41)	8996 (22.9)	489 (5.4)		0.97 (0.79-1.20)	
3	6301 (20.8)	295 (4.7)	1.12 (0.85-1.46)	1.09 (0.82-1.44)	8450 (21.5)	477 (5.6)	0.98 (0.79-1.21)	0.98 (0.80-1.22)	
4	6595 (21.8)	343 (5.2)	1.29 (1.00-1.68)	1.21 (0.93-1.59)	8151 (20.7)	513 (6.3)	0.98 (0.79-1.21)	1.10 (0.89-1.35)	
5 (most deprived)	5604 (18.5)	282 (5.0)	1.32 (1.01-1.73)	1.19 (0.90-1.58)	6989 (17.8)	389 (5.6)	1.06 (0.85-1.32)	1.02 (0.82-1.27)	
Severe Immunosuppression									
HIV	22 (0.1)	2 (9.1)	4.35 (0.62-30.60)	3.79 (0.47-30.34)	45 (0.1)	2 (4.4)	1.71 (0.26-11.41)	1.95 (0.29-13.09)	0.540
Leukaemia	27 (0.1)	7 (25.9)	7.05 (2.13-23.32)	7.12 (1.78-28.44)	49 (0.1)	4 (8.2)	1.33 (0.34-5.21)	1.39 (0.35-5.51)	0.045
Lymphoma	60 (0.2)	7 (11.7)	2.81 (0.96-8.23)	2.80 (0.87-9.04)	110 (0.3)	7 (6.4)	1.16 (0.42-3.22)	1.27 (0.45-3.56)	0.199
Myeloma	63 (0.2)	12 (19.1)	3.31 (1.41-7.77)	2.47 (0.94-6.45)	124 (0.3)	14 (11.3)	1.59 (0.76-3.36)	1.64 (0.77-3.48)	0.250
Oral corticosteroids[3]	87 (0.3)	10 (11.5)	2.31 (0.94-5.64)	1.65 (0.60-4.49)	137 (0.4)	18 (13.1)	2.12 (1.08-4.14)	1.88 (0.94-3.77)	0.792
Other immunosuppressive therapy[3]	327 (1.1)	25 (7.7)	1.42 (0.82-2.46)	1.09 (0.57-2.06)	592 (1.5)	42 (7.1)	1.32 (0.87-2.02)	1.05 (0.64-1.71)	0.451
Autoimmune conditions									
Rheumatoid Arthritis	495 (1.6)	51 (10.3)	1.72 (1.16-2.56)	1.40 (0.86-2.26)	911 (2.3)	77 (8.5)	1.26 (0.92-1.74)	1.23 (0.86-1.75)	0.112
Systemic Lupus Erythematosis	68 (0.2)	10 (14.7)	3.69 (1.47-9.31)	3.42 (1.31-8.94)	117 (0.3)	7 (6.0)	1.24 (0.45-3.45)	1.11 (0.39-3.12)	0.026
Inflammatory Bowel Disease	326 (1.1)	24 (7.4)	1.54 (0.88-2.70)	1.53 (0.84-2.79)	529 (1.3)	39 (7.4)	1.37 (0.88-2.13)	1.22 (0.77-1.95)	0.323
Other comorbidities									
COPD	1092 (3.6)	144 (13.1)	2.01 (1.56-2.58)	1.69 (1.29-2.22)	1711 (4.4)	202 (11.8)	1.55 (1.26-1.90)	1.42 (1.15-1.77)	0.043
Asthma	1992 (6.6)	106 (5.3)	1.33 (1.01-1.75)	1.38 (1.04-1.83)	2839 (7.2)	157 (5.5)	1.12 (0.90-1.40)	1.07 (0.84-1.34)	0.088
Chronic Kidney Disease	1203 (4.0)	116 (9.6)	1.25 (0.96-1.65)	1.14 (0.86-1.53)	2173 (5.5)	228 (10.5)	1.26 (1.03-1.53)	1.16 (0.95-1.42)	0.916
Depression	1315 (4.3)	70 (5.3)	1.44 (1.03-2.00)	1.21 (0.85-1.74)	1797 (4.6)	132 (7.4)	1.62 (1.26-2.07)	1.51 (1.17-1.95)	0.475
Personality disorder	192 (0.6)	13 (6.8)	1.76 (0.82-3.76)	1.64 (0.74-3.64)	239 (0.6)	13 (5.4)	1.07 (0.51-2.26)	0.93 (0.43-2.03)	0.149
Diabetes	1924 (6.4)	150 (7.8)	1.24 (0.98-1.58)	1.12 (0.87-1.44)	2926 (7.4)	265 (9.1)	1.32 (1.10-1.58)	1.26 (1.05-1.52)	0.665

Table e-8: Associations between postherpetic neuralgia and demographic risk factors, comorbidities and health behaviours, stratified by whether a patient received antivirals during acute zoster. Analyses are restricted to 69,661 patients for whom antiviral status was most likely to be available* (continued)

Recent cancer diagnosis	265 (0.9)	20 (7.5)	1.10 (0.60-2.04)	1.17 (0.62-2.19)	417 (1.1)	37 (8.9)	1.30 (0.83-2.05)	1.42 (0.90-2.24)	0.421
Health behaviours and characteristics of zoster episode									
Smoking									
Non-smoker	11583 (38.7)	430 (3.7)	1.00	1.00	14876 (38.0)	791 (5.3)	1.00	1.00	0.002
Current smoker	8505 (28.4)	399 (4.7)	1.66 (1.37-2.01)	1.49 (1.21-1.83)	9452 (24.2)	469 (5.0)	1.14 (0.97-1.33)	1.09 (0.93-1.29)	
Ex-smoker	9857 (32.9)	580 (5.9)	1.38 (1.16-1.64)	1.29 (1.07-1.56)	14779 (37.8)	981 (6.6)	1.08 (0.95-1.23)	1.03 (0.90-1.18)	
BMI Category									
Underweight (BMI <18.5)	582 (2.1)	39 (6.7)	1.38 (0.87-2.17)	1.18 (0.73-1.93)	671 (1.9)	65 (9.7)	1.54 (1.07-2.20)	1.45 (1.01-2.09)	0.712
Normal Weight (BMI 18.5-24.9)	10981 (40.2)	497 (4.5)	1.00	1.00	14125 (39.2)	787 (5.6)	1.00	1.00	
Overweight (BMI 25-30)	9942 (36.4)	473 (4.8)	0.96 (0.81-1.14)	1.01 (0.84-1.21)	13320 (37.0)	793 (6.0)	1.03 (0.90-1.18)	1.04 (0.90-1.19)	
Obese (BMI ≥30)	5818 (21.3)	317 (5.5)	1.21 (1.00-1.47)	1.15 (0.94-1.42)	7921 (22.0)	486 (6.1)	1.17 (1.00-1.37)	1.12 (0.95-1.32)	

†Adjusted for age, gender, socioeconomic status, HIV, leukaemia, lymphoma, myeloma, other unspecified cellular immune deficiencies, immunosuppressive therapies, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, COPD, asthma, chronic kidney disease, depression, personality disorder, diabetes, recent cancer diagnosis, smoking and BMI category. Please note hematopoietic stem cell transplantation and other unspecified cellular immune deficiencies were excluded due to too few numbers. Interaction terms between antiviral use and other risk factors were added to the model one at a time. ††P-value for interaction. [1]ORs estimate the effect of a 10-year increase in age on PHN derived, in age groups <50, 50-79 and ≥80, from piecewise linear splines. [2]Measured by Index of Multiple deprivation score. [3]Includes patients currently taking a 14 day course of immunosuppressive medications, or terminating a 14 day course of immunosuppressive medications less than one month prior to the zoster diagnosis. Oral corticosteroid prescriptions were required to be high dose (≥20mg per day). *Patients excluded were those diagnosed with zoster in HES, or with a hospital visit for zoster (primary diagnosis of any episode) in the 7 days after first zoster diagnosis, patients without linked HES data and patients with evidence of non-truncal zoster, as their antiviral use may not be recorded in CPRD.

7.4. Chapter summary

Identifying risk factors for PHN in CPRD

- A large cohort study followed up 119,413 zoster patients, of whom 5.8% developed PHN. A range of medical conditions and patient characteristics were associated with increased risk of PHN, including; autoimmune conditions (RA, SLE and IBD), COPD, depression, diabetes, asthma, lower SES, smoking, under- or overweight and non-truncal zoster.
- Antiviral use was not associated with PHN. There was some evidence that the increased risk of PHN with SLE, leukaemia, COPD and smoking was attenuated in patients given antivirals.
- The strongest risk factors for PHN are severely immunosuppressive conditions, which are vaccine contraindications for the currently available zoster vaccine, emphasising the need for alternative risk reduction strategies (such as a non-live vaccine and antiviral prophylaxis) among these groups.

Chapter 8: Summary and conclusions

The research presented in this thesis aimed to improve the understanding of risk factors for zoster and PHN to inform vaccination policy, by undertaking a literature review, a systematic review and meta-analysis, and three large observational studies using UK EHR data. The first observational study, a case-control study (reported in chapter 4) examined risk factors for zoster. The second observational study, a cohort study (reported in chapter 7) examined risk factors for PHN. An additional observational study was conducted to evaluate the extent to which antiviral treatment during acute zoster is administered according to treatment guidelines.

Specific issues relating to individual studies were discussed within the preceding chapters. This final chapter provides an overview of the key findings from these individual studies, in the context of previous research, and then sets out the strengths and limitations of using EHR data to address the research questions in this thesis. The chapter ends by highlighting implications for clinical practice and outlining unanswered questions for future research.

8.1. Overview of key findings

8.1.1. Risk factors for zoster

8.1.1.1. What was already known on this topic

- A zoster vaccine became available in 2006 and vaccination programmes are underway in a number of high-income countries including the UK, USA, Canada and Japan. The zoster vaccine is currently targeted at older individuals only, as increasing age is one of the few well-established risk factors for zoster.
- The other well known risk factor for zoster is severe immunosuppression, explaining around 5% of zoster cases. However, patients with severe immunosuppression are not eligible for the currently available vaccine, due to safety concerns with a live vaccine.
- As described in the literature review of zoster risk factors (see chapter 2) a number of clinical conditions not currently listed as contraindications for the zoster vaccine were associated in some studies with an increased risk of zoster; these included certain autoimmune conditions such as RA, SLE, and IBD, and other chronic conditions such as diabetes mellitus, COPD, CKD, asthma and depression.

- However, these studies tended to be small and inadequately powered to investigate the association of these conditions with zoster.
- Studies also suffered from poor control of confounding factors (for example age was often included as a categorical variable with wide intervals) and studies rarely investigated whether the effects of some conditions were mediated by immunosuppressive drugs.
- Additionally, few studies assessed several risk factors simultaneously, and the lack of a consistent methodological approach did not allow direct comparison of the relative strength of various risk factors.
- Finally, it is not clear if younger age groups, particularly individuals with specific patient characteristics, might benefit from vaccination. The zoster vaccine is currently only licensed for use in patients aged ≥50 years, however over 30% of zoster cases occur under the age of 50 years. No previous studies have assessed how the effects of a broad range of comorbid conditions on zoster risk vary by age.

8.1.1.2. What the study adds

- The zoster case-control study (described in chapter 4) showed that the highest risk of zoster was associated with severe immunosuppressive conditions, for example lymphoma (adjOR: 3.90, 99% CI 3.21-4.74) and myeloma (adjOR: 2.16, 99%CI 1.84-2.53). This study finding highlights how the patients most in need of zoster prevention are not able to benefit from the currently available zoster vaccine, emphasising the need for alternative risk reduction strategies in this group, such as non-live vaccines and antiviral prophylaxis.
- Consistent with previous studies, patients with autoimmune conditions (specifically, SLE, IBD and RA) were 1.3 to 1.7 times more likely to develop zoster, compared to the general population.
- Patients with the respiratory conditions asthma or COPD were at 20 to 30% greater risk of zoster.
- The effects of RA, IBD, COPD and asthma were attenuated after adjusting for immunosuppressive medications. Each of these conditions are frequently treated with immunomodulating drugs and this finding suggests that at least part of the risk associated with these conditions is mediated by the drugs, rather than the disease itself.

- The other conditions which were associated with increased risk of zoster, albeit with associations that were smaller than reported in previous studies (ranging from 1.1 to 1.3 times the odds), were depression, CKD and type 1, but not type 2, diabetes.
- The relative effects of the observed risk factors were larger in younger patients. For example, the OR point estimates for CKD were 1.53, 1.21 and 1.11 among patients 18-49 years, 50-59 years and 60-69 years respectively. The estimated rate of zoster in younger patients with CKD still remained low, due to the underlying low rate in younger patients. However, this finding raises questions about the utility of vaccinating younger patients with certain characteristics.
- Of 97,789 zoster cases aged under 70 years, 3619 (3.7%) had a predicted risk of zoster as high as that for the general population aged 70 years or over. This finding indicates there may be some benefit to targeting specific patient groups under 70 years of age, though cost-effectiveness studies would be required to further investigate whether this approach is warranted.
- By including a variety of risk factors in one study, it was possible to compare the strength of association between different risk factors. This approach also allowed tight control of known and potential confounders.

8.1.2. Which zoster patients receive antivirals?

8.1.2.1. What was already known

- Antivirals are recommended for all immunosuppressed patients presenting with zoster and certain immunocompetent patients (specifically, people aged ≥50 years, or individuals with ophthalmic zoster, other non-truncal disease, moderate to severe pain or rash). Treatment within 72 hours of rash onset is recommended, although antivirals may be given up to one week after zoster onset. The evidence base suggests that antiviral treatment reduces the severity and duration of the acute zoster episode, though the effect of antiviral treatment on PHN is disputed.
- Little research existed exploring the extent to which antiviral prescription guidelines are adhered to. A previous study of CPRD data indicated that antivirals were under-prescribed in the UK; 56.3% of 27,225 immunocompetent patients with zoster aged ≥50 years received antivirals between 2000 and 2006. However, there were no data on the proportion of immunosuppressed patients receiving antivirals in UK primary care.
- Studies from the USA, Italy, and Australia reported higher proportions of adult patients with zoster receiving antiviral prescriptions, of between 70 to 80%, though they included secondary care data and the health care systems have significant differences.

- Previous studies have tended to report overall use of antivirals, rather than use by specific risk groups, therefore it is difficult to identify who is receiving antivirals and whether certain patient groups are under-prescribed antivirals.

8.1.2.2. What the study adds

- The descriptive antiviral study (described in chapter 5) demonstrated that of 142,216 zoster patients diagnosed with zoster between 2000 and 2011, 58.1% received antivirals within 7 days of zoster diagnosis, in keeping with an earlier study in CPRD.
- This study additionally looked at patterns of use, in both immunosuppressed and immunocompetent patients, to better understand who receives antivirals in UK primary care.
- The study demonstrated that antivirals are under-prescribed in patients for whom guidelines recommend treatment. Specifically:
    - Although immunosuppressed patients were 30% more likely to receive antivirals than immunocompetent patients, antivirals were not given routinely to this group. In total, 35.1% of patients with severe immunosuppression did not receive antivirals in primary care.
    - The proportion of patients receiving antivirals increased with age up to 65-74 years, then declined among patients aged ≥85 years, for whom only 56.8% received treatment.
    - Patients were less commonly prescribed antivirals in primary care if they had ophthalmic (proportion given antivirals, 49.4%) or other non-truncal zoster (30.9%) than patients with zoster in whom site of zoster was not specified (58.4%). This was a surprising finding, as the guidelines clearly advise treatment for these patients. This finding may in part be explained by patients with zoster in "high risk" sites being referred immediately to secondary care for treatment or attending emergency departments.
- Being female and of higher SES were associated with higher antiviral receipt, which may be explained by greater health-seeking behaviours in these groups Antiviral prescriptions increased every year from 45.7% in 2000 to 65.3% in 2010 and the trend remained after adjusting for confounders. Use also varied by region, with highest use in Northern Ireland (67.7%) and lowest use in the north-east of England, specifically the Yorkshire and Humber region (51.9%), an effect which remained after adjusting for covariates.

- Patients with autoimmune conditions considered to be associated with moderate immunosuppression were more likely to receive antivirals; in particular, there was greater antiviral use among patients with RA and SLE, irrespective of whether they were receiving immunosuppressive therapy, and also patients with IBD treated with immunosuppressive therapy.
- Under-treatment with antivirals cannot be attributed to adverse effects or cost, as these drugs are well-tolerated and relatively inexpensive. Patients may present too late to receive antiviral therapy, however previous research from UK data suggests that the majority of patients present soon after rash onset. It is therefore plausible that under-treatment may reflect poor adherence to treatment guidelines.

8.1.3. Risk factors for PHN

8.1.3.1. What was known

- Older age was a well-known risk factor for PHN, with very few cases occurring under the age of 50 years.
- Other frequently reported risk factors for PHN related largely to characteristics of the acute zoster episode, such as the severity of the acute pain. Despite these characteristics being commonly cited as predictors of PHN, the evidence had never been systematically reviewed and the magnitude of their effect was largely unknown.
- Finally, an understanding of patient characteristics and conditions identifiable before the zoster episode which may increase the risk of PHN and potentially be useful when considering vaccination policy, had yet to be summarised.

8.1.3.2. What the systematic review adds

- The systematic review and meta-analyses of risk factors for PHN within zoster cohorts (described in chapter 6) demonstrated that risk factors for PHN are poorly understood and that existing evidence is often conflicting and underpowered.
- Meta-analyses demonstrated that features of the acute zoster episode, including prodromal pain, severe acute pain or rash and ophthalmic involvement, were associated with greater than twice the risk of PHN.
- Regarding vaccine-targetable risk factors for PHN, the review demonstrated a clear increased risk of PHN with greater age; nine studies reported an effect estimate for a

ten-year increase in age on PHN risk, with estimates ranging from 1.22 to 3.11. Exactly how the risk of PHN varies as people age is not understood.

- There was a suggestion from three out of five studies in the systematic review that patients with immunosuppression may be at greater risk of PHN. However, the evidence was conflicting and different definitions of severe immunosuppression were used, limiting the ability to compare study results.
- Other patient conditions associated with an increased risk of PHN (investigated in single studies only) were SLE, recent trauma and personality disorder symptoms. There was no evidence of higher PHN risk with depression (in four studies) or cancer (in five studies). Diabetes was associated with increased risk of PHN in one of four studies.
- No previous studies were identified which investigated the effects of RA, IBD, COPD, asthma or CKD on PHN risk.
- There were key differences between studies included in the review, such as: (i) the demographic characteristics of participants, particularly their age distribution; (ii) the definition of PHN used, for example assessing pain at one, three or six months following zoster, as well as including "any" or "severe pain" following zoster; and (iii) differences in the confounders accounted for in the analyses. Comparisons between study results must therefore be made cautiously.
- Overall the majority of studies currently published are limited in size, reducing their power to detect associations; in total, 17 out of 19 studies included in the review had under 1000 participants. Although the review required effect estimates to be age-adjusted, many studies included age as a binary or categorical variable with wide intervals, potentially leading to residual confounding by age.

8.1.3.3. What the original research study adds

- The cohort study (described in chapter 7) showed that PHN risk is increased for a number of patient characteristics and comorbidities, most notably age and immunosuppressive conditions. The study both confirmed previously described risk factors for PHN, as well as identifying novel risk factors.
- One of the most well-reported and strongest risk factors for PHN is age. This study confirmed older age as a key risk factor. The risk rose most sharply between 50 and 79 years, where a 10-year increase in age within this age-band was associated with 70% increased risk of PHN. A 10-year increase among patients aged 80 years and above was

associated with just 10% increased risk of PHN, although patients in this age group would have a higher baseline risk.

- Previous research on the impact of severe immunosuppression on PHN was inconclusive. This study demonstrated that severe immunosuppression was a strong risk factor for PHN. Furthermore, rather than combining patients with any condition or course of therapy associated with severe immunosuppression, this study had sufficient power to assess the effect of specific conditions and therapies on PHN risk. Leukaemia or lymphoma diagnosed in the previous two years, myeloma, other unspecified cellular immune deficiencies, or recently taking a course of high-dose (≥20 mg per day) corticosteroids, were each associated with a more than doubling in the risk of PHN.
- Conditions also associated with increased risk of PHN, and recognised in previous studies, comprised SLE, which was associated with over 80% increased risk of PHN, and type 2 diabetes, which was associated with 20% increased risk. In contrast with previous research, this study suggested recent depression was associated with almost 40% increased risk of PHN, whereas there was no evidence that personality disorder predicted PHN, after adjusting for covariates. Novel risk factors for PHN, not identified in any previous research, included RA, IBD, COPD and asthma.
- This study was one of the few to look at the association between lifestyle risk factors and PHN. Being a current or ex-smoker, as well as being underweight or obese, was associated with 10 to 30% greater risk of PHN.
- The only clinical feature of acute zoster available in CPRD was site of zoster and, consistent with previous studies, PHN was twice as common in patients with non-truncal (including ophthalmic) zoster.
- The study was also unique in exploring the effects of antiviral use. Antiviral use was not associated with PHN (OR=1.04, 0.97-1.12). There was also some weak evidence that the increased risk of PHN associated with leukaemia, SLE, COPD and smoking was less pronounced in patients given antivirals.
- This study benefited from being the largest to date exploring risk factors for PHN, as well as tightly accounting for the confounding effects of age by using a continuous non-linear function in the modelling.

8.2. Strengths and weaknesses of using electronic health records for research into zoster and PHN

The studies included in this thesis used primary care data from the UK (CPRD), linked to hospitalisation (HES) data. As data are routinely collected in these databases, they are hugely advantageous for researchers, as they reduce the time and cost involved in traditional data collection. This section reviews the strengths and weaknesses of using these databases in addressing the study questions. As HES data were used specifically to identify zoster and PHN patients, and as the large majority of individuals with zoster and PHN were identified in CPRD, this section largely refers to CPRD data.

8.2.1. Strengths

8.2.1.1. Size and long-term follow-up

A key strength of CPRD is its size, which allowed the studies to look at less common conditions, such as SLE, and explore age interactions, with sufficient statistical power. For example, the case-control study in chapter 4 included over half a million individuals (and more than 140,000 zoster cases) who had an average of more than 8 years active follow-up. Furthermore, the cohort study in chapter 7 was the largest known analysis to date of PHN risk factors. In all three studies, there was sufficient power to look at certain individual conditions associated with immunosuppression, rather than combining these conditions into one category.

8.2.1.2. Breadth of data

CPRD is one of the few EHR databases in the world holding information on lifestyle data, including BMI, smoking status, alcohol use and SES, as well as clinical diagnoses and prescription data. The availability of lifestyle and anthropometric data allowed these factors to be explored and accounted for in the analyses, in contrast to much previous research on zoster and PHN risk factors. Furthermore, CPRD is one of the few large and ongoing databases to have linkage to secondary care data, which was used to identify cases of zoster and PHN diagnosed in hospital.

8.2.1.3. Prospectively collected data

Another strength of using CPRD and HES is that data are collected prospectively, as patients attend their general practice or hospital for healthcare. This meant that the studies assessing risk factors for zoster and PHN were not subject to biased ascertainment of past exposure status (when a patient's outcome influences their memory and thereby reporting of the exposure) or observer bias (where the patient's outcome influences the observer's recording of the exposure). Furthermore, use of this prospectively collected data meant the matched

case control study of zoster risk factors was nested in the CPRD cohort. This meant controls were drawn from the same population that gave rise to the cases, thus reducing the possibility of selection bias.

8.2.1.4. Representativeness

As described in chapter 3, CPRD patients are broadly representative of the UK population in terms of age, sex and ethnicity (although the database may not fully represent all practices in the UK in terms of geography and size).[85] This means that by selecting all patients with zoster, and suitable controls, the conclusions for the studies presented in this thesis are likely to have good external validity and be generalizable to the UK population.

8.2.2. Limitations

Although CPRD and HES have many strengths for investigating the study questions explored in this thesis, it must also be acknowledged that using the databases introduced some limitations. The limitations of each study have been described within the individual chapters. Below is a summary of these discussions, considering the research project as a whole.

8.2.2.1. Information bias

Information bias may have been introduced due to measurement or ascertainment errors within CPRD and HES data. In the following section misclassification of zoster, PHN and other covariates are discussed, along with the potential impact of this misclassification on the study findings.

Misclassification of zoster

Zoster diagnosis in UK primary and secondary care is based on clinical judgement, without laboratory confirmation. As discussed in chapter 4, zoster diagnoses have not been validated in CPRD or HES. However a validation study of zoster in a primary care setting in the Netherlands demonstrated a high PPV of zoster diagnosis of 91%, when confirmed by the presence VZV of antibodies.[198]

The most likely misclassification of zoster is believed to be with herpes simplex. However, herpes simplex rarely presents with a dermatomal distribution, therefore the extent of this misclassification in this body of research is believed to be minimal. If patients with herpes simplex were incorrectly included as zoster cases in the matched case-control study (chapter

4), assuming simplex is not associated with the risk factors of interest, any misclassification would have led to an underestimation of the effect estimates. If the risk factors of interest were associated with greater risk of herpes simplex, there might have been an overestimation of effect estimates. In chapter 7, the analysis of PHN risk factors within a zoster cohort, patients with herpes simplex potentially misdiagnosed as zoster patients were removed in a sensitivity analysis (specifically, zoster cases with zoster codes appearing within the year following first zoster diagnosis, many of whom had a further antiviral prescription on the same day) and there was no appreciable impact on the study findings.

Zoster diagnoses may be missed in the EHR data, either due to: 1) misdiagnosis of zoster, for example misdiagnosing zoster cases as herpes simplex or difficulties in diagnosing zoster in the rare situation in which a rash does not appear, known as zoster sine herpete; or 2) zoster being recorded in the free text but not coded in CPRD; or 3) zoster patients not attending health services, for example if the pain is mild or patients are unable to seek healthcare. Use of both CPRD and linked HES data allowed more complete capture of zoster cases attending either healthcare setting. However, the frequency with which diagnoses of zoster are *not* captured in either CPRD or HES is not known. Missed zoster diagnoses may be more common in younger patients among whom zoster is less prevalent and may be less severe. Studies establishing the validity of "non-diagnoses" in EHR data (i.e. patients *without* specific diseases) are rarely carried out, as this requires sampling a number of patients *without* the disease (whereas the PPV only requires sampling of patients *with* the disease).[89] Assuming inclusion of some zoster patients in the control pool is random and non-differential according to the exposures, this misclassification would have caused an underestimation of effect estimates.

Patients were required to have 12-months registration in CPRD without a zoster diagnosis, to exclude past history of zoster recorded shortly after registration. It is possible that a 12-month cut-off was insufficient to remove past history of zoster or PHN cases (misdiagnosed as acute zoster). A 24-month cut-off may have increased the likelihood of the included patients being incident. Previous research has however shown that the incidence rate of zoster is slightly higher in CPRD during the first 3 months after registration, however reached baseline levels 4-6 months following registration, suggesting the chosen cut-off was appropriate.

Validity of zoster diagnosis timing

The precise timing of zoster onset may not always be attainable from CPRD and HES data. The date at which zoster patients presented to their GP with zoster was used as a proxy for rash onset date. In reality, the true date of rash onset will, in some cases, be a few days prior to

this. As acknowledged in chapter 7, incorrect rash onset date might have affected the observed null association between antiviral use during acute zoster and PHN; some studies have reported that antivirals are effective at reducing PHN risk if given *within 72 hours* of rash onset, therefore delay in presenting to primary care may explain the null finding.

Misclassification of postherpetic neuralgia

As with zoster, PHN has not been validated in CPRD or HES. As discussed in detail within chapter 3, section 3.3.2, diagnosing PHN in EHR databases is a particular challenge. The difficulties result from a variety of reasons, including different definitions of PHN being used, PHN treatments being non-specific to PHN and therapeutic indication not being recorded in CPRD.

As discussed in chapter 3, of particular concern was that patients with depression were wrongly defined as having PHN, due to the use of tricyclic antidepressants in defining PHN patients. Several steps were taken to reduce this misclassification, such as ensuring all PHN cases had recently been diagnosed with zoster, ensuring PHN cases did not have diagnosis codes suggesting depression when PHN was defined through use of tricyclic antidepressants, and ensuring prescriptions were "new" (no previous prescriptions of a tricyclic antidepressant in the 12 months to two weeks prior to zoster). However, the association between PHN and depression disappeared when PHN was defined through use of diagnosis codes only (i.e. a Read or HES code for PHN), therefore it is possible that some misclassification of PHN occurred, which may have increased the association between depression and PHN.

Part of the PHN definition incorporated use of anti-convulsants and hence patients with a history of epilepsy were excluded from the study cohort. However, anticonvulsants can also be used a mood stabiliser for patients with bipolar, personality disorder and schizoaffective disorder. Therefore, there may have been some misclassification of PHN cases resulting from the inclusion of anticonvulsants as part of the PHN definition, which could have further increased the association observed between depression and PHN.

It is also possible that some individuals with PHN will have been included in the non-PHN comparison cohort; this misclassification is potentially supported by the relatively low prevalence of PHN, compared to other non-EHR studies. As discussed in chapter 7, it was hypothesised *a priori* that misclassification of PHN status may be differential according to the investigated PHN risk factors, because patients with risk factors of interest may attend their

general practice more frequently, and thus be more commonly diagnosed with PHN. However, little evidence was found to suggest the presence of this bias (ascertainment bias, see section 7.2.4). Instead, misclassification of PHN status is more likely to be non-differential according to the explored PHN risk factors and therefore PHN patients may have made a small contribution to the risk estimates of the comparison group, which would marginally reduce the reported risk estimates.

Finally, differential health-seeking behaviours may be driving the increased risk of PHN among females (compared to males), as women are known to attend general practice more commonly than men.

Misclassification of other conditions

Using stand-alone CPRD to define medical conditions

Although GPs are requested to record all patient diagnoses, recording of some clinical outcomes in CPRD may be incomplete, particularly those made in secondary care. Hospital letters will be sent to the GP and may be stored on the system, but a Read code may not always be entered, therefore the information may be missed by researchers. Most risk factors in this study requiring secondary care were chronic and of sufficient significance that they are likely to be recorded in the patient's primary care records; many conditions, such as diabetes, are treated largely in primary care (and also from 2004 diabetes has been part of QoF) and for these conditions this may be a reasonable assumption. However, since the research in this thesis was conducted, there has been evidence to suggest that using stand-alone databases to identify patients with certain conditions can lead to under-capture. This misclassification appears particularly pertinent to acute events such as myocardial infarction[199] and community acquired pneumonia,[200] but also with regard to some chronic conditions such as asthma.[201] Therefore, it seems likely that some patients with the conditions of interest will have been misclassified as "unexposed" patients. Misclassification of medical conditions is likely to be non-differential according to the outcomes (zoster or PHN), therefore in the risk factor analyses this would have caused an underestimation of effect estimates.

Incomplete clinical information

Detailed clinical information, which may be gathered in a traditional epidemiological study with active data collection, is also not always available to CPRD researchers. In CPRD, some information may never be recorded, or may be within the free text field. Incomplete clinical detail may have led to misclassification. For example, regarding the categorisation of diabetes

into type 1 or 2, the definition relied on: 1) age at diagnosis, which may be problematic if patients moved practice after their first diagnosis of diabetes; and 2) treatment, which could be missed if only given in secondary care. This categorisation may have led to some type 1 diabetes patients being misclassified as type 2 diabetes, if their real age of first diagnosis was earlier than recorded and they were receiving insulin in secondary care.

Misclassification of prescriptions

Although the CPRD has excellent capture of primary care prescriptions, there are some limitations. First, CPRD doesn't provide data on adherence to treatment or timing of treatment initiation; the issue date may not necessarily be the date the prescription was collected, or the date the patient started using the drug. The issue of non-adherence is particularly relevant to ICS prescriptions, which are often used intermittently when required. Regarding severely immunosuppressive drug exposures prior to zoster onset (for example oral corticosteroids or methotrexate), non-adherent patients, or those initiating treatment after the issue date, could be misclassified as having been exposed when in fact they were unexposed. This misclassification may be differential according to the outcomes, zoster and PHN, specifically that non-adherent patients may be less likely to develop zoster or PHN. Thus any misclassification due to non-adherence may have caused an underestimation of the effects of immunosuppressive drugs on zoster risk.

Secondly, neither CPRD nor HES record therapy given in secondary care. Antivirals given in secondary care would be missed, and as acknowledged in chapter 5, may partly explain the low use of antivirals among patients with ophthalmic or non-truncal zoster, for whom guidelines specifically recommend treatment. Additionally, immunosuppressive medications may be given in hospital, for example chemotherapy and biologics, and thus may be unrecorded in primary care. Part of the effect of cancers studied here (specifically, leukaemia, lymphoma and myeloma) will have been driven by chemotherapy and it was not possible to disentangle the effect of the cancers themselves versus their treatments. Regarding anti-TNF biologic medications, these drugs do not form the mainstay of treatment in the UK for inflammatory conditions, but are used in approximately 10% of RA patients and 13% of adult Crohn's disease patients.[202] As described in chapter 2, these drugs may be associated with an increased risk of zoster in RA and IBD patients. Part of the associations observed between autoimmune conditions and zoster or PHN may therefore be explained by biologic or other immunosuppressive therapy not captured in the GP records.

As discussed in section 3.4.2, daily prescription doses for oral corticosteroids were cleaned and some missing data imputed. This imputation may have led to some misclassification of high-dose oral corticosteroid exposure; however, this misclassification is unlikely to be related the outcomes (zoster and PHN), therefore estimates of the effect of oral corticosteroids on zoster risk would only have been reduced toward the null.

Finally, over the counter medications are not recorded in CPRD. This is not an issue for identifying antiviral or immunosuppressive medications, as these drugs are prescription only. However, patients may self-medicate for PHN with over the counter pain medications, if the pain can be controlled with mild analgesics, therefore some PHN patients are likely to have been misclassified. As explained in chapter 7, this limitation may not cause biased results, however it may limit the generalisability of the results to patients with severe, rather than mild, PHN.

8.2.2.2. Confounding by indication

Confounding by indication can occur because within observational data, drugs are not randomly allocated but may instead be indicated for a disease based on severity and prognosis. Therefore risk of the outcome, prior to treatment, may not be similar between treated and untreated individuals. For example, in chapter 7, *a priori* it was anticipated that any protective effect of antiviral use during acute zoster on PHN risk may be attenuated; this is because patients with more severe zoster are more likely to receive antivirals as well as being at greater risk of PHN, potentially masking any protective effect of antivirals. In the final multivariable model, there was no association between antivirals and PHN, and this observation may therefore be explained by confounding by indication. Two statistical methods exist which can, in theory, better deal with confounding by indication: 1) propensity scores.[203] and 2) instrumental variables. [204] These methods will be considered in future analyses.

8.2.2.3. Residual confounding

CPRD data are collected primarily as a tool for physicians to record a patient's medical history and therefore certain data may not be sufficiently recorded to fully adjust for the confounding effects of that variable. Residual confounding by measured variables may arise from two sources. The first source is from confounders being misclassified. For example, as described in

section 8.2.2.1 above, part of the observed effect between RA and zoster may be due to residual confounding by biologics. The second source is from confounders being defined in broad categories, and residual confounding arises if the risk of the outcome varies within a category of the confounder. For example, patients classified as current smokers would have represented a range of smoking habits, from occasional to very heavy smokers, and this may have caused residual confounding by smoking.

In addition to incomplete capture of included risk factors, uncontrolled variables not available within CPRD may have caused residual confounding. For examples, physicians do not routinely record certain factors associated with zoster, such as exposure to individuals with varicella and dietary habits, such as fruit intake. The possibility of residual confounding incurred from not accounting for two unmeasured factors, psychological stress and ethnicity, are discussed below.

Psychological stress

Despite the evidence-base being limited and inconsistent, there is some suggestion that psychological stress may be an important risk factor for zoster (as outlined in chapter 2). The research presented in this thesis did not account for psychological stress. Capturing all psychological stress in CPRD would have been challenging, as stress may be induced by a wide range of conditions or events, such as depression, anxiety, self-harm, bereavement, job loss or divorce. Furthermore, many people who experience acute or chronic stress will not seek care from their GP. It is therefore plausible that this study may suffer from residual confounding by psychological stress. If stress is a risk factor for zoster and was equally distributed among exposed and unexposed patients for specific conditions, this would have led to an underestimation of effect sizes. However, it is plausible that stress may mediate the relationship between some of the conditions investigated in this thesis and zoster (in other words, stress may be on the causal pathway between the exposures and zoster). If this scenario is correct, it would have been inappropriate to control for stress.

Ethnicity

At the time this research project was planned, little was known about the reliability of ethnicity data and a decision was made not to investigate ethnicity as a covariate. Research has subsequently shown that for patients registered with a general practice after April 2006, ethnicity data in CPRD alone is available for 78.3% of patients.[205] However, the authors recommend not using ethnicity data recorded in patients registered prior to April 2006, as

recording is low and likely to be selective. Further investigation has shown that less than 5% of the zoster cases and their matched controls from the study in chapter 4 were registered after April 2006; thus, in retrospect, the decision not to include ethnicity data remains valid. However, not including ethnicity as a covariate may have implications on the study findings. As mentioned in chapter 4, the lack of association between type 2 diabetes and zoster may be partly driven by negative confounding by ethnic group (patients of South Asian origin are at higher risk of type 2 diabetes, yet lower risk of zoster).

8.2.2.4. Selection bias due to missing data

In the thesis, lifestyle data, including BMI, smoking and alcohol were explored and accounted for in the analyses. All these variables contain some missing data. These lifestyle data are recorded opportunistically for many patients and missing data are unlikely to be 'missing completely at random'. For example, BMI completeness is higher in females, in clinical subgroups where BMI recording is incentivised (such as type 2 diabetes) and in older age groups.[125] It is also plausible that the missing data depend on the variable itself (for example, patients with healthy BMI may not have their BMI recorded by the GP). In the main analyses in chapter 4 and 7, patients with missing data were excluded from the analysis (complete case analysis). This method may lead to biased effect estimates, as the included sample are unlikely to be representative of the full cohort, potentially introducing selection bias. However, complete case analysis is valid, if the reasons for missing-ness are unrelated to the outcome, given the covariates.[206] In terms of the lifestyle variables BMI, smoking and alcohol use, it is assumed that non-recording of these variables is unlikely to be related to developing zoster or PHN.

However, as an alternative approach to handling missing data, data that was missing for BMI, smoking and alcohol was also accounted for through multiple imputation in a sensitivity analysis. That the study findings were consistent when applying a complete case and multiple imputation method suggests the results are robust, and major selection bias is unlikely to have been introduced.

8.2.2.5. Data on underlying mechanisms

The mechanisms through which exposures increase the risk of zoster and PHN is assumed to be through impairing T cell-mediated immunity. It was not possible to confirm the pathway in this thesis, as the CPRD doesn't contain biological markers of cellular immune-suppression.

8.2.2.6. Multiple testing

The risk factor analyses in chapter 4 and 7 involved testing multiple associations. Testing multiple associations results in the possibility that some of the observed "statistically significant" associations may have occurred by chance. However, in order to protect against this, 99% CIs were used. Furthermore all risk factors were specified *a priori*, based on previous epidemiological research and/or supporting data regarding plausible biological mechanisms.

8.2.2.7. Lack of clinical information on risk factor sub-groups

The EHR data was insufficiently detailed to investigate potentially important differences between sub-groups of certain risk factors. For example, all stages of CKD severity were grouped together, as were symptomatic and asymptomatic HIV, the latter of whom may not be associated with cell-mediated immune suppression.[104] It is therefore not possible to see how the effects of these risk factors on zoster and PHN varied according to severity of disease. Furthermore, it was not possible to determine whether the observed effects were driven solely by patients with more severe disease.

8.3. Implications for clinical practice

Recognising that certain patients are at increased risk of zoster and PHN, as well as identifying the under-prescription of antivirals in patients with zoster, could have important implications for clinical practice:

- This thesis adds to the case for vaccinating individuals against zoster prior to the introduction of immunosuppressive therapies. Given the increased risks of zoster and PHN in patients on immunosuppressive treatment, and the contraindication to use the currently available live vaccine in severely immunosuppressed individuals, vaccination prior to commencement of immunosuppressive treatment may warrant consideration, although evidence to support this strategy is currently lacking. The new sub-unit vaccine which has been designed for use in patients with immunosuppression (and is currently being investigated in Phase 3 trials) may enable vaccination in this group.

- This study highlights the need for greater prescribing of antivirals and considerations could be given to improving the implementation of the guidelines on antiviral prescription following acute zoster. Antivirals are important in lessening the time and severity of the acute zoster episode. Although antivirals have not conclusively been shown to protect against PHN, the study of PHN risk factors showed some weak evidence that their use may be associated with a reduction in PHN risk in patients with leukaemia, SLE, COPD and smoking. Together, these factors support better adherence to antiviral treatment guidelines during acute zoster.
- The UK guidelines for antiviral use currently recommend that patients presenting after 72 hours of zoster onset be given antivirals within one week of rash onset, if they are at high risk of severe shingles or complications. Considering that a number of conditions and patient characteristics have been identified which increase the risk of PHN in this thesis, consideration could be given to suggesting that patients with identified risk factors for PHN also be given antivirals if presenting after 72 hours of rash onset.

8.4. Implications for further research

8.4.1. Risk factors for zoster and PHN

- This study has identified a number of patient characteristics as risk factors for zoster and/or PHN. It also showed younger patients with certain conditions were at higher risk of zoster. Cost-effectiveness studies would be needed to determine whether vaccination of groups with particular characteristics would be worthwhile.
- Although this study has demonstrated that certain patient characteristics and conditions are associated with increased risks of zoster and PHN, further research is needed to understand the mechanisms underlying the increased risk, particularly for PHN for which the pathogenesis of continued pain is poorly understood.
- The safety of the currently available *Zostavax* vaccine in immunosuppressed groups is also poorly understood and its contraindication is largely based on expert opinion rather than clinical data. Further research assessing its safety among immunosuppressed patients is needed. Recent RCTs have supported zoster vaccine guidelines, such as a small RCT (n=295) demonstrating that the vaccine is safe in patients currently on a maintenance dose (5-20 mg per day) of corticosteroids[207] and preliminary results suggest HIV patients with CD4 counts ≥200 per mm^3 and on ART are not at increased risk of zoster after receiving the *Zostavax* vaccine.[208] However,

research among patients with current vaccine contraindications is needed. For example, there is some evidence from observational studies that autoimmune patients on anti-TNF biologics and non-TNF biologics may not experience an increased risk of zoster following *Zostavax* vaccination in the primary safety risk window (42 days following vaccination),[53] however trials are needed to confirm these findings to ensure the effects are causal.

- The new subunit vaccine offers more potential for use in immunosuppressed patients and requires further research on safety and efficacy in this group. As this newer vaccine is not live, it does not pose the same risk of triggering a varicella-like or herpes zoster illness as the *Zostavax* vaccine. Furthermore, initial results suggest the new subunit vaccine has limited safety concerns and appears equally as effective among older groups, wherein *Zostavax* vaccine efficacy is significantly reduced.[209]
- Work is needed to establish the role of psychological stress on zoster risk. Despite stress being viewed as an important risk factor among the lay public and medical professionals, stress has not been consistently shown as a risk factor in the epidemiological literature.
- Finally, this research used a current dose model when exploring the effect of prescription drugs on the risk of zoster and PHN; further research could take into account the impact of historical therapy on zoster and PHN risk.

8.4.2. Antiviral prescribing patterns in UK primary care

- Further research into the causes of under-prescription of antivirals to acute zoster patients, specifically among older and immunosuppressed groups, would be helpful in determining strategies to increase the number of patients given antivirals. For example a qualitative research study among GPs may help clarify reasons for non-prescription of antivirals, where the guidelines specify antivirals should be administered. This could then be followed up by a quantitative cross-sectional survey to determine the most common reasons for under-prescription of antivirals.
- Research on antiviral use during acute zoster is currently limited to assessing antiviral effectiveness when given within 72 hours of rash onset. This treatment window may be unrealistic in clinical practice, as there may be a delay of >72 hours between rash onset and presentation in primary care. Therefore, to further encourage physicians to prescribe antivirals, research into the effectiveness of antivirals given within a week of rash onset may be helpful.

8.5. Overall conclusions

Herpes zoster is a common disease with appreciable morbidity, which is preventable through vaccination. This thesis has carried out a systematic literature review, a literature review and two large observational studies using UK primary care data, to investigate risk factors for zoster and PHN. There was an increased risk of both zoster and PHN among patients with selected autoimmune conditions (RA, SLE and IBD), COPD, asthma and depression. The greatest risk of both zoster and PHN was among patients with severely immunosuppressive conditions, highlighting the need for alternative risk reduction strategies in this group, for which the new subunit vaccine appears promising. Whilst data on the underlying mechanisms were not part of the work described in this thesis, the increased risk of PHN among patients with autoimmune and other immunosuppressive conditions suggests that lower cell-mediated immunity may play an important role in the pathogenesis of PHN, as well as zoster. A third study also draws attention to the under-prescription of antivirals during acute zoster in UK primary care, suggesting physicians are not fully adhering to treatment guidelines. This thesis has highlighted a number of risk factors for PHN and zoster; cost-effectiveness studies are now needed to determine the value in providing zoster vaccination to patients with these risk factors.

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Appendix I: Scientific protocol

The candidate was employed under an NIHR Clinician Scientist fellowship awarded to Sinéad Langan entitled, “The natural history and management of herpes zoster: the role of moderate immunosuppression from common diseases”. The scientific protocol can be found below.

The natural history and management of herpes zoster: the role of moderate immunosuppression from common diseases

Lay Summary

Shingles is a common disease with very important consequences that have lead to large scale vaccination programmes being introduced in the USA and planned in the UK. This research aims to answer a number of key questions which will inform the shingles vaccination policy in the UK
Firstly, this research will find out how common shingles and important complications are; including possibly risks of heart attack. Secondly, it is well known that people with suppressed immune systems, e.g. from chemotherapy, are at increased risk of shingles. However we know very little about the impact of common disorders such as obesity and diabetes which may increase risks of shingles and related problems. Thirdly, this study will provide important information about patterns of use of shingles treatments and their effectiveness in clinical practice in the UK. Finally I will focus on the benefit of shingles vaccination in the population.
To answer these questions, I will use a very large general population cohort in the UK. This is a novel timely study of particular relevance to the NHS in the early stages of introducing a large scale HZ vaccination program.

Background

Herpes zoster (HZ) is a common disease. The lifetime risk for HZ is between 25% and 35% rising to almost 50% among people surviving to aged 85 years or greater, and it is estimated that there are more than 88,650 incident cases annually in the UK among immunocompetent people aged greater than 60 years. [1-3]

Common comorbidities

Age is the major predictor of HZ incidence; this is believed to be due to waning specific cell mediated immunity. In specific profoundly immunosuppressed high risk groups, HZ incidence rates and complications are increased, e.g. HIV infection, immunosuppressive therapies for cancer/post-transplant and specific autoimmune diseases (e.g. inflammatory bowel disease and Wegener's granulomatosis).[4-7] Risks of HZ and its sequelae could also be increased among those with common disorders of major public health importance possibly associated with lesser degrees of immunosuppression, such as diabetes mellitus, obesity and chronic obstructive pulmonary disease (COPD).[8, 9] Despite the importance of these conditions, HZ natural history has not been adequately studied in these groups. Diabetes has been identified as a possible risk factor for HZ in a case-control study from Israel.[10] A recent study from Taiwan has also suggested that individuals with COPD may be at increased risk of HZ.[11] Obesity has not been previously studied in relation to HZ. Improved understanding of HZ among people with impaired cell mediated immunity is crucial to establish potential benefits and risks of vaccination.[12]

Consequences of HZ

The most common overall complication of HZ is post-herpetic neuralgia (PHN), affecting 30% of individuals with HZ aged 80-84 years in the UK in routine practice and resulting in prolonged morbidity.[13] However, a range of other severe sequelae can occur following HZ, and the epidemiology of these outcomes is poorly understood. Specific areas requiring study in a population-based study include the incidence of serious events (encompassing cardiovascular and other sequelae), hospitalisation and all cause mortality. Work undertaken by my mentor established that acute systemic infections in adults are associated with more than a three-fold transient increased risk of stroke in the first few days following infection and more than a two-fold increased risk of myocardial infarction.[14, 15] The effect of specific infections has been less explored; HZ could plausibly result in an increased risk of cardiovascular outcomes. Work is currently being undertaken by our group (ISAC 10_089) to determine if

there is an association between herpes zoster and stroke. The incidence of myocardial infarction following HZ has not been investigated. Overall mortality may also be increased following HZ, e.g. related to pneumonia, venous thromboembolism and major cardiovascular events; this has not been specifically studied. Current UK mortality estimates are based on two sources: cause of death from death certificates (which may underreport HZ) and deaths during hospitalization which relate to short-term mortality only.[16]

Antiviral therapy

The efficacy of antivirals for treating acute HZ has been demonstrated in randomized controlled trials (RCTs). [17] No study has described overall patterns of use, effectiveness and adverse outcomes of antivirals for HZ in UK clinical practice. These studies will provide information needed about absolute event probabilities to inform risk- and cost-benefit studies.[18]

Herpes zoster vaccine

The development of a HZ vaccine has been a major breakthrough in this field. Oxman *et al* demonstrated a 51% reduction in episodes and a 66% reduction in post herpetic neuralgia in a US randomized controlled trial (RCT) of HZ vaccine.[19] It is unclear what the impact of HZ vaccination has on other HZ-associated complications. No stratification by comorbidity has been published showing HZ vaccine efficacy or side effects in individuals with mild to moderate immunosuppression. These individuals may have greater risks of HZ infection and adverse outcomes and may benefit from earlier vaccination, analogous to UK influenza vaccination policy.[20] This group may have also increased risks of vaccine adverse effects.

Routine HZ vaccination was introduced in the US for immunocompetent individuals aged ≥60 years in 2006.[19] A similar program is planned in the UK for people aged ≥70 years. HZ and varicella vaccines are currently not recommended in severe immunosuppression. Varicella vaccine has been used in children with leukaemia, HIV and following transplants.[21, 22] No similar published experience exists for HZ vaccine, the dose of which is 14 times higher than varicella vaccine.

Further study is required to understand the natural history of HZ particularly in groups with common comorbidities and possible impaired cell mediated immunity. The proposed study combines cohort, nested case-control and self-controlled case series studies using the UK General Practice Research Database (GPRD) to study HZ outcomes, the impact of mild to moderate immunosuppression, patterns of use and effectiveness of antivirals and the benefit of HZ vaccination. Looking at GPRD data allows study of absolute outcomes in a large real population, rather than clinical trial populations. Study of the impact of vaccination on HZ incidence and sequelae may be monitored by the Health Protection Agency but its impact on less established HZ complications are likely to be outside routine surveillance and will require further study.

What is not known?

- What is the recent incidence of HZ in the UK, including among immunocompromised individuals?
- What is the incidence of serious conditions e.g. myelitis, encephalitis, myocardial infarction and all cause mortality after incident HZ?
- Do novel risk factors associated with some immunosuppression, such as diabetes, obesity and COPD, increase the risk of incident HZ and complications?
- What are the patterns of use and effectiveness of HZ antivirals in clinical practice in the UK?
- How effective is HZ vaccination at preventing HZ and complications in pragmatic use?
- Should systemic antivirals and vaccination be considered at younger ages for treatment or prevention of HZ respectively in people with diabetes, obesity and COPD?

Aims

This project has two overall aims. Firstly, to update incidence estimates of HZ, the frequency of serious health outcomes following HZ and to identify new risk factors for HZ and severe sequelae. The second

aim is to estimate the effect of HZ vaccination and antiviral therapy on the natural history and complications of HZ.

The specific study objectives are:

1. To obtain up-to-date detailed estimates of the incidence of HZ in the UK;
2. To identify novel risk factors associated with increased incidence of HZ, namely comorbidities associated with some degree of immunosuppression such as diabetes, chronic obstructive pulmonary disease and obesity;
3. To determine a) the frequency of serious medical conditions following HZ infection including myocardial infarction, post-herpetic neuralgia, myelitis, encephalitis, hospitalizations, all cause and cause-specific mortality , and b) to determine to what extent individuals with HZ are at increased risk of specific outcomes;
4. To identify determinants of serious sequelae among individuals with HZ, including:
   (a) Age, sex;
   (b) Comorbidities associated with some degree of immunosuppression such as diabetes, chronic obstructive pulmonary disease and obesity;
5. To describe patterns of use of antiviral therapy for HZ and to determine the effectiveness of antivirals in preventing severe sequelae of HZ in a routine clinical setting.
6. To determine the effect of HZ vaccination in everyday use on HZ natural history and complications in the UK following introduction of the vaccine.

Study type

Hypothesis generating and testing

Plan of investigation, study design and study population

Identification of incident herpes zoster group

Incident HZ individuals will have been registered with their practice for at least 12 months and will be identified by the presence of diagnostic Read/OXMIS codes in GPRD. Incident HZ will be defined as an episode of HZ without evidence of HZ for at least two years previously.

The GPRD has a number of key linkages which are highly useful for this study as follows:

a) Hospital Episode Statistics (HES)

HES contains details of all people admitted to NHS hospitals in England; the HES-GPRD link provides information on patients hospitalised from 1997 onwards.

b) Office of National Statistics (ONS)

ONS mortality data are linked to GPRD and record cause of death from death certificates

c) Myocardial Infarction Audit Project (MINAP)

MINAP is the United Kingdom's national register of acute coronary syndromes which includes all 230 hospitals in England and Wales.

All analyses will be carried out using Stata 10 (Stata Corp., College Station, TX, USA). Descriptive studies will provide updated HZ incidence and mortality data. These will be followed by a nested case control study to identify novel risk factors for incident zoster and a series of cohort studies to determine risk factors for HZ sequelae. Finally cohort studies will be used to study the effectiveness of HZ vaccination in the UK population.

1.Descriptive analyses (Objectives 1,3a, and 5)

Analysis Incidence and mortality rates will be estimated using GPRD age and gender-specific denominators. Incidence and mortality rates will be standardized to the European Standard population (2000). Antiviral usage patterns will be assessed by year, age, gender, region, socioeconomic status, diagnosis and underlying comorbidity.

Outcomes Incidence of HZ by age, gender, region, socioeconomic status and over time (2000-2010 in GPRD), mortality at 0-3, 4-6 and 7-12 months after HZ. Antiviral usage patterns and adverse events.

2. Identifying novel risk factors for developing HZ (Objective 2)
Study design Nested case control study
Cases and controls Individuals with incident HZ and age, gender and practice-matched controls with no history of HZ.
Exposures Diabetes, chronic obstructive pulmonary disease and obesity.
Covariates Age, gender, immunosuppression (HIV, malignant neoplasms, multiple myeloma, sickle cell disease, alcohol dependence syndrome, chronic liver or kidney disease, cirrhosis, nephrotic syndrome, organ/tissue transplant and immunosuppressive medications).
Analysis Conditional logistic regression will be used to study the effect of exposures on HZ incidence adjusting for relevant covariates.
Outcomes Adjusted odds ratios for HZ

3. Determining the increased risk of specific conditions after HZ (Objective 3b)
Study designs: Cohort study and self-controlled case series (SCCS) studies
Exposed and unexposed: i) Cohort study: individuals with and without HZ, matched for age, sex and practice; ii) SCCS studies: within-person comparison of exposed periods (following HZ) and non-exposed periods in individuals with HZ with specific outcomes.
Covariates: Age, and (for cohort) gender, smoking, atrial fibrillation, body mass index, hypertension, diabetes, hyperlipidaemia.
Analyses: Poisson regression will be used to model rates of events following incident episodes of HZ, adjusting for relevant covariates and examining whether any increased risk is modified by prior receipt of antivirals. For SCCS analyses, age-adjusted relative incidence of events in defined intervals after HZ relative to all other observed time periods will be derived.
Outcomes Adjusted rate ratios for myocardial infarction, myelitis, encephalitis, hospitalization within 180 days of incident HZ and death.

4. Investigating factors that increase the risk of sequelae among individuals with HZ (Objective 4)
Study design: Cohort study of all people with incident HZ
Exposures of interest Specific exposures to be assessed include diabetes, chronic obstructive pulmonary disease, obesity and antiviral medications.
Covariates Age, gender, other disorders associated with immunosuppression (objective 2); comorbidities, antivirals and duration of follow up.
Analysis Cox regression will be used to compare hazard ratios for outcomes in exposed individuals compared to unexposed adjusting for any relevant covariates.
Outcomes Incidence rates and hazard ratios for serious complications including post-herpetic neuralgia, myocardial infarction, myelitis, encephalitis, hospitalization within 180 days of incident HZ and death.

5. The effect of HZ vaccination on natural history of HZ (Objective 6)
Study design Cohort study; Individuals aged ≥70 years (UK) after introduction of HZ vaccination.
Exposed and unexposed groups Exposed individuals have had HZ vaccination; unexposed individuals will not have had the HZ vaccine.
Covariates See objective 4.
Analysis Incidence and hazard rates for HZ and complications in vaccinated and unvaccinated individuals. Cox regression will model rates of events comparing these groups. Propensity scores will allow for differences between vaccinees and not vaccinated.

Outcomes Incidence and hazard rate ratios for outcomes identified in objective 3

Power and sample size calculations

There are 126,599 cases of HZ in the GPRD from 2000 to 2010 with five years total follow up.
Novel risk factors for HZ If the true odds ratio for disease in exposed subjects, relative to unexposed subjects is 1.5, we will need to study 11152 HZ individuals with 1 matched control per case to be able to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8 at the 5% level of significance, allowing for multivariable analysis.
Factors increasing the risk of HZ sequelae We need 2059 individuals with both COPD and HZ, or 34,317 HZ patients in total (assuming 6% of the cohort have COPD) to have 80% power to detect a hazard ratio of 1.5 for myocardial infarction in exposed individuals with COPD at the 5% level of significance, allowing for multivariable analysis.
Vaccine effectiveness 9843 exposed (vaccinated) individuals and equivalent numbers of unvaccinated individuals are required to have 80% power to detect a 50% reduction in incident HZ at the 95% level of significance. Assuming 3% of the GPRD population in the eligible age groups are vaccinated (n=14460), this should allow >99% power at the 95% level of significance to assess the effectiveness of the vaccine.

Limitations

Validation work on HZ has not been done in previous GPRD studies and documentation in GP records of clinical presentation or severity of HZ is likely to be limited. The key differential diagnosis for HZ is recurrent herpes simplex, which occasionally presents with a dermatomal distribution. Viral culture and PCR are highly unlikely to have been performed in routine practice and would be cost prohibitive to measure in a large population-based study. However, HZ is usually a straightforward clinical diagnosis based on classical clinical presentation. Excluding cases with recurrence intervals less than two years should exclude misclassified cases whilst not excluding immunosuppression-related HZ recurrence. A range of sensitivity analyses will be undertaken for all objectives, excluding recurrent cases of HZ with different intervals. The propensity score method will be used to address chanelling bias.

Patient or user group involvement

When I did my PhD in Nottingham, I involved service users in the development and selection of tools to measure exposures and outcomes and to disseminate study findings in conjunction with the Nottingham support group for carers of children with eczema. For this study, I will build on this expertise and work with a panel of individuals with a history of herpes zoster. A panel of people with a history of herpes zoster led by an experienced consumer, will advise on planning further studies and dissemination of results

Plans for disseminating and communicating study results

Study results will be widely disseminated by presenting study findings at scientific meetings and by publishing in leading scientific journals.

Amendment 1 (APPROVED: 9 May 2012, protocol number 11_028A2R)

We are now requesting to extract all COPD patients in GPRD to study zoster incidence and risk among COPD patients in greater detail.

This will allow the following additional aim:

To look in greater detail among COPD patients:

- **To calculate incidence of zoster among COPD patients.**
- **To determine if the risk of zoster varies by COPD treatment group.**
- **To determine if there is an increased risk of HZ after COPD exacerbation.**

Study Types:
Incidence of zoster among COPD patients
(as with study type 1 outlined above)

Risk of zoster by COPD treatment group
Study Design: Nested Case control study
Cases and controls: Cases are COPD patients with incident HZ; controls are patients with no history of HZ who are age, gender and practice-matched to COPD cases.
Exposures Short-term treatment for COPD (treatment given three months before index date) and long-term treatment
Covariates Age, gender, immunosuppression (HIV, malignant neoplasms, multiple myeloma, sickle cell disease, alcohol dependence syndrome, chronic liver or kidney disease, cirrhosis, nephrotic syndrome, organ/tissue transplant and immunosuppressive medications), moderate immunosuppression (Diabetes, chronic obstructive pulmonary disease and obesity).
Analysis Conditional logistic regression will be used to study the effect of exposures on HZ incidence adjusting for relevant covariates.
Outcomes Adjusted odds ratios for HZ

Is there an increased risk of HZ after COPD exacerbation?
Study designs: Cohort study and self-controlled case series (SCCS) studies
Exposed and unexposed: i) Cohort study: COPD individuals with and without COPD exacerbations, matched for age, sex and practice; ii) SCCS studies: within-person comparison of exposed periods (within one month following COPD exacerbation) and non-exposed periods in COPD patients with HZ.
Covariates: Age, and (for cohort) gender, immunosuppression (HIV, malignant neoplasms, multiple myeloma, sickle cell disease, alcohol dependence syndrome, chronic liver or kidney disease, cirrhosis, nephrotic syndrome, organ/tissue transplant and immunosuppressive medications), moderate immunosuppression (Diabetes, chronic obstructive pulmonary disease and obesity).
Analyses: Poisson regression will be used to model rates of zoster following COPD exacerbation, adjusting for relevant covariates. For SCCS analyses, age-adjusted relative incidence of zoster in defined intervals after COPD exacerbations relative to all other observed time periods will be derived.
Outcomes Adjusted rate ratios for myocardial infarction, myelitis, encephalitis, hospitalization and death within 180 days of incident HZ.

Amendment 2

- Aim 2: A wider range of risk factors for zoster will be assessed.
Recent research has implicated a number of clinical conditions and lifestyle factors as risk factors for zoster including diabetes mellitus[23, 24], chronic obstructive pulmonary disorder (COPD) [24, 25], chronic kidney disease (CKD) [26-28], asthma[29] and depression [30, 31] all of which may be associated with cell-mediated immune suppression.[32-37] It has also been postulated that obesity leads to a degree of cell mediated immune suppression.[38] However, there has been a lack of large, highly powered studies using a systematic approach looking at a wide range of risk factors. Furthermore, adjustment for confounders has often been inadequate and studies have not quantified the population impact of these risk factors. Given the limited current evidence on a wider range of risk factors than we originally planned to look at, all of which are plausibly associated with cell-mediated immunity, we would like to broaden our analysis to include all of the risk factors mentioned above. The above issues and the proposed change arose from discussions between the PhD student leading this study, and the supervisors and advisory group. Additionally, we wish to conduct a focused analysis to look at the effect of statin use on zoster risk. This will be done as an LSHTM MSc summer dissertation (supervised by Krishnan Bhaskaran), and is in response to a recent study (Antonou et al, Clin Infect Dis 2014, 58:350-6), suggesting an increased risk of zoster in statin patients, We felt that the dataset we have developed for the main study would be ideally suited to looking at this research question, and that this would make an interesting and useful training project for an MSc Epidemiology student. For the MSc project, the student will use the same case-control design, and will be able to adjust for the range of covariates already extracted.

- Aim 4: As well as identifying risk factors for post-herpetic neuralgia (PHN) in zoster patients, we will also look at risk factors in the general population
In our original plan (part 4), we specified a cohort analysis to look at risk factors for developing PHN in a cohort of patients with zoster. After further discussions among the PhD advisory group guiding this study, we would now like to also look at risk factors for PHN in the general population, by re-running the model developed in objective 2 (risk factors for zoster), restricted to cases of zoster who go on to get PHN and their non-zoster controls. This analysis will address the question “what are the risk factors in the general population for contracting ‘complicated zoster ‘, i.e. zoster complicated by PHN”, which is of relevance to informing zoster vaccination policy. The analysis will be stratified by whether PHN patients received antiviral therapy; this is because antivirals may themselves modify the risk of PHN. It will be stated *a priori* that we do not intend to measure the effectiveness of antivirals; this is due to confounding by indication (patients with severe zoster are more likely to get antivirals and more likely to get PHN).

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Appendix – OXMIS and READ codes used to identify zoster diagnoses

a) Zoster codes

GPRD Medcode	Term Type	Read / OXMIS Code	Read / OXMIS Term
201809	OXMIS	054 FK	HERPES ZOSTER GENICULATE
205942	READ	A53x100	Disseminated zoster
206066	READ	AyuA500	[X]Zoster without complications
206774	READ	F011200	Meningitis due to herpes zoster virus
214930	READ	A531.00	Herpes zoster with other central nervous system complication
214931	READ	A531z00	Herpes zoster with other CNS complication NOS
214932	READ	A532z00	Herpes zoster with other ophthalmic complication
214933	READ	A53z.00	Herpes zoster NOS
215755	READ	F011211	Herpes zoster meningitis
215831	READ	F374400	Polyneuropathy in herpes zoster
223962	READ	A532.00	Herpes zoster with ophthalmic complication
223963	READ	A53xz00	Herpes zoster with other specified complication NOS
224801	READ	F030911	Herpes zoster encephalitis
233111	READ	A531400	Zoster encephalitis
233222	READ	AyuA400	[X]Zoster with other complications
234142	READ	F501611	Herpes zoster - otitis externa
242139	READ	A530.00	Herpes zoster with meningitis
242140	READ	A531100	Geniculate herpes zoster
242141	READ	A532000	Herpes zoster with dermatitis of eyelid
242142	READ	A532200	Herpes zoster iridocyclitis
251320	READ	A532100	Herpes zoster with keratoconjunctivitis
288977	READ	F501600	Infective otitis externa due to herpes zoster
292813	OXMIS	054 HZ	HERPES ZOSTER AURICULARIS
302981	OXMIS	53	ZOSTER HERPES

305975	OXMIS	053 A	OPHTHALMIC HERPES ZOSTER

(continued overleaf)

GPRD Medcode	Term Type	Read / OXMIS Code	Read / OXMIS Term
260527	READ	A531000	Herpes zoster with other CNS complications
260528	READ	A53x.00	Herpes zoster with other specified complication
261337	READ	F030900	Encephalitis due to herpes zoster
269751	READ	A53..00	Herpes zoster
269753	READ	A532300	Ophthalmic herpes zoster infection
269754	READ	A532400	Herpes zoster ophthalmicus
269755	READ	A53x000	Herpes zoster otitis externa
269756	READ	A53y.00	Herpes zoster with unspecified complication
287948	READ	A53..11	Shingles
302982	OXMIS	053 NG	SHINGLES
305976	OXMIS	053 AG	OPHTHALMIC SHINGLES
265470	OXMIS	054 RH	SYNDROME RAMSAY HUNT

B) Codes for myocardial infarction

Medcode	Readcode	Read Term	Incident/prevalent MI
7783	323..00	ECG: myocardial infarction	incident
26975	3233.00	ECG: antero-septal infarct.	incident
26972	3234.00	ECG:posterior/inferior infarct	incident
55401	3235.00	ECG: subendocardial infarct	incident
52705	3236.00	ECG: lateral infarction	incident
59032	323Z.00	ECG: myocardial infarct NOS	incident
5221	44H3.00	Cardiac enzymes abnormal	incident
60664	44H3000	Cardiac enzymes abnormal - first set	incident
97001	44p2.00	Cardiac troponin positive	incident
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	incident
241	G30..00	Acute myocardial infarction	incident
13566	G30..11	Attack - heart	incident

2491	G30..12	Coronary thrombosis	incident
30421	G30..13	Cardiac rupture following myocardial infarction (MI)	incident
1204	G30..14	Heart attack	incident
1677	G30..15	MI - acute myocardial infarction	incident
13571	G30..16	Thrombosis - coronary	incident
17689	G30..17	Silent myocardial infarction	incident
12139	G300.00	Acute anterolateral infarction	incident
5387	G301.00	Other specified anterior myocardial infarction	incident
40429	G301000	Acute anteroapical infarction	incident
17872	G301100	Acute anteroseptal infarction	incident
14897	G301z00	Anterior myocardial infarction NOS	incident
8935	G302.00	Acute inferolateral infarction	incident
29643	G303.00	Acute inferoposterior infarction	incident
23892	G304.00	Posterior myocardial infarction NOS	incident
14898	G305.00	Lateral myocardial infarction NOS	incident
63467	G306.00	True posterior myocardial infarction	incident
3704	G307.00	Acute subendocardial infarction	incident
9507	G307000	Acute non-Q wave infarction	incident
10562	G307100	Acute non-ST segment elevation myocardial infarction	incident
1678	G308.00	Inferior myocardial infarction NOS	incident
30330	G309.00	Acute Q-wave infarct	incident
32854	G30B.00	Acute posterolateral myocardial infarction	incident
29758	G30X.00	Acute transmural myocardial infarction of unspecif site	incident
12229	G30X000	Acute ST segment elevation myocardial infarction	incident
34803	G30y.00	Other acute myocardial infarction	incident
28736	G30y000	Acute atrial infarction	incident
62626	G30y100	Acute papillary muscle infarction	incident
41221	G30y200	Acute septal infarction	incident
46017	G30yz00	Other acute myocardial infarction NOS	incident

14658	G30z.00	Acute myocardial infarction NOS	incident
68357	G31y100	Microinfarction of heart	incident
18842	G35..00	Subsequent myocardial infarction	incident
45809	G350.00	Subsequent myocardial infarction of anterior wall	incident
38609	G351.00	Subsequent myocardial infarction of inferior wall	incident
72562	G353.00	Subsequent myocardial infarction of other sites	incident
46166	G35X.00	Subsequent myocardial infarction of unspecified site	incident
36423	G36..00	Certain current complication follow acute myocardial infarct	incident
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct	incident
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	incident
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	incident
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	incident
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	incident
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	incident
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	incident
32272	G38..00	Postoperative myocardial infarction	incident
46112	G380.00	Postoperative transmural myocardial infarction anterior wall	incident
46276	G381.00	Postoperative transmural myocardial infarction inferior wall	incident
41835	G384.00	Postoperative subendocardial myocardial infarction	incident
68748	G38z.00	Postoperative myocardial infarction, unspecified	incident
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	incident
33650	7929100	Percut transluminal coronary thrombolysis with streptokinase	incident
40996	7929111	Percut translum coronary thrombolytic therapy - streptokinase	incident
35674	14A3.00	H/O: myocardial infarct <60	prevalent
40399	14A4.00	H/O: myocardial infarct >60	prevalent
50372	14AH.00	H/O: Myocardial infarction in last year	prevalent
39904	3232.00	ECG: old myocardial infarction	prevalent
34952	32B..00	ECG: Q wave	prevalent
46227	32B2.00	ECG: Q wave abnormal	prevalent

62270	32B3.00	ECG: Q wave pathological	prevalent
66285	32BZ.00	ECG: Q wave NOS	prevalent
23579	G310.00	Postmyocardial infarction syndrome	prevalent
4017	G32..00	Old myocardial infarction	prevalent
16408	G32..11	Healed myocardial infarction	prevalent
17464	G32..12	Personal history of myocardial infarction	Prevalent

C) Codes for encephalitis/myelitis

GPRD Medical Code		Read / OXMIS Code	Read / OXMIS Term
220085	OXMIS	323 EN	ENCEPHALOMYELITIS
220086	OXMIS	323 M	MYELITIS
224834	READ	F210.00	Neuromyelitis optica
238102	OXMIS	341 PT	NEUROMYELITIS OPTICA
242989	READ	F03..11	Encephalomyelitis
242990	READ	F03..13	Transverse myelitis
252120	READ	F03z.11	Encephalomyelitis NOS
252349	READ	Fyu0A00	[X]Encephalitis,myelitis+encephalomyelitis/other diseases CE
261344	READ	F03y.11	Encephalomyelitis NOS
270597	READ	F03..00	Encephalitis, myelitis and encephalomyelitis
270609	READ	F037000	Varicella transverse myelitis
279911	READ	Fyu0800	[X]Encephalitis,myelitis+encephalomyelitis/viral disease CE
283961	OXMIS	3209MM	MENINGOMYELITIS
288794	READ	F03..12	Myelitis
289005	READ	Fyu0600	[X]Other encephalitis, myelitis and encephalomyelitis
293080	OXMIS	323 B	TRANSVERSE MYELITIS
298051	READ	F037.00	Transverse myelitis

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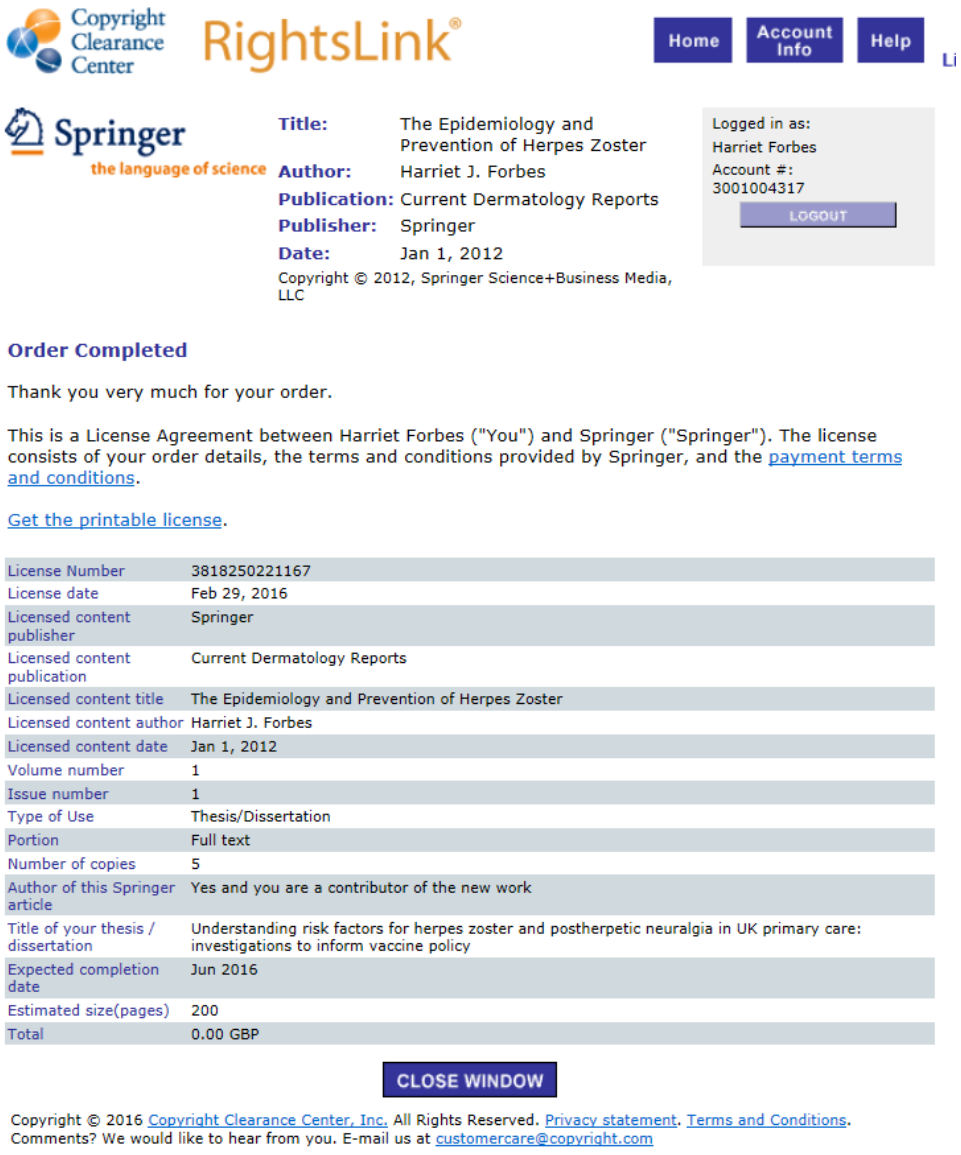

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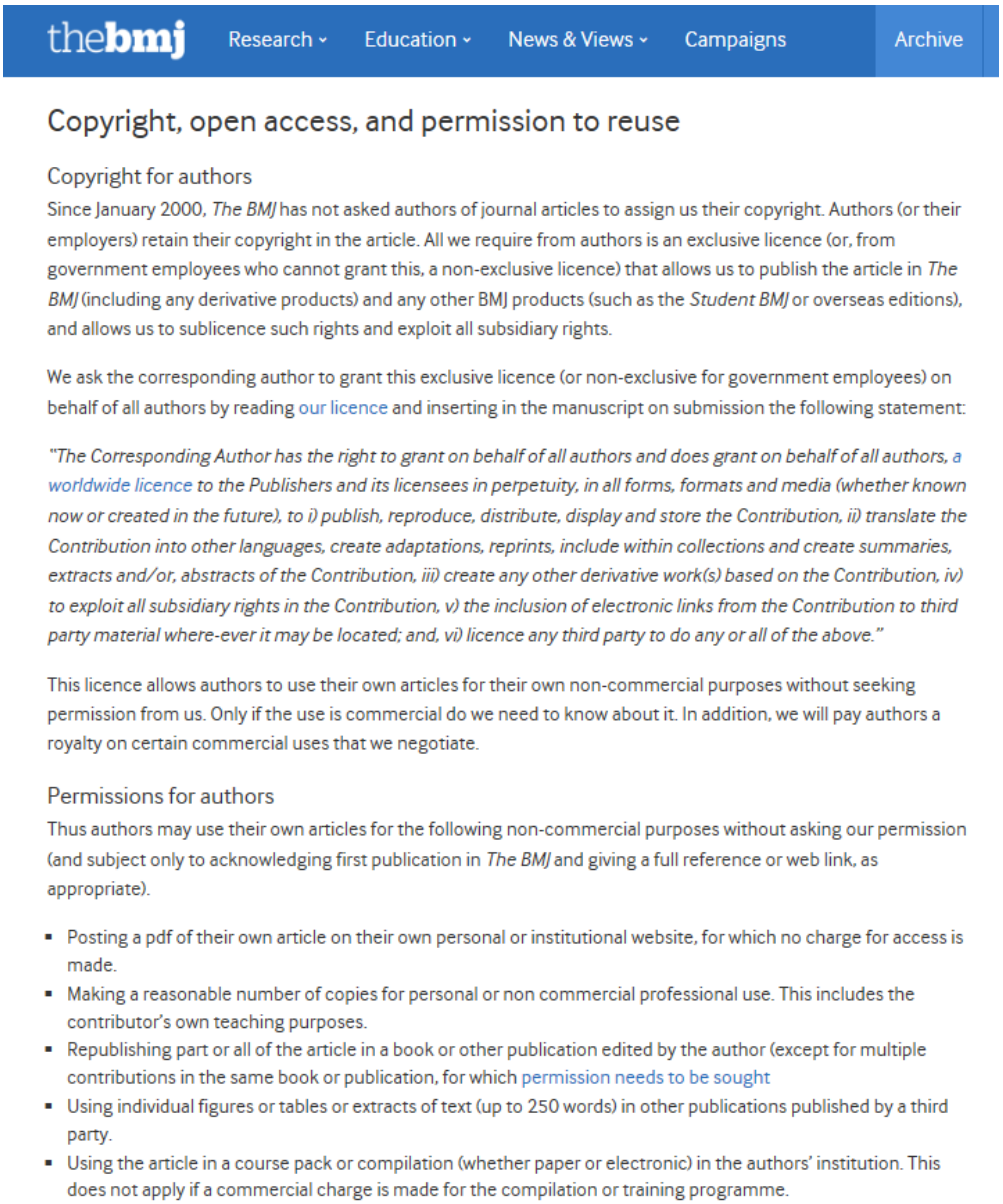

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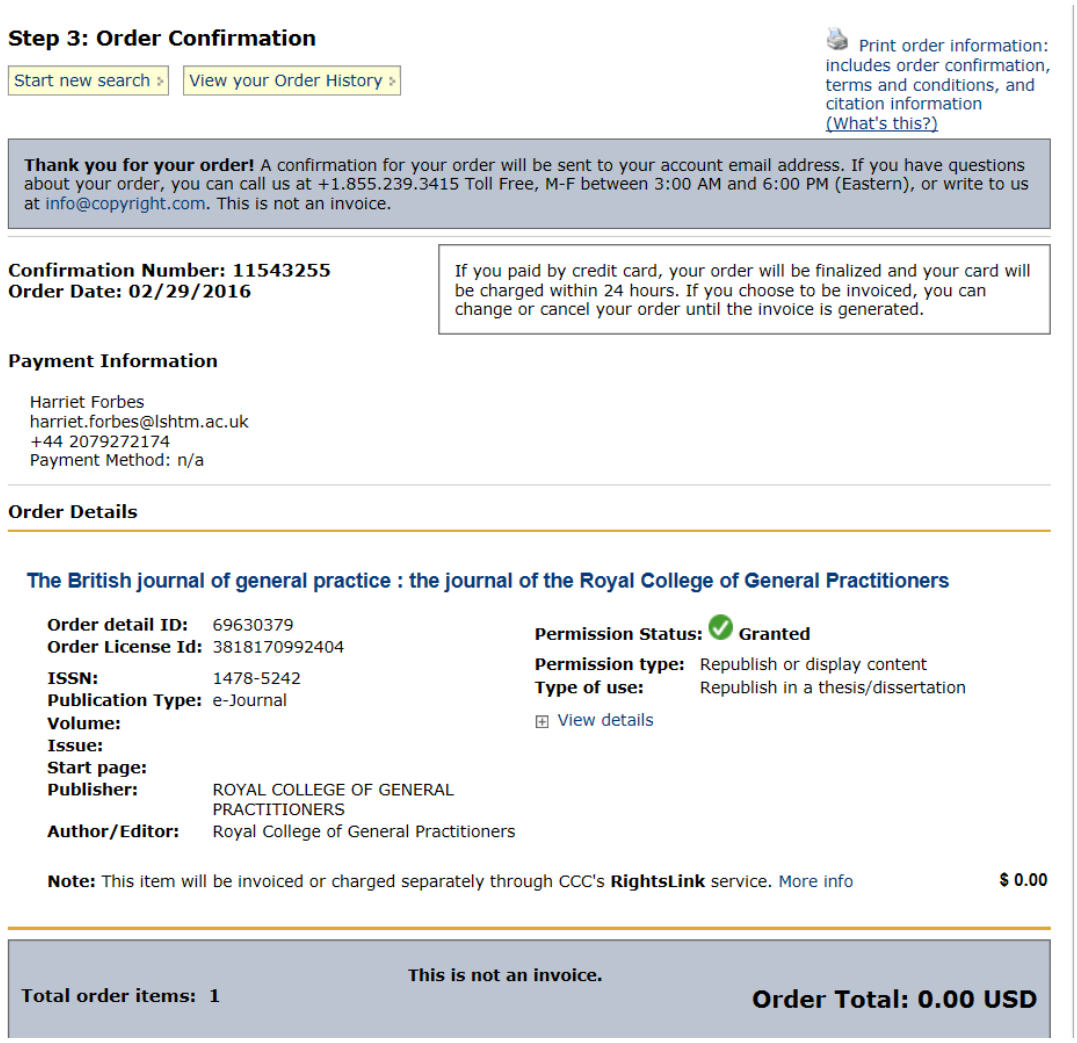

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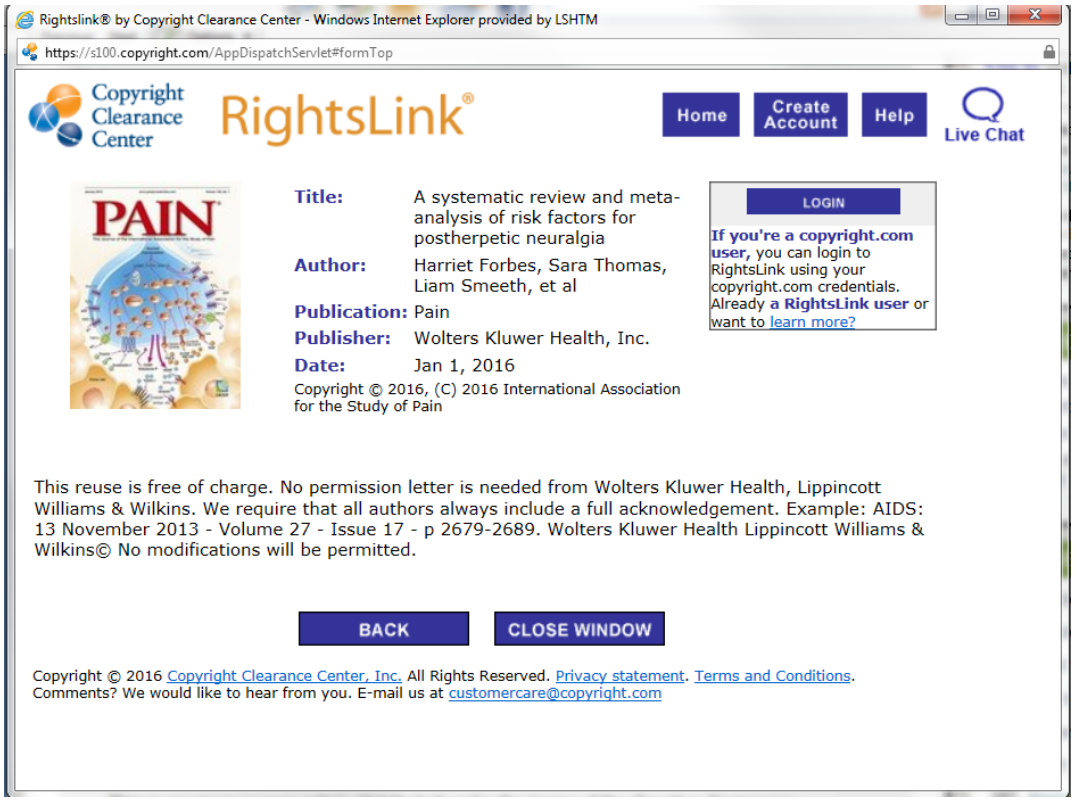

Appendix III: Section A of published appendices from BMJ zoster case control study

The zoster case control study published in the BMJ (chapter 4) has an appendices, for which section A was not included in the main PhD, as its content was described in chapter 3, "Data sources and variable definitions". For transparency, this section of the appendices appears below.

A: Further detail on defining risk factors

We assessed three autoimmune conditions; *rheumatoid arthritis, systemic lupus erythematosis and inflammatory bowel disease.* These were defined as a diagnosis prior to the index date. Chronic obstructive pulmonary disorder patients were defined as those with a diagnosis of chronic obstructive pulmonary disorder, including chronic bronchitis and emphysema, prior to the index date and ≥35 years at first chronic obstructive pulmonary disorder diagnosis). Asthma patients were those with an asthma diagnosis before the index date and an asthma-related prescription [short and long-acting beta-2 agonists and antimuscarinics, inhaled corticosteroids, cromoglycates and nedocromil, theophyllines, leukotriene receptor agonists and omalizumab] within 12 months prior to the index date; patients with a chronic obstructive pulmonary disorder diagnosis ever in their medical history were not classified as asthmatic). Chronic kidney disease patients were those with a diagnosis of mild, moderate or severe chronic kidney disease, kidney transplant or kidney dialysis, any time prior to the index date. Depression was defined as having a diagnosis or symptom of depression (such as “feeling depressed” or “sad mood”) or within one year prior to the index date; symptoms were included due to the trend post-2004 of using symptom rather than diagnosis codes in UK primary care[122].

To define diabetes we required a definite diabetes diagnosis, or a possible diabetes code [e.g. self- monitoring of blood glucose] with a subsequent diabetes-specific prescription [insulin or oral anti-diabetics], or ≥2 diabetes drug prescriptions prior to the index date; gestational diabetes and drug-induced diabetes were excluded. We also used age at first diagnosis, age at first treatment and treatment received to classify patients into Type 1 or 2 diabetes. Patients were categorised as type 1 or type

2 diabetes where possible. Distinguishing between type 1 and type 2 diabetes is not always possible from diabetes codes as patients are frequently given a non-specific code. Furthermore, where type of diabetes is assigned, it has been found to be unreliable.[111] Therefore we chose not to use this information, but instead use age at first diagnosis, age at first treatment and treatment received to classify diabetes type, as in previous Clinical Practice Research Datalink studies.[112 113] Type 1 was assigned where; age at first diagnosis was ≤35 years and treatment ever was exclusively insulin, or patients received at least two insulin prescriptions ≤35 years, but had no diabetes diagnosis. Type 2 was assigned where; age at first diabetes diagnosis was >35; or patients received exclusively oral anti-diabetic's >35 years. Patients with age at diagnoses >35 but treated exclusively with insulin and those not fitting into these categories were assigned as "Unknown type".

Calculating duration of prescriptions in the Clinical Practice Research Datalink and identifying high-dose oral corticosteroids

In order to identify relevant prescriptions, it was necessary to calculate the duration of individual prescriptions prior to the index date.

Variables available

The Clinical Practice Research Datalink does not provide researchers with duration and dose for individual prescriptions. Instead, these must be generated using information from other variables. On prescribing, general practitioners select the drug and can enter information on quantity (of tablets or inhalers prescribed), number of days, number of packs, pack type (number of tablets per pack or number of puffs per inhaler) and also enter free text. The free text field contains the actual prescribing information; in other words how many tablets, grams, milligrams or puffs the patient should take each day. To utilize this prescribing information, the Clinical Practice Research Datalink developed an algorithm to derive a numerical value from the free text and provide this to researchers;[105] this is referred to within the Clinical Practice Research Datalink as the *numeric daily dose (NDD)*. The dose (in milligrams or micrograms) per tablet or puff is typically contained in the product name.

The completeness of each variable is described in table A1 below.

Table A1: Completeness of variables used to identify duration and dose of corticosteroid prescriptions before cleaning.

		% complete		
Description	**Variable name**	**Oral corticosteroids**	**Other immunosuppressive therapy**	**Inhaled corticosteroids**
Quantity[1]	Qty	99	99	99
Number of days	numdays	9	7	8
Number of packs	numpacks	2	3	1
Pack type[2]	packtype	<0.5	4	52
Dose in mg	*extract from product name*	100	100	100
Numeric daily dose	ndd	67	67	81

[1] For ICS prescriptions quantity referred to number of inhalers, otherwise quantity referred to number of tablets
[2] For ICS prescriptions pack type referred to numbers of puffs per inhaler, for OCS prescriptions pack type was largely missing

Data cleaning

We carried out a series of data-checking and data-cleaning tasks including; checking the accuracy of NDD for the 500 most commonly occurring free-texts; extracting data for pack type from other variables (eg quantity variable); checking the clinical and referral records of 20 randomly selected patients to check the duration and dose was consistent with the clinical picture; excluding implausible values of quantity and NDD.

As NDD was not always available it was necessary to impute missing data. A "hot-deck" style imputation method was adopted, which replaced missing data with comparable data from the same set. An algorithm was developed which reviewed each oral corticosteroid and other immunosuppressive therapy record and imputed missing values. An extra binary variable for quantity was created, categorising quantity about the median (42 tablets for steroids, 36 for other immunosuppressants) into low and high. If a patient had any other record with the same quantity and dose, the

median NDD among those records was used where NDD was missing. If a patient had no recorded NDD but had any other record of the same dose and quantity as a binary variable, the median NDD among those records was used. If a patient did not have a recorded NDD or quantity, but had records for the same dose, then the median NDD among those records was used. If there was no record of NDD, dose or quantity, but there were other patients in the dataset in the same 5-year age band, of the same gender, with the same dose and quantity, the using median NDD for those records was used. Finally, if none of the above were possible, patients in the dataset in the same 5-year age band, of the same gender, with the same dose and quantity as a binary variable, the median NDD among these records was used.

Pack type for inhaled corticosteroids was imputed using the most common pack type for the quantity and dose of each prescription. Where NDD was missing for inhaled corticosteroids, the median value of 4 puffs per day was used.

Calculating duration and dose

Using this information we calculated duration of oral corticosteroid or other immunosuppressive therapy prescription as follows: total quantity of tablets prescribed / NDD. Duration of inhaled corticosteroids was calculated: (quantity x pack type)/NDD. Dose was calculated as follow; NDD x dose per tablet or puff.

Algorithm to select smoking, alcohol and BMI status.

Data were derived from medical Read codes and data from the additional details file. Read codes classifying patients by BMI category are very rarely recorded, therefore were not used. Where patients had multiple recordings, the nearest status in the

period -1y to +1month from index was taken (best); if not available, then the nearest in the period +1month to +1y after index was taken (second best); if not available, then the nearest before -1y from index was taken (third best); if not available, then take nearest after +1y from index was taken (least best).

Appendix IV: Section e-I of published appendices from Neurology PHN cohort study

APPENDIX

e-1: Further details on definitions of risk factors

Severe Immunosuppression

Our models included severely immunosuppressive conditions determined to be vaccine contraindications by the Advisory Committee on Immunization Practices,[1] namely recent history (<2 years before zoster diagnosis) of leukaemia or lymphoma, or any history of HIV, hematopoietic stem cell transplantation, myeloma or 'other unspecified cellular immune deficiencies' (e.g. pancytopenia). Use of immunosuppressive therapy was also included; all relevant prescriptions prior to zoster diagnosis were extracted, prescription duration was calculated (using data on quantity of tablets prescribed and numeric daily dose). Oral corticosteroid exposure was defined as a 14-day course of high-dose (≥20 mg/day) oral corticosteroids in the month prior to zoster diagnosis. Exposure to other immunosuppressive therapies in the month prior to the zoster diagnosis was included as an additional covariate.

Other comorbidities

We assessed three autoimmune conditions; *rheumatoid arthritis, systemic lupus erythematosis and inflammatory bowel disease.* These were defined as a diagnosis prior to the zoster diagnosis.

Chronic obstructive pulmonary disorder patients were defined as those with a diagnosis of chronic obstructive pulmonary disorder, including chronic bronchitis and emphysema, prior to the zoster diagnosis and ≥35 years at first chronic obstructive pulmonary disorder diagnosis).

Asthma patients were those with an asthma diagnosis before the zoster diagnosis and an asthma-related prescription [short and long-acting beta-2 agonists and antimuscarinics, inhaled corticosteroids, cromoglycates and nedocromil, theophyllines, leukotriene receptor agonists and omalizumab] within 12 months prior to the zoster diagnosis; patients with a chronic obstructive pulmonary disorder diagnosis ever in their medical history were not classified as asthmatic.

Chronic kidney disease patients were those with a diagnosis of mild, moderate or severe chronic kidney disease, kidney transplant or kidney dialysis any time prior to the zoster diagnosis.

Depression was defined as having a diagnosis or symptom of depression (such as "feeling depressed" or "sad mood") within one year prior to the zoster diagnosis; symptoms were included due to the trend post-2004 of using symptom rather than diagnosis codes in UK primary care.[2]

To define *diabetes* we required a definite diabetes diagnosis, or a possible diabetes code [e.g. self- monitoring of blood glucose] with a subsequent diabetes-specific prescription [insulin or oral anti-diabetics], or ≥2

diabetes drug prescriptions prior to the zoster diagnosis; gestational diabetes and drug-induced diabetes were excluded. We also used age at first diagnosis, age at first treatment and treatment received to classify patients into Type 1 or 2 diabetes. Distinguishing between type 1 and type 2 diabetes is not always possible from diabetes codes as patients are frequently given a non-specific code. Furthermore, where type of diabetes is assigned, it has been found to be unreliable.[3] Therefore we chose not to use this information, but instead use age at first diagnosis, age at first treatment and treatment received to classify diabetes type, as in previous Clinical Practice Research Datalink studies.[4 5] Type 1 was assigned where; age at first diagnosis was ≤35 years and treatment ever was exclusively insulin, or patients received at least two insulin prescriptions ≤35 years, but had no diabetes diagnosis. Type 2 was assigned where; age at first diabetes diagnosis was >35; or patients received exclusively oral anti-diabetics's >35 years. Patients with age at diagnoses >35 but treated exclusively with insulin and those not fitting into these categories were assigned as "Type not specified".

Recent cancer was defined as *any* cancer diagnosed in previous year (excluding leukaemia and lymphoma previously categorised as severely immunosuppressive).

Health behaviours features of acute zoster

For *smoking*, data were derived from medical Read codes and data from the additional details file. For *BMI*, only data from the additional details files was used, as Read codes classifying patients by BMI category are very rarely recorded. Where patients had multiple recordings, the nearest status in the period -1y to +1month from zoster diagnosis date was taken (best); if not available, then the nearest in the period +1month to +1y after zoster diagnosis date was taken (second best); if not available, then the nearest before -1y from zoster diagnosis date was taken (third best); if not available, then take nearest after +1y from zoster diagnosis date was taken (least best).

Site of acute zoster was identified from the presence of specific zoster diagnostic codes. Some Read and ICD codes specify the site of zoster (such as, "Herpes zoster with dermatitis of eyelid"); codes indicating site within 12 months after first diagnosis were used. In line with a previous study identifying ophthalmic zoster in CPRD, we also defined ophthalmic zoster as patients with nonspecific zoster, plus a diagnosis of, or treatment for, acute eye infection (such as keratitis or conjunctivitis) within 2 weeks of zoster onset or from records of first-ever specific chronic eye conditions known to be associated with zoster (such as, conjunctival scarring or episcleritis), within 3 months after zoster onset.[6]

Antiviral use at acute zoster was identified through prescription of acyclovir, valaciclovir or famciclovir within 7 days from zoster diagnosis.

Possible misdiagnosis of herpes simplex as herpes zoster

Of the 119,413 cohort, 1586 (1.6%) patients had a further zoster code 90-365 days after their first zoster. Of these 215 (13.6%) had a PHN medication or a PHN diagnostic code, and in the main analysis these were

categorised as PHN. However, the other 1371 patients had a zoster code without medications or codes suggesting PHN. There were three possible explanations for these patients. The first is that they were recurrent zoster; however this is very rare in immunocompetent patients, who made up 96% of the group. The second is that these are poorly coded PHN patients, however it seems unlikely that no PHN prescriptions would be given. The third, and perhaps most plausible explanation is that these patients were misdiagnosed herpes simplex cases. Herpes simplex is known to recur more frequently than zoster and can, albeit rarely, present with dermatomal distribution similar to herpes zoster. [7] Further to this, half of the patients were prescribed an antiviral at their later zoster diagnosis, which may further indicate misdiagnosis of herpes simplex. Therefore as a sensitivity analysis we excluded all 1586 patients with a further zoster code following first zoster diagnosis.

Risk factors we are unable to assess included: physical trauma[8] or surgical intervention at site of zoster,[8] genetic factors, ethnicity and functional status[9] (appendix section A-I for more details on these variables).

Appendix V: Code lists

Code lists are provided below, and listed alphabetically:

Alcohol
Asthma diagnosis
Asthma therapy
CKD
COPD
Depression
Diabetes diagnosis
Diabetes treatments
Epilepsy
Hematopoietic stem cell transplantation (HSCT)
Herpes Zoster
HIV
Hypothyroidism
IBD
Leukaemia
Lymphoma
Myeloma
Neuropathy
Oral corticosteroids
Other Immune Disorders (OID)
Other immunosuppressive therapies
PHN diagnosis
PHN - Neuralgia diagnosis
PHN - Neuropathic pain
PHN treatment - Anticonvulsants
PHN treatment - Capsaicin Cream
PHN treatment - Lidocaine patches
PHN treatment - Mild painkillers (PKs)
PHN treatment - Tramadol
PHN treatment- Strong painkillers (PKs)
PHN treatment- Tricyclic antidepressants
Rheumatoid arthritis
Smoking
Systemic Lupus Erythematosis

Alcohol

Medical code	Read term	Alcohol status
322	Moderate drinker - 3-6u/day	current drinker
385	Drinks rarely	current drinker
669	non-drinkerdependent alcohol abuse, unspecified	current drinker
749	Drinks occasionally	current drinker
956	ZERIDAME SR tablets 150mg [ACTAVIS]	current drinker
967	Stopped drinking alcohol	ex-drinker
1399	Alcohol problem drinking	current drinker
1476	Delirium tremens	current drinker
1618	Heavy drinker - 7-9u/day	current drinker
2081	Alcoholism	current drinker
2082	Alcohol withdrawal syndrome	current drinker
2083	Alcohol detoxification	current drinker
2084	Alcohol dependence syndrome	current drinker
2689	Beer drinker	current drinker
2925	Alcoholic polyneuropathy	current drinker
3216	Acute alcoholic hepatitis	current drinker
3782	Intoxication - alcohol	current drinker
4447	Herpes zoster with meningitis	non-drinker
4500	Korsakov's alcoholic psychosis	current drinker
4506	Alcoholic gastritis	current drinker
4743	Alcoholic cirrhosis of liver	current drinker
4915	Alcoholic cardiomyopathy	current drinker
5611	[X]Mental and behavioural disorders due to use of alcohol	current drinker
5740	Acute alcoholic intoxication in alcoholism	current drinker
5758	[X]Chronic alcoholism	current drinker
6169	Alcohol dependence syndrome NOS	current drinker
6467	[X]Alcoholic hallucinosis	current drinker
7123	[V]Personal history of alcoholism	current drinker
7545	[V] Alcohol use	current drinker
7602	Chronic alcoholic hepatitis	current drinker
7692	Patient advised about alcohol	current drinker
7746	non-drinkerdependent alcohol abuse	current drinker
7885	Alcoholic liver damage unspecified	current drinker
7943	Alcoholic hepatitis	current drinker
8030	[V]Alcohol abuse counselling and surveillance	current drinker
8363	Oesophageal varices in alcoholic cirrhosis of the liver	current drinker
8388	[V]Alcohol rehabilitation	current drinker
8999	Heavy drinker	current drinker
9169	[D]Alcohol blood level ex-drinkercessive	current drinker
9489	Under care of community alcohol team	current drinker
9508	[X]Acute alcoholic drunkenness	current drinker
9849	Referral to community alcohol team	current drinker
10161	O/E - alcoholic breath	current drinker
10691	Alcoholic fatty liver	current drinker
11106	Korsakov's alcoholic psychosis with peripheral neuritis	current drinker
11140	Advice on alcohol consumption	current drinker
11491	Health ed. - alcohol	current drinker
11670	[X]Korsakov's psychosis, alcohol induced	current drinker
11740	Alcohol misuse - enhanced services administration	current drinker
12353	[X]Mental & behav dis due to use alcohol: psychotic disorder	current drinker
12554	Referral to community drug and alcohol team	current drinker
12949	Teetotaller	non-drinker
12968	Drinks beer and spirits	current drinker
12969	Drinks wine	current drinker
12970	non-drinker drinker alcohol	non-drinker
12971	Spirit drinker	current drinker
12972	Light drinker - 1-2u/day	current drinker
12974	non-drinkerdependent alcohol abuse, episodic	current drinker
12975	Trivial drinker - <1u/day	current drinker
12976	Suspect alcohol abuse - denied	current drinker
12977	Very heavy drinker - >9u/day	current drinker
12979	current drinkerent non-drinker drinker	non-drinker
12980	Light drinker	current drinker
12982	Alcohol intake above recommended sensible limits	current drinker
12983	ex-drinker-very heavy drinker-(>9u/d)	ex-drinker
12984	Very heavy drinker	current drinker
12985	Moderate drinker	current drinker
16225	Alcohol withdrawal delirium	current drinker
16237	Alcoholic psychoses	current drinker

Alcohol

Medical code	Read term	Alcohol status
16587	[V]Problems related to lifestyle alcohol use	current drinker
17259	[X]Delirium tremens, alcohol induced	current drinker
17330	Alcoholic hepatic failure	current drinker
17607	[X]Alcoholic psychosis NOS	current drinker
18156	Alcoholics anon-drinkerymous	current drinker
18636	Wernicke-Korsakov syndrome	current drinker
18711	Lifestyle advice regarding alcohol	current drinker
19217	Alcohol causing toxic effect	current drinker
19401	Binge drinker	current drinker
19493	ex-drinker-heavy drinker - (7-9u/day)	ex-drinker
19494	Hazardous alcohol use	current drinker
19495	ex-drinker-moderate drinker - (3-6u/d)	ex-drinker
20407	Drunkenness - pathological	current drinker
20514	[X]Mental and behav dis due to use alcohol: withdrawal state	current drinker
20762	Alcohol amnestic syndrome	current drinker
21624	Episodic acute alcoholic intoxication in alcoholism	current drinker
21650	Admitted to alcohol detoxification centre	current drinker
21713	Alcoholic fibrosis and sclerosis of liver	current drinker
21879	[X]Mental and behav dis due to use of alcohol: harmful use	current drinker
22277	DTs - delirium tremens	current drinker
22707	Drinking problem scale	current drinker
22933	ex-drinker-trivial drinker (<1u/day)	ex-drinker
23610	non-drinkerdependent alcohol abuse, continuous	current drinker
23945	Fetal alcohol syndrome	current drinker
23978	[X]Evid of alcohol involv determind by level of intoxication	current drinker
24064	Continuous chronic alcoholism	current drinker
24485	Chronic alcoholism in remission	ex-drinker
24735	O/E - breath - alcohol smell	current drinker
24984	Alcohol-induced chronic pancreatitis	current drinker
25110	Alcohol withdrawal hallucinosis	current drinker
26106	Episodic chronic alcoholism	current drinker
26323	[X]Alcoholic dementia NOS	current drinker
26471	ex-drinker-light drinker - (1-2u/day)	ex-drinker
26472	Alcohol intake within recommended sensible limits	current drinker
27342	Alcoholic dementia NOS	current drinker
27518	Hangover (alcohol)	current drinker
27670	Maternal care for (suspected) damage to fetus from alcohol	current drinker
28150	non-drinkerdependent alcohol abuse NOS	current drinker
28780	[X]Alcohol addiction	current drinker
29691	Aversion therapy - alcoholism	current drinker
30162	[X]Alcoholic paranoia	current drinker
30404	Alcoholic paranoia	current drinker
30460	Alcoholism counselling	current drinker
30604	Alcohol-induced epilepsy	current drinker
30695	Harmful alcohol use	current drinker
31443	Chronic alcoholism	current drinker
31569	non-drinkerdependent alcohol abuse in remission	current drinker
31742	Alcoholic myopathy	current drinker
32927	[X]Alcohol withdrawal-induced seizure	current drinker
33635	Chronic alcoholism NOS	current drinker
33670	Other alcoholic psychosis	current drinker
33839	Cerebellar ataxia due to alcoholism	current drinker
35330	Alcohol consumption counselling	current drinker
36296	Acute alcoholic intoxication in alcoholism NOS	current drinker
36748	Alcoholic encephalopathy	current drinker
37264	Alcohol leaflet given	current drinker
37691	[X]Chronic alcoholic brain syndrome	current drinker
37946	Chronic alcoholic brain syndrome	current drinker
38061	Alcohol induced hallucinations	current drinker
39327	[X]Mental and behav dis due to use alcohol: dependence syndr	current drinker
39799	[X]Mental and behav dis due to use alcohol: amnesic syndrome	current drinker
40530	Acute alcoholic intoxication, unspecified, in alcoholism	current drinker
41920	Alcohol amnestic syndrome NOS	current drinker
41983	Alcohol detoxification	current drinker
42843	Other non-drinker-alcoholic chronic liver disease	current drinker
43193	Unspecified chronic alcoholism	current drinker
44299	[X]Mental & behav dis due to use alcohol: acute intoxication	current drinker
44783	Pain in lymph nodes after alcohol consumption	current drinker
45169	[X]Men & behav dis due to use alcohol: oth men & behav dis	current drinker

Alcohol

Medical code	Read term	Alcohol status
46677	Alcohol withdrawal regime	current drinker
46848	DPS - Drinking problem scale	current drinker
47123	Alcohol counselling by other agencies	current drinker
47555	Cerebral degeneration due to alcoholism	current drinker
54209	Advice to change alcohol intake	current drinker
54505	Other alcoholic dementia	current drinker
56410	Delivery of rehabilitation for alcohol addiction	current drinker
56947	Continuous acute alcoholic intoxication in alcoholism	current drinker
57714	Alcohol dependence with acute alcoholic intoxication	current drinker
57939	Pathological alcohol intoxication	current drinker
59574	Acute alcoholic intoxication in remission, in alcoholism	current drinker
61383	Planned reduction of alcohol consumption	current drinker
63529	Alcohol misuse - enhanced service completed	current drinker
64389	[X]Ment & behav dis due use alcohol: unsp ment & behav dis	current drinker
64409	Self-monitoring of alcohol intake	current drinker
65754	Alcohol-induced pseudo-Cushing's syndrome	current drinker
65932	[X]Alcoholic jealousy	current drinker
66019	Suspect fetal damage from maternal alcohol	current drinker
66699	Fetus and newborn affected by maternal use of alcohol	current drinker
67651	Alcoholic psychosis NOS	current drinker
68111	Other alcoholic psychosis NOS	current drinker
84218	Disqualified from driving due to ex-drinkercess alcohol	current drinker
94553	Referral to specialist alcohol treatment service	current drinker
94670	Alcohol misuse	current drinker
95181	Alcohol reduction programme	current drinker
95650	Advice to change drink intake	current drinker
96053	Brief intervention for ex-drinkercessive alcohol consumptn completed	current drinker
96054	ex-drinkertended intervention for ex-drinkercessive alcohol consumptn complt	current drinker
96993	Referral to alcohol brief intervention service	current drinker
97163	Advice to change alcoholic drink intake	current drinker
97261	Brief intervention for ex-drinkercessive alcohol consumptn declined	current drinker
97309	Advised to contact primary care alcohol worker	current drinker
97680	Declined referral to specialist alcohol treatment service	current drinker
97916	Fetal alcohol syndrome	current drinker

Asthma diagnosis

Medical code	Read term
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	ZERIDAME SR tablets 150mg [ACTAVIS]
719	h/o: asthma
1208	childhood asthma
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4836	nocturnal cough / wheeze
4892	status asthmaticus nos
5267	Herpes zoster with meningitis
5627	hay fever with asthma
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7229	asthma prophylactic medication used
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored
9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11022	asthma trigger
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13173	asthma not disturbing sleep
13174	asthma not limiting activities
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma
16070	asthma nos
16667	asthma control step 2
16785	asthma control step 1
18141	asthma monitoring due
18223	step down change in asthma management plan
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
19539	asthma monitoring check done
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma

Asthma diagnosis

Medical code	Read term
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise
25791	asthma clinical management plan
25796	mixed asthma
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
29645	asthma control step 0
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
40864	[x] adverse reaction to theophylline - asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit
47684	detergent asthma
48591	adverse reaction to theophylline (asthma)
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
98185	asthma control test
99793	patient has a written asthma personal action plan
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals

Asthma therapy

Product Code	Product Name
26987	bricanyl compound tablets [astrazenec]
46551	salbutamol cfc free inhaler 100micrograms/inhalation [neolab]
41549	salbutamol tablets 2mg [cp pharm]
23047	ephedrine hydrochloride tablets 60mg
33434	ZERIDAME SR tablets 150mg [ACTAVIS]
27573	ventolin
25218	salbutamol cfc/free b/a
40709	salbutamol unit dose nebulising solution 2.5mg/2.5ml [hillcross]
42103	tulobuterol sugar free syrup 1mg/5ml
32283	orciprenaline injection 0.5mg/ml
32102	salbutamol tablets 4mg [hillcross]
25829	pirbuterol syrup 7.5mg/5ml
44713	salbutamol aerosol inhaler 100micrograms/inhalation [celltech]
26873	cobutolin tablets 2mg [actavis]
36677	reproterol elixir 10mg/5ml
23688	ventolin rotacaps
41832	monovent syrup 1.5mg/5ml [sandoz]
23054	Herpes zoster with meningitis
22082	alupent expectorant tablets [boeh ingl]
33461	iso-autohaler aerosol inhaler [3m]
33373	salbutamol cyclocaps capsules (for inhalation) 200micrograms [teva]
26829	brelomax tablets 2mg [abbott]
31082	salbuvent respirator solution 5mg/ml [pharmacia]
32033	dextromethorphan with ephedrine syrup 7.5mg + 15mg/5ml
27340	salbuvent injection 0.5mg/ml [pharmacia]
31290	salbulin cfc free
29267	salbuvent tablets 4mg [pharmacia]
22790	reproterol respirator solution 10mg/ml
26654	aerolin inhaler auto refil
25820	bronchodil elixir 10mg/5ml [viatris]
42867	terbutaline syrup 1.5mg/5ml [sandoz]
20838	salbuvent tablets 2mg [pharmacia]
26525	ventolin
34702	salbutamol aerosol inhaler 100micrograms/inhalation [cp pharm]
31262	orciprenaline with bromhexine hydrochloride mixture
20781	salbutamol u.dose nebulising 2.5mg/2.5ml
42497	salbutamol tablets 8mg
17874	monovent syrup 1.5mg/5ml [lagap]
43046	salipraneb unit dose nebulising solution 500micrograms + 2.5mg/2.5ml [breath]
38419	terbutaline syrup 1.5mg/5ml [hillcross]
15356	ephedrine hydrochloride tablets 30mg [cp pharm]
22512	salbutamol inhaler
42921	isoprenaline sulphate aerosol inhaler 400micrograms/actuation
42279	steripoule salbutamol unit dose nebuliser solution 2.5mg/2.5ml [galen]
22467	salbutamol respirator soln
25073	salbutamol
41691	salbutamol sugar free oral solution 2mg/5ml [sandoz]
26744	expulin decongestant sugar free linctus [shire]
28577	ventolin injection 50micrograms/ml [a & h]
32812	numotac tablets 10mg [3m]
31845	salapin syrup 2mg/5ml [pinewood]
41548	salbutamol tablets 2mg [aps]
40655	salbuvent aerosol inhaler 100micrograms/actuation [pharmacia]
44064	onbrez breezhaler capsules for inhalation + inhaler 300micrograms [novartis]
26716	airomir autohaler cfc free b/a
37612	terbutaline unit dose nebulising solution 2.5mg/ml [galen]
12470	alupent expectorant mixture [boeh ingl]
33089	salbutamol aerosol inhaler 100micrograms/inhalation [kent]
10353	salbuvent rondo
40599	steripoule salbutamol unit dose nebuliser solution 5mg/2.5ml [galen]
9720	ephedrine hydrochloride elixir 15mg/5ml
25821	exirel syrup 7.5mg/5ml [3m]

Asthma therapy

Product Code	Product Name
45863	salbutamol unit dose nebulising solution 5mg/2.5ml [gen (uk)]
22225	beclomethasone /salbutamol
27793	salbutamol cyclohaler type 5 insufflator [bms]
10958	salbutamol .25 mg inj
19121	beclometasone with salbutamol capsules (for inhalation) 100micrograms + 200micrograms
34618	salbutamol tablets 2mg [actavis]
34938	salbutamol tablets 4mg [actavis]
45610	indacaterol capsules for inhalation + inhaler 300micrograms
31091	ephedrine hydrochloride tablets 15mg [cp pharm]
38097	salbutamol cyclocaps 200micrograms [du pont]
22550	duovent
8252	pirbuterol capsules 15mg
15483	bricanyl expectorant [astrazenec]
24380	sodium cromoglicate with salbutamol inhaler and spacer
34311	salbutamol aerosol inhaler 100micrograms/inhalation [berk]
22430	spacehaler salbutamol spacehaler 100micrograms/inhalation [celltech]
20180	sodium cromoglicate with isoprenaline capsules (for inhalation)
17875	terbutaline with guaifenesin expectorant
19732	cobutolin inh
19376	beclometasone with salbutamol capsules (for inhalation) 200micrograms + 400micrograms
27505	ipratropium bromide with fenoterol hydrobromide breath actuated inhaler 40micrograms + 100micrograms/actuation
15613	salbutamol injection 500micrograms/1ml
30212	salbutamol cyclohaler
12463	pirbuterol 15 mg tab
28881	salbutamol sugar free oral solution [hillcross]
32050	salbutamol cyclocaps capsules (for inhalation) 400micrograms [teva]
7452	ventolin .25 mg inj
34018	salbutamol unit dose nebulising solution 5mg/2.5ml [galen]
33817	salbutamol cfc free inhaler 100micrograms/inhalation [actavis]
34619	salbutamol cfc free inhaler 100micrograms/inhalation [kent]
18456	salbutamol with beclometasone capsules (for inhalation) 200micrograms + 100micrograms
18622	salbulin tablets 2mg [3m]
20675	salbutamol rotahaler complete unit
15441	fenoterol hydrobromide .5 % sol
4055	salbulin syrup 2mg/5ml [3m]
9706	ephedrine elixir 15mg/5ml
15075	bronchodil tablets 20mg [viatris]
34134	aerolin 400 aerosol inhaler 100micrograms/actuation [3m]
38214	salbutamol dry powder inhalation cartridge (refill) 100micrograms
38416	salbutamol cyclocaps 400micrograms [du pont]
1346	salbutamol injection 0.05mg/ml
3322	aerolin inh 400 100 mcg aer
23269	maxivent steripoule unit dose nebulising solution 2.5mg/2.5ml [ashbourne]
19799	tulobuterol tablets 2mg
33588	salbutamol aerosol inhaler 100micrograms/inhalation [gen (uk)]
10490	isoprenaline sulphate aerosol inhaler 80micrograms/actuation
25339	maxivent steripoule unit dose nebulising solution 5mg/2.5ml [ashbourne]
12479	aerolin inh auto refil 100 mcg aer
26420	exirel 10 mg tab
30118	salbutamol cfc free inhaler 100micrograms/inhalation [aps]
34162	salbutamol unit dose nebulising solution 2.5mg/2.5ml [galen]
35522	bricanyl injection 500micrograms/1ml [astrazenec]
17901	bricanyl nebule 2.5 ml
8151	orciprenaline aerosol refill 750micrograms/inhalation
24645	ventolin concentrate for solution for infusion 5mg/5ml [a & h]
14482	bricanyl 2.5 mg inj
9651	asmasal spacehaler 100micrograms/inhalation [celltech]
22663	respacal tablets 2mg [ucb]
8504	exirel 15 mg tab
34310	salbutamol cfc free inhaler 100micrograms/inhalation [hillcross]
8429	ventolin i/v 5 mg inj

Asthma therapy

Product Code	Product Name
15165	reproterol aerosol inhaler 500micrograms/dose
43085	bricanyl respules unit dose nebuliser solution 5mg/2ml [astrazenec]
21102	salbutamol sugar free syrup 2mg/5ml [lagap]
35862	terbutaline injection 500micrograms/1ml
13365	berotec nebuliser solution 5mg/ml [boeh ingl]
15467	ephedrine tablets 60mg
13996	salamol cfc free inhaler 100micrograms/inhalation [sandoz]
38079	salbutamol dry powder inhalation cartridge with device 100micrograms
19726	ventolin s/r
22330	ephedrine hydrochloride sugar free liquid 4mg/5ml
3254	salbulin tablets 4mg [3m]
18968	salbutamol concentrate for solution for infusion 5mg/5ml
19653	ventolin respirator
43893	onbrez breezhaler capsules for inhalation + inhaler 150micrograms [novartis]
22661	pirbuterol capsules 10mg
43738	indacaterol capsules for inhalation + inhaler 150micrograms
35557	ipramol steri-neb unit dose nebulising solution 500micrograms + 2.5mg/2.5ml [ivax]
23787	exirel capsules 10mg [3m]
35744	bricanyl injection 2.5mg/5ml [astrazenec]
26616	ipratropium bromide with fenoterol hydrobromide aerosol inhaler 40micrograms + 100micrograms/actuation
8676	terbutaline respirator solution 10mg/ml
35861	terbutaline injection 2.5mg/5ml
31933	salbutamol aerosol inhaler 100micrograms/inhalation [hillcross]
14561	salbutamol with beclometasone capsules (for inhalation) 400micrograms + 200micrograms
18299	fenoterol with ipratropium bromide unit dose nebulising solution 1.25mg + 500micrograms/4ml
10858	pulmadil auto aerosol inhaler [3m]
4842	fenoterol aerosol inhaler 100micrograms/actuation
8012	exirel capsules 15mg [3m]
17185	ventolin injection 500micrograms/1ml [a & h]
8572	rimiterol aerosol inhaler
28508	salbutamol aerosol inhaler 100micrograms/inhalation [ivax]
1635	salbuvent syrup 2mg/5ml [pharmacia]
38226	salbulin mdpi novolizer dry powder inhalation cartridge (refill) 100micrograms [meda]
18484	ventide paediatric rotacaps [a & h]
30204	salbutamol capsules (for inhalation) 200micrograms
20680	aerolin autohaler
16236	pirbuterol acetate aerosol inhaler
9270	ipratropium bromide with fenoterol hydrobromide unit dose nebulising solution 500micrograms + 1.25mg/4ml
15816	ephedrine hydrochloride tablets 30mg
38136	salbulin mdpi novolizer dry powder inhalation cartridge with device 100micrograms [meda]
14525	salbutamol vortex metered dose inhaler 100micrograms/inhalation
35165	serevent diskhaler inhalation powder 50micrograms [glaxo]
8339	fenoterol hydrobromide complete unit inh
30240	aerolin autohaler cfc free breath actuated inhaler 100micrograms/actuation [3m]
18314	aerocrom syncroner [castlemead]
19649	ventolin rotahaler
13956	ephedrine hydrochloride with chlorphenamine tablets 15mg + 10mg
14382	ephedrine hydrochloride tablets 15mg
34029	salbutamol capsules (for inhalation) 400micrograms
3838	salbutamol 400mcg/beclometh.100mcg r/cap inh
35542	salmeterol inhalation powder blisters with device 50micrograms
3189	salbuvent inh inh
7965	salbutamol respirator solution 5mg/ml
12486	bronchodil aerosol inhaler 500micrograms/dose [viatris]
13575	bambec tablets 20mg [astrazenec]
8267	sodium cromoglicate with salbutamol aerosol inhaler
8149	alupent aerosol refill 750micrograms/inhalation [boeh ingl]
35825	serevent diskhaler (refill) inhalation powder 50micrograms [glaxo]
4222	bricanyl respirator solution 10mg/ml [astrazenec]
7943	orciprenaline tablets 20mg

Asthma therapy

Product Code	Product Name
13307	bricanyl injection 500micrograms/ml [astrazenec]
35725	easyhaler formoterol dry powder inhaler 12micrograms/actuation [orion]
3443	salbutamol spacehaler 100micrograms/inhalation [celltech]
16207	duovent udvs nebuliser solution [boeh ingl]
461	orciprenaline aerosol inhaler 750micrograms/inhalation
25784	atimos modulite cfc free inhaler 12micrograms/actuation [chiesi]
19642	ventolin nebules
12808	fenoterol with ipratropium bromide breath actuated inhaler 100micrograms + 40micrograms/actuation
14483	terbutaline injection 500micrograms/ml
7711	terbutaline spacer inhaler 250micrograms/actuation
7719	ephedrine tablets 30mg
2259	medihaler -iso forte aerosol inhaler [3m]
1436	haymine tablets [chemidex]
10979	ephedrine tablets 15mg
8321	alupent tablets 20mg [boeh ingl]
8872	medihaler -iso aerosol [3m]
35503	salmeterol inhalation powder blisters (refill) 50micrograms
8636	ventolin s/r 8 mg spa
10360	aerocrom aerosol inhaler [castlemead]
14306	formoterol fumarate cfc free inhaler 12micrograms/actuation
14527	bambec tablets 10mg [astrazenec]
3763	terbutaline respules inh
22313	ventmax sr modified release capsules 8mg [opus]
11307	salbutamol with beclometasone aerosol inhaler 100mcg + 50mcg
1794	berotec aerosol inhaler 100micrograms/actuation [boeh ingl]
12563	exirel aerosol inhaler [3m]
2395	salbutamol 2 mg/5ml syr
17696	ventmax sr modified release capsules 4mg [opus]
8522	terbutaline modified release tablet 7.5mg
16625	ventide rotacaps [a & h]
5185	fenoterol aerosol inhaler 200micrograms/actuation
5837	salamol steri-neb unit dose nebulising solution 5mg/2.5ml [numark]
10458	ventolin cr tablets 4mg [a & h]
510	ventolin respirator solution 5mg/ml [a & h]
37470	beclometasone extrafine particle with formoterol cfc free inhaler 100micrograms + 6micrograms/actuation
5898	salamol steri-neb unit dose nebulising solution 2.5mg/2.5ml [numark]
21859	asmaven aerosol inhaler 100micrograms [berk]
10825	terbutaline tablets 5mg
3758	pulmadil aerosol inhaler [3m]
30230	salbutamol breath actuated inhaler 100micrograms/actuation
4908	ventolin rotahaler insufflator [a & h]
12909	salbutamol with ipratropium bromide aerosol inhaler 100micrograms + 20micrograms/actuation
1628	terbutaline refill canister 250micrograms/actuation
7954	bricanyl spacer inhaler [astrazenec]
696	salbutamol modified release capsules 8mg
8508	alupent aerosol inhaler 750micrograms/inhalation [boeh ingl]
3556	beclometasone with salbutamol aerosol inhaler 50micrograms + 100micrograms/inhalation
9805	salbutamol infusion 100micrograms/ml
4541	bricanyl sa tablets 7.5mg [astrazenec]
12144	bambuterol tablets 20mg
4640	bricanyl unit dose nebuliser solution 5mg/2ml [astrazenec]
16577	easyhaler salbutamol dry powder inhaler 200micrograms/actuation [orion]
8511	cam sugar free liquid 4mg/5ml [cambhealth]
12822	salbutamol with ipratropium bromide unit dose nebulising solution 2.5mg + 500micrograms/2.5ml
3534	bricanyl tablets 5mg [astrazenec]
2149	steri-neb salamol 2.5 mg inh
2862	duovent autohaler breath actuated inhaler [boeh ingl]
1975	oxis 6 turbohaler dry powder inhaler 6 micrograms/actuation [astrazenec]
7192	bambuterol tablets 10mg

Asthma therapy

Product Code	Product Name
13273	fluticasone with salmeterol dry powder inhaler 100micrograms + 50micrograms/inhalation
9384	salbutamol modified release capsules 4mg
12042	ventolin cr tablets 8mg [a & h]
5308	terbutaline unit dose nebuliser solution 5mg/2ml
5889	salamol cfc free inhaler 100micrograms/inhalation [kent]
6526	formoterol fumarate capsules (for inhalation) 12mcg
9711	formoterol fumarate dry powder inhaler 6 micrograms/actuation
3764	bricanyl respules (5mg/2ml) 2.5 mg/ml inh
10968	foradil capsules (for inhalation) 12mcg [nov/ciba]
2610	intal compound capsules (for inhalation) [rhone]
4634	steri-neb salamol unit dose nebulising solution 2.5mg/2.5ml [ivax]
7935	maxivent aerosol inhaler 100micrograms/inhalation [ashbourne]
13038	pulvinal salbutamol dry powder inhaler 200micrograms/actuation [chiesi]
4171	ventolin tablets 2mg [a & h]
2020	berotec aerosol inhaler 200micrograms/actuation [boeh ingl]
12994	fluticasone with salmeterol cfc free inhaler 50micrograms + 25micrograms/actuation
13181	easyhaler salbutamol dry powder inhaler 100micrograms/actuation [orion]
13040	fluticasone with salmeterol dry powder inhaler 250micrograms + 50micrograms/inhalation
7017	salbutamol dry powder inhaler 100micrograms/actuation
7953	terbutaline sugar free oral solution 1.5mg/5ml
42886	bricanyl turbohaler dry powder inhaler 500micrograms [astrazenec]
2758	bricanyl refill canister [astrazenec]
3584	bricanyl sugar free oral solution 1.5mg/5ml [astrazenec]
1414	steri-neb salamol unit dose nebulising solution 5mg/2.5ml [ivax]
881	salbutamol tablets 2mg
4665	salbulin cfc free inhaler 100micrograms/actuation [3m]
11410	fluticasone with salmeterol dry powder inhaler 500micrograms + 50micrograms/inhalation
42858	ventolin accuhaler dry powder inhaler 200micrograms/actuation [glaxo]
11046	ipratropium bromide with salbutamol unit dose nebulising solution 500micrograms + 2.5mg/2.5ml
3786	fenoterol with ipratropium bromide aerosol inhaler 100micrograms + 40micrograms/actuation
37432	fostair cfc free inhaler 100micrograms + 6micrograms/actuation [chiesi]
11588	fluticasone with salmeterol cfc free inhaler 125micrograms + 25micrograms/actuation
6462	salbutamol dry powder inhaler 95micrograms
862	salbulin aerosol inhaler [3m]
3994	salbutamol modified release tablet 4mg
3163	salbutamol disc 200micrograms
987	ventolin tablets 4mg [a & h]
7268	serevent evohaler cfc free inhaler 25micrograms/actuation [glaxo]
882	salbutamol capsules (for inhalation) 200micrograms
2869	salbutamol modified release tablet 8mg
1087	asmasal clickhaler dry powder inhaler 95micrograms [focus]
11618	fluticasone with salmeterol cfc free inhaler 250micrograms + 25micrograms/actuation
1974	oxis 12 turbohaler dry powder inhaler 12micrograms/actuation [astrazenec]
1801	ventide aerosol inhaler [a & h]
7133	formoterol fumarate dry powder inhaler 12micrograms/actuation
2490	orciprenaline sugar free oral solution 10mg/5ml
3297	salmeterol disc 50micrograms
860	salbutamol tablets 4mg
957	salamol easi-breathe breath actuated inhaler 100micrograms/actuation [ivax]
1961	volmax tablets 4mg [a & h]
5753	salbutamol disc 400micrograms
10218	budesonide with formoterol dry powder inhaler 100micrograms + 6micrograms/actuation
1957	ventolin nebules unit dose nebulising solution 5mg [a & h]
1960	volmax tablets 8mg [a & h]
2901	alupent sugar free oral solution 10mg/5ml [boeh ingl]
910	serevent diskhaler 50micrograms [glaxo]
1093	salamol aerosol inhaler 100micrograms/actuation [ivax]
2224	serevent accuhaler 50micrograms/actuation [glaxo]
5740	airomir autohaler cfc free breath actuated inhaler 100micrograms/actuation [ivax]
958	ventolin easi-breathe breath actuated inhaler 100micrograms/actuation [a & h]
6938	salmeterol with fluticasone dry powder inhaler 50micrograms + 100micrograms/inhalation

Asthma therapy

Product Code	Product Name
3305	combivent udvs nebuliser solution 2.5ml [boeh ingl]
2851	ventolin rotacaps 200micrograms [a & h]
7013	symbicort turbohaler dry powder inhaler 100micrograms + 6micrograms/actuation [astrazenec]
6746	budesonide with formoterol dry powder inhaler 400micrograms + 12micrograms/actuation
856	ventolin syrup 2mg/5ml [a & h]
942	aerolin autohaler breath actuated inhaler 100micrograms/actuation [3m]
674	ventolin nebules unit dose nebulising solution 2.5mg [a & h]
665	seretide 100 accuhaler dry powder inhaler [glaxo]
2850	salbutamol capsules (for inhalation) 400micrograms
5143	seretide 50 evohaler cfc free inhaler [a & h]
2655	airomir cfc free inhaler 100micrograms/inhalation [teva]
6616	salmeterol with fluticasone cfc free inhaler 25micrograms + 50micrograms/actuation
6780	symbicort turbohaler dry powder inhaler 400micrograms + 12micrograms/actuation [astrazenec]
2722	duovent aerosol inhaler 40micrograms + 100micrograms/actuation [boeh ingl]
1882	ventodisks disc 200micrograms/blister [a & h]
2978	salbutamol dry powder inhaler 200micrograms/actuation
1620	terbutaline aerosol inhaler 250micrograms/actuation
719	salmeterol dry powder inhaler 50micrograms/actuation
5170	salamol cfc free inhaler 100micrograms/inhalation [ivax]
235	bricanyl aerosol inhaler [astrazenec]
5558	salmeterol with fluticasone dry powder inhaler 50micrograms+ 500micrograms/inhalation
4497	ventolin accuhaler 200micrograms/actuation [glaxo]
282	salbutamol sugar free oral solution 2mg/5ml
5942	salmeterol with fluticasone dry powder inhaler 50micrograms + 250micrograms/inhalation
1950	ventodisks disc 400micrograms/blister [a & h]
1952	ventolin rotacaps 400micrograms [a & h]
7270	salmeterol cfc free inhaler 25micrograms/actuation
1711	salbutamol unit dose nebulising solution 5mg/2.5ml
638	seretide 250 accuhaler dry powder inhaler [glaxo]
1630	salbutamol unit dose nebulising solution 2.5mg/2.5ml
3666	seretide 500 accuhaler dry powder inhaler [glaxo]
2152	ipratropium bromide with salbutamol aerosol inhaler 20mcg + 100mcg
5516	salamol easi-breathe cfc free breath actuated inhaler 100micrograms/actuation [ivax]
6796	budesonide with formoterol dry powder inhaler 200micrograms + 6micrograms/actuation
1698	salbutamol breath actuated inhaler 100micrograms/actuation
6569	salmeterol with fluticasone cfc free inhaler 25micrograms + 125micrograms/actuation
549	serevent aerosol inhaler 25micrograms/actuation [glaxo]
5161	seretide 125 evohaler cfc free inhaler [a & h]
6325	symbicort turbohaler dry powder inhaler 200micrograms + 6micrograms/actuation [astrazenec]
556	combivent aerosol inhaler 20mcg + 100mcg [boeh ingl]
5864	salmeterol with fluticasone cfc free inhaler 25micrograms + 250micrograms/actuation
907	bricanyl turbohaler 500micrograms [astrazenec]
5172	seretide 250 evohaler cfc free inhaler [a & h]
1619	terbutaline dry powder inhaler 500micrograms
1741	salbutamol cfc free breath actuated inhaler 100micrograms/actuation
42830	ventolin evohaler cfc free inhaler 100micrograms/inhalation [glaxo]
465	salmeterol aerosol inhaler 25micrograms/actuation
898	ventolin evohaler 100micrograms/inhalation [glaxo]
31	ventolin aerosol inhaler 100micrograms/inhalation [glaxo]
8	salbutamol aerosol inhaler 100micrograms/inhalation
17	salbutamol cfc free inhaler 100micrograms/inhalation
25020	ipratropium bromide (forte)
30229	ipratropium bromide unit dose nebuliser solution 250micrograms/ml [galen]
20803	ipratropium bromide nebuliser solution
37791	ipratropium bromide inhalation solution 250micrograms/ml
40177	ipratropium bromide unit dose nebulising solution 250micrograms/ml [hillcross]
20720	atrovent forte
40637	steripoule ipratropium unit dose nebuliser solution 250micrograms/ml [galen]
23961	ipratropium bromide inhalation solution 250micrograms/ml [galen]
40832	steripoule ipratropium unit dose nebuliser solution 500micrograms/2ml [galen]

Asthma therapy

Product Code	Product Name
43090	atrovent aerocaps inhalation powder capsules 40mcg [boeh ingl]
43105	atrovent aerohaler inhalation powder capsules with device 40mcg [boeh ingl]
19737	atrovent nebuliser solution (1ml vial)
13757	tropiovent steripoule unit dose nebulising solution 250micrograms/ml [ashbourne]
19805	atrovent
18140	respontin nebules unit dose nebulising solution 500micrograms/2ml [glaxo]
23567	respontin nebules unit dose nebulising solution 250micrograms/ml [glaxo]
23709	steri-neb ipratropium unit dose nebulising solution 500micrograms/2ml [ivax]
6758	steri-neb ipratropium unit dose nebulising solution 250micrograms/ml [ivax]
18421	respontin nebules unit dose nebulising solution 250micrograms/ml [glaxo]
9658	oxitropium bromide breath actuated inhaler 100micrograms/actuation
11779	ipratropium bromide capsules for inhalation + inhaler 40mcg
3850	oxivent autohaler breath actuated inhaler 100micrograms/actuation [boeh ingl]
9681	atrovent aerohaler 40mcg [boeh ingl]
2994	atrovent aerocaps 40mcg [boeh ingl]
8333	ipratropium bromide capsules (for inhalation) 40mcg
6911	atrovent udvs nebuliser solution 250micrograms/1ml [boeh ingl]
1410	ipratropium bromide nebuliser solution 0.25mg/ml
7140	atrovent udvs nebuliser solution 500micrograms/2ml [boeh ingl]
1415	steri-neb ipratropium unit dose nebulising solution 250micrograms/ml [ivax]
1697	atrovent autohaler breath actuated inhaler 20micrograms/actuation [boeh ingl]
2437	oxitropium bromide aerosol inhaler 100micrograms/actuation
6081	ipratropium bromide breath actuated inhaler 20micrograms/dose
6772	ipratropium bromide unit dose nebuliser solution 250micrograms/ml
3306	atrovent forte aerosol inhaler 40micrograms/actuation [boeh ingl]
36869	spiriva respimat inhalation solution 2.5 micrograms/actuation [boeh ingl]
34995	spiriva inhalation powder capsules with device 18 micrograms [boeh ingl]
6719	ipratropium bromide unit dose nebuliser solution 500micrograms/2ml
3039	oxivent aerosol inhaler 100micrograms/actuation [boeh ingl]
36864	tiotropium inhalation solution 2.5 micrograms/actuation
4268	ipratropium bromide aerosol inhaler 40micrograms/metered inhalation
6512	atrovent cfc free inhaler 20micrograms/actuation [boeh ingl]
35000	spiriva inhalation powder capsules (refill) 18 micrograms [boeh ingl]
1411	ipratropium bromide unit dose nebulising solution 250micrograms/ml
6050	spiriva capsules (for inhalation) 18 micrograms [boeh ingl]
35014	tiotropium inhalation powder capsules with device 18 micrograms
1962	atrovent udvs nebuliser solution 0.25mg/ml [boeh ingl]
534	atrovent aerosol inhaler 20micrograms/actuation [boeh ingl]
746	tiotropium capsules (for inhalation) 18 micrograms
1409	ipratropium bromide aerosol inhaler 20micrograms/dose
6522	ipratropium bromide cfc free inhaler 20micrograms/actuation
35011	tiotropium inhalation powder capsules (refill) 18 micrograms
32461	choline theophyllinate 90 mg tab
42910	aminophylline injection 250mg/10ml [martindale]
25937	aminophylline intramuscular 500 mg inj
27558	choledyl
42511	aminophylline injection 25mg/ml [celltech]
32893	theophylline 100mg/lysine 74mg mg tab
26724	ephedrine hcl/aminophylline e/c tab
25093	theophylline s/r
26079	uniphyllin paediatric continus
27842	aminophylline 2 ml inj
28786	ephedrine hcl 25mg/aminophylline 130mg mg cap
19350	aminophylline 62.5 mg sup
8705	ephedrine hcl 24mg/theophylline 120mg mg tab
31758	uniphyllin continus
38120	theophylline modified release tablet 500mg
28241	min-i-jet aminophylline injection 250mg/10ml [ucb]
27944	tedral elixir [parke]
22080	aminophylline 20 ml inj
30596	aminophylline modified release tablet 225mg [actavis]
10432	theophylline 300 mg sup

Asthma therapy

Product Code	Product Name
15409	theophylline 3 mg sol
10289	aminophylline 200 mg sup
19735	uniphyllin continus
20225	aminophylline 500 mg inj
22669	choline theophyllinate 270 mg tab
20171	aminophylline 180 mg sup
25125	aminophylline suppository 360mg
25022	aminophylline 150 mg sup
29273	aminophylline modified release tablet 225mg [hillcross]
27593	aminophylline 350 mg sup
6988	aminophylline hydrate modified release tablet 100mg
24117	aminophylline 300 mg sup
10744	theophylline 80 mg eli
18308	aminophylline 100 mg sup
27040	phyllocontin continus
15025	aminophylline 25 mg sup
24207	aminophylline paed 50 mg sup
180	phyllocontin sup
15365	theophylline sugar free elixir 10mg/5ml
24023	theodrox tablets [3m]
1832	theograd tablets 350mg [abbott]
27249	do-do chesteze tablets [novartis]
8470	aminophylline 225 mg sup
24674	biophylline tablets 500mg [lorex]
19953	theophylline with ephedrine and caffeine tablets
8610	aminophylline 1 gm sup
18288	choline theophyllinate tablets 100mg
8955	theophylline 100 mg tab
26860	theophylline with ephedrine sulphate tablets 120mg + 15mg
23572	aminophylline sr tablets 225mg [ivax]
24418	biophylline tablets 350mg [lorex]
10723	theophylline syrup 125mg/5ml
24035	ephedrine 15mg/theophylline 120mg 15 mg tab
9092	theophylline modified release tablet 350mg
12699	pecram sustained release tablets 225mg [novartis]
218	aminophylline 100 mg cap
17140	aminophylline tablets 200mg
18988	choline theophyllinate syrup 62.5mg/5ml
14991	aminophylline injection 250mg/10ml
7832	choline theophyllinate tablets 200mg
10561	aminophylline injection 250mg/ml
15561	ephedrine 11mg/theophylline 120mg 11 mg tab
18937	sabidal sr 270 270 mg tab
12274	tedral tablets [parke]
8653	aminophylline 360 mg sup
15153	theophylline with ephedrine hydrochloride tablets 120mg + 11mg
273	theophylline 200 mg cap
10831	biophylline syrup 125mg/5ml [lorex]
4591	choledyl tablets 100mg [parke]
16994	aminophylline hydrate modified release tablet 350mg
12240	theophylline modified release capsules 300mg
21769	lasma tablets 300mg [pharmax]
14739	norphyllin sr tablets 225mg [ivax]
8056	aminophylline tablets 100mg
39040	phyllocontin forte continus tablets 350mg [napppharm]
11993	pro-vent capsules 300mg [wellcome]
3187	choledyl syrup 62.5mg/5ml [parke]
8057	aminophylline modified release tablet 100mg
10433	theophylline liquid 60mg/5ml
4593	theophylline tablets 125mg
4592	choledyl tablets 200mg [parke]
4514	aminophylline modified release tablet 350mg

Asthma therapy

Product Code	Product Name
11719	slo-phyllin capsules 60mg [merck ser]
880	theophylline modified release capsules 60mg
10407	phyllocontin continus paediatric tablets 100mg [napppharm]
13529	amnivent sustained release tablets 225mg [ashbourne]
7477	franol plus tablets [sanofi/ave]
7841	nuelin tablets 125mg [3m]
7730	theo-dur tablets 300mg [astrazenec]
7731	theo-dur tablets 200mg [astrazenec]
879	theophylline modified release capsules 125mg
8806	phyllocontin continus forte tablets 350mg [napppharm]
15284	slo-phyllin capsules 125mg [merck ser]
7733	theophylline modified release tablet 250mg
2609	franol tablets [sanofi s]
10331	nuelin liquid 60mg/5ml [3m]
1097	slo-phyllin capsules 60mg [lipha]
7732	theophylline modified release tablet 300mg
3388	theophylline modified release tablet 175mg
863	slo-phyllin capsules 125mg [lipha]
17002	aminophylline hydrate modified release tablet 225mg
6315	slo-phyllin capsules 250mg [merck ser]
2147	theophylline modified release capsules 250mg
1834	theophylline modified release tablet 400mg
1833	theophylline modified release tablet 200mg
5261	nuelin sa-250 tablets [meda]
2757	slo-phyllin capsules 250mg [lipha]
5941	uniphyllin continus prolonged release tablet 300mg [napppharm]
2995	nuelin sa tablets 175mg [meda]
5453	uniphyllin continus prolonged release tablet 400mg [napppharm]
1423	uniphyllin continus prolonged release tablet 200mg [napppharm]
555	aminophylline modified release tablet 225mg
590	phyllocontin continus tablets 225mg [napppharm]
25087	betamethasone /clioquinol
20763	becloforte
20825	spacehaler bdp spacehaler 250micrograms/actuation [celltech]
27915	fluticasone prop disk refill
24660	betamethasone valerate
41269	beclometasone cyclocaps capsules (for inhalation) 400micrograms [teva]
24205	betamethasone /neomycin
24219	becotide rotacaps
27083	betamethasone valerate .1 mg tab
27583	pulmicort
29322	betamethasone loz
28311	betamethasone /salicylic acid
26665	pulmicort complete
41412	beclometasone aerosol inhaler 400micrograms/actuation
22827	betamethasone .1 mg pel
30805	betamethasone valerate pel
21465	betamethasone .1 mg tab
34428	beclometasone aerosol inhaler 50micrograms/actuation [neolab]
27970	betamethasone sod phos 0.1%/neomycin 0.5
28761	spacehaler bdp spacehaler 50micrograms/actuation [celltech]
46157	beclometasone cyclocaps capsules (for inhalation) 200micrograms [teva]
34794	beclometasone aerosol inhaler 200micrograms/actuation [hillcross]
22180	betamethasone 0.1%/neomycin 0.5% een dro
19736	becotide susp for nebulisation
24898	spacehaler bdp spacehaler 100micrograms/actuation [celltech]
27525	becotide 50
34859	beclometasone aerosol inhaler 250micrograms/actuation [neolab]
20707	becotide 100
26414	betamethasone benzoate % cre
23675	pulmicort l.s. refil
32874	beclometasone aerosol inhaler 50micrograms/actuation [actavis]

Asthma therapy

Product Code	Product Name
20750	betamethasone sodium phosphate eye
7643	betamethasone dipropionate .1 % oin
36021	fluticasone inhalation powder blisters with device 50micrograms
33849	beclometasone aerosol inhaler 100micrograms/actuation [neolab]
18394	bdp spacehaler 50micrograms/actuation [celltech]
22160	betamethasone sod.phos. ear/eye/nose dro
34315	beclometasone aerosol inhaler 250micrograms/actuation [actavis]
19389	asmabec spacehaler 50micrograms/actuation [celltech]
37447	fluticasone inhalation powder blisters (refill) 50micrograms
34739	beclometasone aerosol inhaler 50micrograms/actuation [aps]
35986	flixotide diskhaler (refill) inhalation powder 50micrograms [a & h]
8232	betamethasone valerate /lignocaine hyd./ .05 % oin
7706	betamethasone 1 % oin
30238	beclometasone breath actuated inhaler 50micrograms/actuation [aps]
10321	budesonide capsules (for inhalation) 400micrograms
35392	flixotide diskhaler inhalation powder 500 micrograms [a & h]
36290	flixotide diskhaler inhalation powder 50micrograms [a & h]
18537	budesonide capsules (for inhalation) 200micrograms
2720	betamethasone /clioquinol oin
20812	pulmicort refill
33258	beclometasone aerosol inhaler 250micrograms/actuation [hillcross]
39200	aerobec forte autohaler 250micrograms/actuation [meda]
35374	flixotide diskhaler (refill) inhalation powder 500 micrograms [a & h]
35700	fluticasone inhalation powder blisters with device 500 micrograms
8251	pulmicort refil 50 mg inh
35225	flixotide diskhaler inhalation powder 100micrograms [a & h]
3860	betamethasone drops eye
35580	beclometasone inhalation powder blisters with device 100micrograms
4803	beclazone aerosol inhaler 250micrograms/actuation [actavis]
8829	betamethasone .05 % lot
16054	budesonide refillable breath actuated dry powder inhaler 200micrograms/actuation
7724	betamethasone valerate aerosol inhaler 100micrograms/actuation
14590	asmabec spacehaler 250micrograms/actuation [celltech]
28073	beclometasone breath actuated inhaler 250micrograms/actuation [aps]
3188	pulmicort complete 50 mcg inh
35638	fluticasone inhalation powder blisters with device 100micrograms
7964	beclometasone nebuliser suspension 50micrograms/ml
34919	beclometasone aerosol inhaler 50micrograms/actuation [hillcross]
36090	flixotide diskhaler (refill) inhalation powder 100micrograms [a & h]
35602	budesonide dry powder inhalation cartridge (refill) 200micrograms
35107	beclometasone inhalation powder blisters with device 400micrograms
9477	asmabec spacehaler 100micrograms/actuation [celltech]
35106	becodisks diskhaler inhalation powder 100micrograms [a & h]
36462	fluticasone inhalation powder blisters (refill) 500 micrograms
19031	bdp spacehaler 100micrograms/actuation [celltech]
35772	fluticasone inhalation powder blisters (refill) 100micrograms
14700	budesonide aerosol inhaler 400micrograms/actuation
26063	beclometasone aerosol inhaler 100micrograms/actuation [aps]
11198	beclometasone vortex metered dose inhaler 50micrograms/actuation
35461	flixotide diskhaler inhalation powder 250micrograms [a & h]
9599	beclazone aerosol inhaler 50micrograms/actuation [actavis]
35510	budesonide dry powder inhalation cartridge with device 200micrograms
3442	pulmicort complete 200 mcg inh
36401	fluticasone inhalation powder blisters with device 250micrograms
28640	beclometasone aerosol inhaler 100micrograms/actuation [actavis]
14524	bdp spacehaler 250micrograms/actuation [celltech]
35611	flixotide diskhaler (refill) inhalation powder 250micrograms [a & h]
35118	becodisks diskhaler inhalation powder 400micrograms [a & h]
35652	beclometasone inhalation powder blisters (refill) 100micrograms
19401	beclometasone inhaler with compact spacer 250micrograms/actuation
35293	beclometasone inhalation powder blisters with device 200micrograms

Asthma therapy

Product Code	Product Name
30649	easyhaler budesonide dry powder inhaler 400micrograms/actuation [orion]
35430	becodisks diskhaler inhalation powder 200micrograms [a & h]
35408	becodisks inhalation powder (refill) 100micrograms [a & h]
35288	beclometasone inhalation powder blisters (refill) 400micrograms
35905	fluticasone inhalation powder blisters (refill) 250micrograms
23741	novolizer budesonide breath actuated dry powder inhaler 200micrograms/actuation [meda]
43074	flixotide accuhaler dry powder inhaler 500micrograms/inhalation [a & h]
11497	beclometasone dry powder inhaler 400micrograms/actuation
31774	beclometasone aerosol inhaler 50micrograms/actuation [gen (uk)]
9571	beclometasone vortex metered dose inhaler 250micrograms/actuation
13815	beclazone aerosol inhaler 100micrograms/actuation [actavis]
35299	becodisks inhalation powder (refill) 400micrograms [a & h]
25204	beclometasone aerosol inhaler 100micrograms/actuation [hillcross]
35631	budelin novolizer inhalation powder with device 200micrograms [meda]
8433	budesonide aerosol inhaler 100micrograms/actuation
35724	budelin novolizer inhalation powder (refill) 200micrograms [meda]
42985	flixotide accuhaler dry powder inhaler 50micrograms/inhalation [a & h]
27679	beclometasone breath actuated inhaler 100micrograms/actuation [aps]
15706	beclometasone vortex metered dose inhaler 100micrograms/actuation
2124	pulmicort refil 200 mcg inh
21224	alvesco cfc free inhaler 80micrograms/actuation [nycomed]
27188	easyhaler budesonide dry powder inhaler 200micrograms/actuation [orion]
39099	pulmicort cfc free inhaler 100micrograms [astrazenec]
35071	becodisks inhalation powder (refill) 200micrograms [a & h]
11478	fluticasone unit dose nebulising suspension 2mg/2ml
29325	beclometasone aerosol inhaler 250micrograms/actuation [gen (uk)]
39102	budesonide cfc free inhaler 100micrograms
17590	asmanex twisthaler dry powder inhaler 400micrograms/actuation [m s d]
14736	pulvinal beclometasone dipropionate dry powder inhaler 400micrograms/actuation [chiesi]
40057	pulmicort cfc free inhaler 200micrograms [astrazenec]
8450	flixotide diskhaler-community pack 50 mcg
42994	flixotide accuhaler dry powder inhaler 250micrograms/inhalation [a & h]
35113	beclometasone inhalation powder blisters (refill) 200micrograms
16433	asmanex twisthaler dry powder inhaler 200micrograms/actuation [m s d]
16305	flixotide nebules unit dose nebulising suspension 2mg/2ml [a & h]
2892	becloforte disks (refill pack) 400micrograms/actuation [a & h]
19563	becotide for nebuliser
17465	fluticasone unit dose nebulising suspension 500micrograms/2ml
5992	beclometasone dry powder inhaler 50micrograms/actuation
6839	alvesco cfc free inhaler 160micrograms/actuation [nycomed]
3363	becloforte diskhaler 400micrograms/actuation [a & h]
5551	flixotide nebules unit dose nebulising suspension 500micrograms/2ml [a & h]
17670	easyhaler budesonide dry powder inhaler 100micrograms/actuation [orion]
3065	bextasol aerosol inhaler [a & h]
42928	flixotide accuhaler dry powder inhaler 100micrograms/inhalation [a & h]
16018	mometasone furoate dry powder inhaler 200micrograms/actuation
3570	budesonide refill canister 200micrograms/actuation
3743	filair aerosol inhaler 50micrograms/actuation [meda]
30210	beclometasone aerosol inhaler 250micrograms/actuation [aps]
7356	ciclesonide cfc free inhaler 80micrograms/actuation
9356	becotide rotahaler insufflator [a & h]
9577	asmabec clickhaler dry powder inhaler 50micrograms [focus]
39879	budesonide cfc free inhaler 200micrograms
10254	mometasone furoate dry powder inhaler 400micrograms/actuation
14757	pulvinal beclometasone dipropionate dry powder inhaler 100micrograms/actuation [chiesi]
3988	flixotide diskhaler-community pack 100 mcg
947	budesonide refill canister 50micrograms/actuation
7602	fluticasone disc 50micrograms
3119	becloforte integra inhaler with compact spacer 250micrograms/actuation [glaxo]

Asthma therapy

Product Code	Product Name
21482	beclometasone aerosol inhaler 100micrograms/actuation [gen (uk)]
10102	ciclesonide cfc free inhaler 160micrograms/actuation
2159	aerobec autohaler 50micrograms/actuation [meda]
8111	becloforte vm pack 250micrograms/actuation [a & h]
5804	beclometasone dry powder inhaler 250micrograms/actuation
13037	pulvinal beclometasone dipropionate dry powder inhaler 200micrograms/actuation [chiesi]
21005	beclometasone cfc free inhaler 250micrograms/actuation
8635	flixotide disc 50micrograms [a & h]
17654	easyhaler beclometasone dry powder inhaler 200micrograms/actuation [orion]
5521	beclometasone dry powder inhaler 200micrograms/actuation
1727	becotide easi-breathe breath actuated inhaler 50micrograms/actuation [a & h]
11732	beclometasone extrafine particle cfc free breath actuated inhaler 50micrograms/actuation
4545	pulmicort ls refill canister 50micrograms [astrazenec]
3753	flixotide diskhaler-community pack 250 mcg
16584	beclometasone cfc free inhaler 50micrograms/actuation
14321	beclometasone cfc free inhaler 200micrograms/actuation
3993	filair forte aerosol inhaler 250micrograms/actuation [meda]
1725	beclazone easi-breathe breath actuated inhaler 50micrograms/actuation [ivax]
4801	budesonide nebuliser suspension 0.5mg/2ml
7891	fluticasone disc 500micrograms
9921	beclometasone extrafine particle cfc free breath actuated inhaler 100micrograms/actuation
1426	flixotide disc 500micrograms [a & h]
4131	fluticasone disc 100micrograms
14567	asmabec clickhaler dry powder inhaler 250micrograms [focus]
4759	beclometasone capsules (for inhalation) 100micrograms
4365	beclometasone disc 100micrograms
3289	flixotide aerosol inhaler 25micrograms/actuation [a & h]
4499	aerobec forte autohaler 250micrograms/actuation [meda]
3989	flixotide disc 100micrograms [a & h]
1269	becotide nebuliser suspension 50micrograms/ml [a & h]
5522	beclometasone dry powder inhaler 100micrograms/actuation
2723	fluticasone aerosol inhaler 25micrograms/actuation
1885	beclazone aerosol inhaler 200micrograms/actuation [ivax]
4942	budesonide nebuliser suspension 1mg/2ml
3927	filair aerosol inhaler 100micrograms/actuation [meda]
5580	flixotide accuhaler 50micrograms/inhalation [a & h]
1518	flixotide aerosol inhaler 50micrograms/actuation [a & h]
4601	asmabec clickhaler dry powder inhaler 100micrograms [focus]
7653	beclometasone capsules (for inhalation) 400micrograms
4688	fluticasone aerosol inhaler 50micrograms/actuation
9164	fluticasone dry powder inhaler 50micrograms/inhalation
14294	qvar easi-breathe cfc free breath actuated inhaler 50micrograms/actuation [ivax]
2160	beclometasone breath actuated inhaler 50micrograms/actuation
18848	qvar easi-breathe cfc free breath actuated inhaler 100micrograms/actuation [ivax]
5309	flixotide evohaler cfc free inhaler 50micrograms/actuation [a & h]
2440	flixotide accuhaler 500micrograms/inhalation [a & h]
9233	beclometasone capsules (for inhalation) 200micrograms
7638	fluticasone disc 250micrograms
1552	becloforte easi-breathe breath actuated inhaler 250micrograms/actuation [a & h]
1959	pulmicort respules nebuliser suspension 0.5mg/2ml [astrazenec]
2992	beclazone aerosol inhaler 50micrograms/actuation [ivax]
5718	flixotide evohaler cfc free inhaler 125micrograms/actuation [a & h]
2125	pulmicort refill canister 200micrograms [astrazenec]
2282	fluticasone dry powder inhaler 500micrograms/inhalation
959	budesonide aerosol inhaler 50micrograms/actuation
2148	beclometasone disc 400micrograms
15326	beclometasone cfc free inhaler 100micrograms/actuation
10090	beclometasone extrafine particle cfc free inhaler 50micrograms/actuation
1676	flixotide aerosol inhaler 125micrograms/actuation [a & h]

Asthma therapy

Product Code	Product Name
1680	pulmicort ls aerosol inhaler 50micrograms [astrazenec]
1424	flixotide disc 250micrograms [a & h]
2893	beclometasone disc 200micrograms
4926	flixotide accuhaler 100micrograms/inhalation [a & h]
4132	fluticasone aerosol inhaler 125micrograms/actuation
1243	beclazone easi-breathe breath actuated inhaler 250micrograms/actuation [ivax]
3220	qvar autohaler cfc free breath actuated inhaler 50micrograms/actuation [ivax]
3150	beclometasone extrafine particle cfc free inhaler 100micrograms/actuation
1861	aerobec autohaler 100micrograms/actuation [meda]
1956	pulmicort respules nebuliser suspension 1mg/2ml [astrazenec]
5885	fluticasone dry powder inhaler 100micrograms/inhalation
911	flixotide accuhaler 250micrograms/inhalation [a & h]
7948	fluticasone dry powder inhaler 250micrograms/inhalation
5683	flixotide evohaler cfc free inhaler 250micrograms/actuation [a & h]
3947	becotide rotacaps 100micrograms [a & h]
896	becotide easi-breathe breath actuated inhaler 100micrograms/actuation [a & h]
2229	becodisks disc 100micrograms [a & h]
16148	clenil modulite cfc free inhaler 250micrograms/actuation [chiesi]
3437	becotide rotahaler type 4 insufflator [a & h]
5223	fluticasone cfc free inhaler 50micrograms/actuation
3075	becotide rotacaps 400micrograms [a & h]
7788	budesonide dry powder inhaler 100micrograms/actuation
2600	beclometasone breath actuated inhaler 250micrograms/actuation
4413	qvar autohaler cfc free breath actuated inhaler 100micrograms/actuation [ivax]
5975	fluticasone cfc free inhaler 125micrograms/actuation
1412	flixotide aerosol inhaler 250micrograms/actuation [a & h]
895	beclazone easi-breathe breath actuated inhaler 100micrograms/actuation [ivax]
1551	beclazone aerosol inhaler 250micrograms/actuation [ivax]
960	pulmicort turbohaler dry powder inhaler 100micrograms/actuation [astrazenec]
2951	fluticasone aerosol inhaler 250micrograms/actuation
883	becodisks disc 200micrograms [a & h]
1951	becodisks disc 400micrograms [a & h]
16151	clenil modulite cfc free inhaler 200micrograms/actuation [chiesi]
909	budesonide aerosol inhaler 200micrograms/actuation
1642	budesonide dry powder inhaler 400micrograms/actuation
5822	fluticasone cfc free inhaler 250micrograms/actuation
1100	beclazone aerosol inhaler 100micrograms/actuation [ivax]
1537	becotide rotacaps 200micrograms [a & h]
16158	clenil modulite cfc free inhaler 50micrograms/actuation [chiesi]
454	pulmicort aerosol inhaler 200micrograms [astrazenec]
908	pulmicort turbohaler dry powder inhaler 400micrograms/actuation [astrazenec]
1258	becotide 200 aerosol inhaler 200micrograms/actuation [a & h]
1406	becotide 50 aerosol inhaler 50micrograms/actuation [a & h]
2092	budesonide dry powder inhaler 200micrograms/actuation
1734	beclometasone breath actuated inhaler 100micrograms/actuation
956	pulmicort turbohaler dry powder inhaler 200micrograms/actuation [astrazenec]
3546	qvar cfc free inhaler 50micrograms/actuation [ivax]
3018	beclometasone aerosol inhaler 50micrograms/actuation
2335	qvar cfc free inhaler 100micrograms/actuation [ivax]
1236	becloforte aerosol inhaler 250micrograms/actuation [a & h]
13290	clenil modulite cfc free inhaler 100micrograms/actuation [chiesi]
1259	beclometasone aerosol inhaler 200micrograms/actuation
1242	beclometasone aerosol inhaler 250micrograms/actuation
99	becotide 100 aerosol inhaler 100micrograms/actuation [a & h]
38	beclometasone aerosol inhaler 100micrograms/actuation
28977	intal spincaps
24387	intal
12633	tilarin nasal spray 1% [rhone]
14448	nedocromil sodium nasal spray 1%
19643	intal nebuliser solution (2ml)
3585	steri-neb cromogen nebuliser solution 10mg/ml [ivax]
37615	sodium cromoglicate aerosol inhaler 1mg/inhalation

Asthma therapy

Product Code	Product Name
15765	sodium cromoglicate inhaler and spacer 5mg/inhalation
4647	intal syncroner 5mg/inhalation [aventis]
14603	sodium cromoglicate inhaler and spacer 5mg/actuation
38501	intal cfc free inhaler 5mg [sanofi/ave]
10361	intal syncroner 5 mg inh
7580	intal whistle
25119	tilade cfc free inhaler 2mg/inhalation [sanofi/ave]
38471	sodium cromoglicate cfc free inhaler 5mg
8498	sodium cromoglicate nebuliser solution 10mg/ml
19597	intal
2158	sodium cromoglicate breath actuated inhaler 5mg/inhalation
13256	nedocromil sodium cfc free inhaler 2mg/inhalation
1728	cromogen easi-breathe breath actuated inhaler 5mg/inhalation [ivax]
10597	tilade mint syncroner 2mg/inhalation [sanofi/ave]
4100	intal autohaler 5mg/inhalation [aventis]
7972	intal fisonair aerosol inhaler 5mg/inhalation [aventis]
8608	nedocromil sodium aerosol inhaler 2mg/inhalation
1629	intal nebuliser solution 10mg/ml [aventis]
2911	sodium cromoglicate capsules (for inhalation) 20mg
3688	tilade mint inhaler 2mg/inhalation [sanofi/ave]
8215	tilade aerosol inhaler 2mg/inhalation [sanofi/ave]
1422	cromogen aerosol inhaler 5mg/inhalation [ivax]
2260	intal spinhaler insufflator [aventis]
964	sodium cromoglicate aerosol inhaler 5mg/inhalation
1683	intal spincaps inhalation powder capsules [aventis]
314	intal aerosol inhaler [aventis]
17701	zafirlukast
17894	accolate
20817	tilade aerosol
14200	singulair paediatric granules 4mg/sachet [m s d]
1973	accolate tablets 20mg [astrazenec]
14162	singulair paediatric chewable tablet 4mg [m s d]
7088	montelukast (as sodium salt) granules 4mg/sachet
5594	singulair paediatric chewable tablet 5mg [m s d]
7132	zafirlukast tablets 20mg
622	montelukast (as sodium salt) chewable tablet 4mg
5957	montelukast (as sodium salt) chewable tablet 5mg
695	singulair tablets 10mg [m s d]
808	montelukast (as sodium salt) tablets 10mg

Chronic Kidney Disease

Medical code	Read term
512	Chronic renal failure
1803	Nephrotic syndrome with membranous glomerulonephritis
2088	Acute glomerulonephritis
2471	Nephrotic syndrome in diabetes mellitus
2475	ZERIDAME SR tablets 150mg [ACTAVIS]
2773	Nephritis, nephrosis and nephrotic syndrome
2994	Peritoneal dialysis
2995	Acquired arteriovenous fistula
2996	Haemodialysis NEC
2999	Nephrotic syndrome
3205	Creation of arteriovenous fistula NEC
4480	Renal sclerosis NOS
4668	Hypertensive renal disease
4669	Chronic focal glomerulonephritis
4809	Uraemia NOS
4850	Nephritis and nephropathy unspecified
5182	Unspecified glomerulonephritis NOS
5291	Herpes zoster with meningitis
5417	Acute nephritis
6712	End stage renal failure
7190	Glomerulosclerosis
7804	Chronic glomerulonephritis
8037	Insertion of ambulatory peritoneal dialysis catheter
8330	End-stage renal disease
8607	Analgesic nephropathy
8668	Glomerular disease
8828	H/O: nephritis
8919	Impaired renal function disorder
9379	Acute interstitial nephritis
9765	Ligation of acquired arteriovenous fistula
9840	Nephrotic syndrome with proliferative glomerulonephritis
10081	Chronic uraemia
10418	Type 1 diabetes mellitus with nephropathy
10636	Hepatorenal syndrome
10647	Nephritis - chronic
10809	Chronic membranous glomerulonephritis
11553	Kidney transplant failure and rejection
11773	Dialysis for renal failure
11873	Nephropathy, unspecified
11875	Nephropathy - chronic
12465	Membranoproliferative nephritis unspecified
12479	Chronic kidney disease stage 4
12566	Chronic kidney disease stage 3
12585	Chronic kidney disease stage 5
12586	Chronic kidney disease stage 2
12640	Type 2 diabetes mellitus with nephropathy
12720	Chronic renal impairment
13279	Other specified diabetes mellitus with renal complications
15097	Chronic glomerulonephritis NOS
15106	Hypertensive renal disease NOS
15780	Nephritis, nephrosis and nephrotic syndrome NOS
16008	Proliferative nephritis unspecified
16465	Persistent proteinuria
16502	Diabetes mellitus with renal manifestation
16929	Anaemia secondary to renal failure
17253	Renal transplant planned
17365	Nephrotic syndrome, diffuse crescentic glomerulonephritis
17434	Nephrosclerosis
18209	Type 2 diabetes mellitus with renal complications
18390	Type 2 diabetes mellitus with persistent microalbuminuria
18777	Type 2 diabetes mellitus with renal complications
18779	Repair of acquired arteriovenous fistula

Chronic Kidney Disease

Medical code	Read term
19316	Nephrotic syndrome, diffuse membranous glomerulonephritis
19454	Polyneuropathy in uraemia
20027	Acute glomerulonephritis in diseases EC
20073	Renal dialysis
20074	Bright's disease
20129	Acute glomerulonephritis NOS
20196	H/O: renal dialysis
20516	Salt-losing nephritis
21297	Chronic nephritic syndrome
21423	Berger's IgA or IgG nephropathy
21687	Gout due to impairment of renal function
21837	Hypertensive heart&renal dis wth (congestive) heart failure
21947	Nephrotic syn difus mesangial prolifertiv glomerulonephritis
21983	Type 1 diabetes mellitus with renal complications
21989	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis
22205	Lupus nephritis
22252	[V]Renal dialysis status
22852	Nephrotic syndrome, focal and segmental glomerular lesions
22897	Henoch-Schonlein nephritis
23773	Removal of ambulatory peritoneal dialysis catheter
23913	Nephrotic syndrome, minor glomerular abnormality
23990	Tubulo-interstit nephritis, not specif as acute or chron
24151	Arteriovenous shunt
24384	Familial glomerulonephritis in Alport's syndrome
24736	Drug/heavy-metal-induced tubulo-interstitial and tub conditn
24836	Type 2 diabetes mellitus with nephropathy
25394	Anaemia secondary to chronic renal failure
25521	Creation of brachial-cephalic fistula
25980	Impaired renal function disorder NOS
26054	Type 2 diabetes mellitus with persistent proteinuria
26220	Renal sclerosis unspecified
26862	Exploration of renal transplant
27335	Other nephritis and nephrosis in diseases EC
27427	Nephrotic syndrome NOS
28158	Kidney dialysis with complication, without blame
28269	Creation of radial-cephalic fistula
28684	Hypertensive heart and renal disease with renal failure
29013	Chronic kidney disease stage 1
29384	Acute proliferative glomerulonephritis
29634	Nephrotic syndrome with minimal change glomerulonephritis
29638	Renal osteodystrophy
30294	Type 1 diabetes mellitus with persistent microalbuminuria
30301	Unsp nephrit synd, diff mesang prolif glomerulonephritis
30323	Type 1 diabetes mellitus with persistent proteinuria
30709	Insertion of temporary peritoneal dialysis catheter
30756	Continuous ambulatory peritoneal dialysis
31478	Removal of infected arteriovenous shunt
31549	Compensation for renal failure
31581	Acute nephritic syndrome
32423	Hypertensive renal disease with renal failure
33580	Nephritis and nephropathy unspecified
34637	Renal osteodystrophy NOS
34648	Renal dwarfism
34669	Other interstitial nephritis
34998	Chronic proliferative glomerulonephritis
35065	Other nephritis and nephrosis unspecified
35105	Diabetes mellitus adult onset with renal manifestation
35107	Diabetes mellitis with nephropathy NOS
35921	Failure of sterile precautions during perfusion
36125	Unspecif nephr synd, diff concentric glomerulonephritis
36205	Hereditary nephropathy not elsewhere classified
36342	Mesangioproliferative glomerulonephritis NEC

Chronic Kidney Disease

Medical code	Read term
36442	Placement ambulatory dialysis apparatus - compens renal fail
38572	Xanthogranulomatous pyelonephritis
39649	Malignant hypertensive renal disease
39840	Other impaired renal function disorder
40349	Lipoid nephrosis
40413	Chronic nephritic syndrm focal+segmental glomerular lesions
40956	Acute pericarditis - uraemic
41013	Renal function impairment with growth failure
41148	Renal tubulo-interstitial disorder in SLE
41159	Nephropathy induced by other drugs meds and biologl substncs
41239	Hereditary nephropathy NEC,focal+segmnt glomerular lesion
41285	Rapid progres neph syn diffuse membranous glomerulonephritis
41676	Renal cortical necrosis unspecified
41881	Mesangiocapillary glomerulonephritis NEC
42632	Medullary cystic disease
43611	Isolated proteinuria with specified morphological lesion
43935	Benign hypertensive renal disease
44055	Other nephritis and nephrosis NOS
44270	Hereditry nephropathy NEC,difus membran glomerulnephritis
44422	H/O: kidney dialysis
44541	Recurrent and persistent haematuria dense deposit disease
44804	Isolatd proteinur/specifd morphlgcl les foc+seg glom lesn
45160	[V]Aftercare involving peritoneal dialysis
45499	Kimmelstiel - Wilson disease
45523	Renal tubulo-interstitial disorders in diseases EC
45867	Renal medullary necrosis unspecified
45904	Ren tub-interst disordr/blood dis+disordr inv immune mech
46145	[V]Aftercare involving renal dialysis NOS
46438	[X] Peritoneal dialysis associated peritonitis
46963	Insulin-dependent diabetes mellitus with renal complications
47135	Medullary cystic disease adult type
47582	Type 1 diabetes mellitus with renal complications
47672	Nephrotic syndrome in systemic lupus erythematosus
47838	Other acute glomerulonephritis NOS
47922	Nephrotic syndrome in amyloidosis
48022	Other specified compensation for renal failure
48057	Renal tubulo-interstitial disordrs in transplant rejectn
48261	Acute focal nephritis
48475	Renal acidaemia
48639	Mechanical complication of dialysis catheter
49150	Other specified nephritis, nephrosis or nephrotic syndrome
49642	Recur+persist haemuria df mesangial prolif glomerulnephritis
50200	Rapid progressive nephritic syndrome, dense deposit disease
50225	Type II diabetes mellitus with renal complications
50305	Hypocomplementaemic persistent glomerulonephritis NEC
50472	Nephrotic syn,difus endocapilary proliftv glomerulonephritis
50728	Renal infantilism
50804	Other impaired renal function disorder NOS
50893	Toxic nephropathy, not elsewhere classified
51039	Bilateral nephrectomy
51113	Hereditary nephropathy NEC, minor glomerular abnormality
52088	[V]Preparatory care for dialysis
52303	Non-insulin-dependent diabetes mellitus with renal comps
52969	Gouty nephropathy
53852	End stage renal failure
53940	[X]Other chronic renal failure
54312	Acute neph syn, diffuse mesangiocapillary glomerulonephritis
54844	[X]Failure sterile precautions dur kidney dialys/other perf
55100	Acute diffuse nephritis
55389	Acut neph syn, diffuse mesangial prolifrative glomnephritis
55548	Glom disordr in blood diseas+disordr invlvg imun mechansm
56760	Placement ambulatory apparatus compensation renal failure

Chronic Kidney Disease

Medical code	Read term
56893	Chron neph syn difus mesangial prolifrtiv glomerulonephritis
56939	Hypokalaemic nephropathy
56987	Nephrotic syndrome, dense deposit disease
57072	Other familial glomerulonephritis
57168	Chron nephritic syndrom difuse membranous glomerulonephritis
57278	Type II diabetes mellitus with renal complications
57621	Insulin dependent diabetes mellitus with nephropathy
57784	Nephropathy induced by unspec drug medicament or biol subs
57926	Steroid sensitive nephrotic syndrome
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
58060	Rpd prog neph syn df mesangial prolifratv glomerulonephritis
58164	Rapidly progressive nephritis unspecified
58618	Arteriovenous shunt NOS
58671	Heredtry nephrpthy NEC difus mesangial prolif glomnephrit
58750	Nephrotic syndrome in polyarteritis nodosa
59194	Placement ambulatory apparatus- compensate renal failure OS
59315	Stenosis of arteriovenous dialysis fistula
59365	Non-insulin dependent diabetes mellitus with nephropathy
59992	Isolated proteinuria with unspecified morpholog changes
60128	Unspecified nephritic syndrome, dense deposit disease
60198	Chronic nephritic syndrome, dense deposit disease
60302	Creation of graft fistula for dialysis
60446	Care of haemodialysis equipment
60484	Recur+persist hmuria df mesangiocapilary glomerulonephritis
60498	Reversing haemodialysis lines
60743	[V]Aftercare involving intermittent dialysis
60796	Type II diabetes mellitus with persistent proteinuria
60856	Recur+persist haematuria difus crescentic glomerulonephritis
60857	Chronic nephritic syn diffuse crescentic glomerulonephritis
60960	Other chronic glomerulonephritis
61145	Gouty nephropathy NOS
61317	Recur+persist haematuria difus membranous glomerulonephritis
61344	Type I diabetes mellitus with renal complications
61494	Chronic membranoproliferative glomerulonephritis
61811	Isoltd prteinur+specfd morph les df mesangiocap glomnephr
61814	Acute nephrotic syndrm diffuse crescentic glomerulonephritis
62320	Rapid progres nephritic syn df crescentic glomerulonephritis
62520	Unsp nephrit synd, diff endocap prolif glomerulonephritis
62868	Anaphylactoid glomerulonephritis
62980	Hereditary nephropathy, unspecif morphological changes
63000	Benign hypertensive heart and renal disease
63038	[V]Unspecified aftercare involving intermittent dialysis
63063	Insertion of arteriovenous prosthesis
63190	Attention to arteriovenous shunt
63305	Thrombectomy of arteriovenous fistula
63466	Hypertensive heart and renal disease
63488	[V]Other specified aftercare involving intermittent dialysis
63502	Peritoneal dialysis bag procedure
63599	Other acute glomerulonephritis
63615	Other chronic glomerulonephritis NOS
63786	Congenital nephrotic syndrome
64030	[X]Persistent proteinuria unspecified
64571	Type II diabetes mellitus with nephropathy
64622	Renal tubulo-interstitial disorder/ neoplastic diseases
64636	Compensation for renal failure NOS
64828	Peritoneal dialysis NEC
65064	Chronic rapidly progressive glomerulonephritis
65089	Placement other apparatus- compensate for renal failure NOS
65398	Other specified arteriovenous shunt
65400	Chronic diffuse glomerulonephritis
66062	Renal rickets
66136	Acute nephritic syndrome, focal+segmental glomerular lesions

Chronic Kidney Disease

Medical code	Read term
66503	Acute nephritic syn, diffuse membranous glomerulonephritis
66505	Chronic nephritic syndrome, minor glomerular abnormality
66613	Isoltd prteinur/spcfd morph lesn df mesngl prolf glomneph
66714	Renal dialysis with complication, without blame
66872	Type I diabetes mellitus with nephropathy
67193	Nephritis unsp+OS membranoprolif glomerulonephritis lesion
67197	Haemorrhagic nephrosonephritis
67232	Malignant hypertensive heart and renal disease
67261	Ren tub-interstitl disordr/systemc connectv tiss disorder
67460	Acute nephritis with lesions of necrotising glomerulitis
67995	Focal membranoproliferative glomerulonephritis
68112	Nephropathic amyloidosis
68364	Recur+persist haematuria focal+segmental glomerular lesions
68659	Hypertensive heart and renal disease NOS
69266	Failure of sterile precautions during kidney dialysis
69427	Accid cut puncture perf h'ge - perfusion NOS
69760	[X]Other dialysis
71124	Haemofiltration
71174	Rapidly progressive nephritic syndrome
71709	[X]Unsp nephrit synd, diff mesang prolif glomerulonephritis
71964	Isolatd proteinur/specfd morphlgcl les df membrn glomneph
72303	Finnish nephrosis syndrome
72336	Priming haemodialysis lines
72478	[X]Nephropathy induced by other drugs+biological substances
73026	Chronic neph syn difus mesangiocapillary glomerulonephritis
74905	Haemodialysis training
83513	Placement other apparatus for compensation for renal failure
85659	IgA nephropathy
85991	Type II diabetes mellitus with persistent microalbuminuria
88597	Automated peritoneal dialysis
89332	Predicted stage chronic kidney disease
90952	Pre-transplantation of kidney work-up, recipient
91738	Hereditary nephropathy, NEC, dense deposit disease
93922	Diabetes mellitus juvenile type with renal manifestation
94261	Acute exudative nephritis
94350	Nephritis unsp+membranoprolif glomerulonephritis lesion NOS
94373	Nephrotic syndrome with other pathological kidney lesions
94789	Chronic kidney disease stage 1 with proteinuria
94793	Chronic kidney disease stage 3 with proteinuria
94842	[X]Renal tubulo-interstitial diseases
94965	Chronic kidney disease stage 3A
95121	Chronic kidney disease stage 2 without proteinuria
95122	Chronic kidney disease stage 4 with proteinuria
95123	Chronic kidney disease stage 3 without proteinuria
95145	CKD stage 3 with proteinuria
95146	Chronic kidney disease stage 2 with proteinuria
95175	Chronic kidney disease stage 3A without proteinuria
95176	CKD stage 3A without proteinuria
95177	Chronic kidney disease stage 3B without proteinuria
95178	Chronic kidney disease stage 3B with proteinuria
95179	Chronic kidney disease stage 3B
95180	CKD stage 3B with proteinuria
95188	CKD stage 3 without proteinuria
95405	Chronic kidney disease stage 5 without proteinuria
95406	Chronic kidney disease stage 4 without proteinuria
95408	Chronic kidney disease stage 3A with proteinuria
95508	Chronic kidney disease stage 5 with proteinuria
95546	Recurrent+persistnt haematuria minor glomerular abnormality
95571	CKD stage 3A with proteinuria
95572	Chronic kidney disease stage 1 without proteinuria
96131	Banding of arteriovenous fistula
96184	Accid cut,puncture,perf,h'ge - kidney dialysis

Chronic Kidney Disease

Medical code	Read term
96347	Ligation of arteriovenous dialysis fistula
96819	[X]Other disorders resulting/impaired renal tubular function
97388	Mixed membranous and proliferative glomerulonephritis NEC
97533	[X]Hypertension secondary to other renal disorders
97587	CKD stage 4 without proteinuria
97683	CKD stage 5 without proteinuria
97734	Rapid progres nephritic syn focal+segmental glomerulr lesion
97758	Chronic glomerulonephritis + diseases EC
97978	CKD stage 2 without proteinuria
97979	CKD stage 2 with proteinuria
97980	CKD stage 1 with proteinuria
99139	Balkan nephropathy
99160	CKD stage 5 with proteinuria
99312	CKD stage 4 with proteinuria
99628	[X]Glomerular disorders in diabetes mellitus
99644	Nephrotic syndrome+membranoproliferative glomerulonephritis
99685	Acute nephritic syndrome dense deposit disease
100205	Acute-on-chronic renal failure
100235	Ligation of acquired arteriovenous fistula
100292	[X]Unspecified diabetes mellitus with renal complications
100558	Acute nephritic syndrome minor glomerular abnormality
100633	CKD stage 3B without proteinuria
100693	[X]Renal tubulo-interstitial disorders/transplant rejection
101358	Ac neph syn difus endocaplry prolifrative glomerulonephritis
101453	[X]Other chronic tubulo-interstitial nephritis
101572	Isolated proteinuria with oth specif morpholog changes
101756	Thomas intravascular shunt for dialysis
102163	Insulin dependent diabetes mellitus with nephropathy
102201	Type II diabetes mellitus with nephropathy
102620	Type I diabetes mellitus with persistent microalbuminuria

COPD

Medical code	Read term
794	emphysema
998	chronic obstructive airways disease
1001	chronic obstructive pulmonary disease
1446	acute exacerbation of chronic obstructive airways disease
3243	ZERIDAME SR tablets 150mg [ACTAVIS]
5710	chronic obstructive airways disease nos
7884	chron obstruct pulmonary dis wth acute exacerbation, unspec
9520	chronic obstructive pulmonary disease monitoring
9876	severe chronic obstructive pulmonary disease
10802	moderate chronic obstructive pulmonary disease
10863	mild chronic obstructive pulmonary disease
10980	centrilobular emphysema
11019	admit copd emergency
11150	mucopurulent chronic bronchitis
11287	chronic obstructive pulmonary disease annual review
12166	other specified chronic obstructive airways disease
14798	emphysematous bronchitis
15157	Herpes zoster with meningitis
15626	chronic catarrhal bronchitis
18476	copd follow-up
18501	copd self-management plan given
18621	chronic obstructive pulmonary disease follow-up
18792	chronic obstructive pulmonary disease monitoring admin
19003	emergency copd admission since last appointment
19106	copd accident and emergency attendance since last visit
21061	chronic obstruct pulmonary dis with acute lower resp infectn
23492	chronic bullous emphysema nos
24248	mixed simple and mucopurulent chronic bronchitis
25603	simple chronic bronchitis
26018	chronic obstructive pulmonary disease monitoring by nurse
26306	chronic bullous emphysema
27819	obstructive chronic bronchitis
28755	chronic obstructive pulmonary disease monitoring 1st letter
33450	emphysema nos
34202	chronic obstructive pulmonary disease monitoring 2nd letter
34215	chronic obstructive pulmonary disease monitoring 3rd letter
37247	chronic obstructive pulmonary disease nos
37371	chronic obstructive pulmonary disease monitoring due
37959	fetid chronic bronchitis
38074	chronic obstructive pulmonary disease monitor phone invite
40159	purulent chronic bronchitis
42258	chronic obstructive pulmonary disease monitoring verb invite
42624	coad follow-up
44525	obstructive chronic bronchitis nos
45770	chronic obstructive pulmonary disease disturbs sleep
45771	chronic obstructive pulmonary disease does not disturb sleep
45777	chronic obstructive pulmonary disease clini management plan
45998	chronic obstructive pulmonary disease monitoring by doctor
46036	multiple copd emergency hospital admissions
46578	panlobular emphysema
56860	segmental bullous emphysema
60188	giant bullous emphysema
61118	simple chronic bronchitis nos
61513	mucopurulent chronic bronchitis nos
64721	chronic emphysema due to chemical fumes
65733	[x]other specified chronic obstructive pulmonary disease
66043	other chronic bronchitis
67040	other specified chronic obstructive pulmonary disease
68066	other chronic bronchitis nos
93568	very severe chronic obstructive pulmonary disease
96931	at risk of chronic obstructive pulmonary diseas exacerbation
98283	copd structured smoking assessment declined - enh serv admin

COPD

Medical code	Read term
98284	refer copd structured smoking assessment - enhanc serv admin
99536	bullous emphysema with collapse
99948	copd patient unsuitable for pulmonary rehab - enh serv admin
101042	issue of chronic obstructive pulmonary disease rescue pack
102685	chronic obstructive pulmonary disease 3 monthly review
103007	chronic obstructive pulmonary disease 6 monthly review
103400	referred for copd structured smoking assessment

Depression

Medical code	Read term
324	Depressive disorder NEC
543	[X]Depression NOS
595	Endogenous depression
655	Anxiety with depression
1055	ZERIDAME SR tablets 150mg [ACTAVIS]
1131	Neurotic depression reactive type
1533	Brief depressive reaction
1908	O/E - depressed
1996	Depressed
2147	Poor self esteem
2560	Depressive psychoses
2639	Postnatal depression
2923	Puerperal depression
2930	C/O - feeling unhappy
2970	[X]Depressive episode, unspecified
2972	Postviral depression
3291	[X]Depressive disorder NOS
3292	Herpes zoster with meningitis
4323	Chronic depression
4639	[X]Depressive episode
4824	C/O - feeling depressed
4979	[X]Postpartum depression NOS
5879	Agitated depression
5987	[X] Reactive depression NOS
6482	Recurrent depression
6546	Endogenous depression first episode
6854	[X]Other depressive episodes
6932	Endogenous depression - recurrent
6950	Endogenous depression first episode
7011	Single major depressive episode NOS
7412	Loss of confidence
7604	[X]Single episode of reactive depression
7737	[X]Neurotic depression
7749	[X]Mild anxiety depression
7953	[X]Dysthymia
8478	Reactive depressive psychosis
8584	[X]Depressive neurosis
8826	[X]SAD - Seasonal affective disorder
8851	[X]Recurrent episodes of depressive reaction
8902	[X]Recurrent episodes of reactive depression
8928	Low mood
9055	[X]Single episode of depressive reaction
9183	Masked depression
9211	[X]Moderate depressive episode
9667	[X]Severe depressive episode without psychotic symptoms
9796	Symptoms of depression
10015	Depressed mood
10290	[X]Depressive personality disorder
10438	Depressive symptoms
10455	Depressive personality disorder
10610	Single major depressive episode
10667	[X]Mild depression
10720	[X]Atypical depression
10825	Seasonal affective disorder
11055	[X]Schizoaffective disorder, depressive type
11252	[X]Major depression, recurrent without psychotic symptoms
11329	[X]Endogenous depression without psychotic symptoms
11717	[X]Mild depressive episode
11913	[X]Mixed anxiety and depressive disorder
12099	[X]Severe depressive episode with psychotic symptoms
12122	Depression medication review
12399	Depression annual review

Depression

Medical code	Read term
13307	[X]Postnatal depression NOS
14709	Recurrent major depressive episodes, moderate
15099	Recurrent major depressive episode
15155	Single major depressive episode, moderate
15219	Single major depressive episode, severe, without psychosis
15220	[X]Persistant anxiety depression
16506	Single major depressive episode, mild
16632	Prolonged depressive reaction
16861	[X]Recurrent severe episodes of psychotic depression
17770	Psychotic reactive depression
18510	[X]Single episode of psychogenic depression
19054	[X]Recurrent brief depressive episodes
19696	[X]Recurrent episodes of psychogenic depression
20785	[X]Post-schizophrenic depression
21887	Senile dementia with depression
22806	[X]Single episode major depression w'out psychotic symptoms
23731	[X]Endogenous depression with psychotic symptoms
24112	[X]Single episode of psychotic depression
24117	[X]Single episode of major depression and psychotic symptoms
24171	Recurrent major depressive episodes, severe, with psychosis
25435	Loss of capacity for enjoyment
25563	Recurrent major depressive episode NOS
25697	Recurrent major depressive episodes, severe, no psychosis
26028	Sad mood
27491	Atypical depressive disorder
27677	Presenile dementia with depression
27759	[X] Senile dementia, depressed or paranoid type
28248	[X]Prolonged single episode of reactive depression
28756	[X]Seasonal depressive disorder
28863	[X]Single episode of reactive depressive psychosis
29342	Recurrent major depressive episodes, mild
29520	[X]Recurrent depressive disorder, current episode moderate
29527	[D]Postoperative depression
29784	[X]Recurrent depressive disorder, current episode mild
30405	Depression interim review
30740	Loss of interest
31757	[X]Recurr severe episodes/psychogenic depressive psychosis
32159	Single major depressive episode, severe, with psychosis
32941	[X]Recurr severe episodes/major depression+psychotic symptom
33469	[X]Recurr depress disorder cur epi severe without psyc sympt
34390	Single major depressive episode, unspecified
35274	[X]Schizoaffective psychosis, depressive type
35671	Recurrent major depressive episodes, unspecified
36246	Brief depressive reaction NOS
36616	[X]Monopolar depression NOS
37764	[X]Recurrent severe episodes/reactive depressive psychosis
41022	[X]Schizophreniform psychosis, depressive type
41089	Senile dementia with depressive or paranoid features NOS
41989	[X]Single episode agitated depressn w'out psychotic symptoms
43292	Arteriosclerotic dementia with depression
44300	[X]Recurrent depressive disorder, unspecified
44674	Senile dementia with depressive or paranoid features
44848	Depression management programme
47009	[X]Recurrent depress disorder cur epi severe with psyc symp
47731	[X]Other recurrent depressive disorders
52678	[X]Single episode of psychogenic depressive psychosis
53148	Loss of hope for the future
56609	[X]Single episode of masked depression NOS
59386	[X]Single episode vital depression w'out psychotic symptoms
59869	Loss of interest in previously enjoyable activity
73991	[X]Vital depression, recurrent without psychotic symptoms
98252	[X]Major depression, moderately severe

Depression

Medical code	Read term
98346	[X]Major depression, mild
98414	[X]Major depression, severe without psychotic symptoms
98417	[X]Major depression, severe with psychotic symptoms

Diabetes diagnoses

Medical code	Read term	Diabetes category
1038	Insulin dependent diabetes mellitus	Type 1 diabetes mellitus
1549	Type 1 diabetes mellitus	Type 1 diabetes mellitus
1647	Insulin dependent diabetes mellitus	Type 1 diabetes mellitus
6509	Insulin dependent diabetes mellitus with retinopathy	Type 1 diabetes mellitus
6791	Insulin dependent diabetes mellitus - poor control	Type 1 diabetes mellitus
10418	Type 1 diabetes mellitus with nephropathy	Type 1 diabetes mellitus
10692	Type 1 diabetes mellitus with ketoacidosis	Type 1 diabetes mellitus
12455	Type I diabetes mellitus	Type 1 diabetes mellitus
17545	Type I diabetes mellitus with diabetic cataract	Type 1 diabetes mellitus
17858	Type 1 diabetes mellitus	Type 1 diabetes mellitus
18230	Type 1 diabetes mellitus with neuropathic arthropathy	Type 1 diabetes mellitus
18387	Type 1 diabetes mellitus with retinopathy	Type 1 diabetes mellitus
18505	IDDM-Insulin dependent diabetes mellitus	Type 1 diabetes mellitus
18642	Type 1 diabetes mellitus with arthropathy	Type 1 diabetes mellitus
18683	Type 1 diabetes mellitus with ulcer	Type 1 diabetes mellitus
21983	Type 1 diabetes mellitus with renal complications	Type 1 diabetes mellitus
22871	Type 1 diabetes mellitus with exudative maculopathy	Type 1 diabetes mellitus
24423	Type I diabetes mellitus	Type 1 diabetes mellitus
24490	Diabetes mellitus, juvenile type, no mention of complication	Type 1 diabetes mellitus
24694	Insulin dependent diabetes mellitus with mononeuropathy	Type 1 diabetes mellitus
26855	Unstable insulin dependent diabetes mellitus	Type 1 diabetes mellitus
30294	Type 1 diabetes mellitus with persistent microalbuminuria	Type 1 diabetes mellitus
30323	Type 1 diabetes mellitus with persistent proteinuria	Type 1 diabetes mellitus
31310	Insulin dependent diabetes maturity onset	Type 1 diabetes mellitus
32359	Perceived control of insulin-dependent diabetes	Type 1 diabetes mellitus
35288	Type 1 diabetes mellitus - poor control	Type 1 diabetes mellitus
38076	Insulin lipohypertrophy	Type 1 diabetes mellitus
38161	Type I diabetes mellitus with retinopathy	Type 1 diabetes mellitus
39070	Type 1 diabetes mellitus with hypoglycaemic coma	Type 1 diabetes mellitus
39809	Insulin dependent diab mell with neuropathic arthropathy	Type 1 diabetes mellitus
40023	Diabetes mellitus, juvenile type, with hyperosmolar coma	Type 1 diabetes mellitus
40682	Type 1 diabetes mellitus maturity onset	Type 1 diabetes mellitus
40837	Type 1 diabetes mellitus with ketoacidotic coma	Type 1 diabetes mellitus
41049	Type 1 diabetes mellitus with retinopathy	Type 1 diabetes mellitus
41716	Insulin dependent diabetes mellitus with polyneuropathy	Type 1 diabetes mellitus
42567	Diabetes mellitus, juvenile type, with ketoacidotic coma	Type 1 diabetes mellitus
42729	Type I diabetes mellitus with hypoglycaemic coma	Type 1 diabetes mellitus
42831	Type 1 diabetes mellitus with neurological complications	Type 1 diabetes mellitus
43493	Insulin site lipohypertrophy	Type 1 diabetes mellitus
43921	Unstable type 1 diabetes mellitus	Type 1 diabetes mellitus
44260	Insulin dependent diabetes mellitus with diabetic cataract	Type 1 diabetes mellitus
44440	Insulin dependent diabetes mellitus with hypoglycaemic coma	Type 1 diabetes mellitus
44443	Insulin dependent diabetes mellitus with ulcer	Type 1 diabetes mellitus
45276	Insulin dependent diabetes mellitus with multiple complicat	Type 1 diabetes mellitus
45914	Type 1 diabetes mellitus - poor control	Type 1 diabetes mellitus
46301	Type 1 diabetes mellitus with polyneuropathy	Type 1 diabetes mellitus
46850	Type I diabetes mellitus - poor control	Type 1 diabetes mellitus
47582	Type 1 diabetes mellitus with renal complications	Type 1 diabetes mellitus
47649	Type 1 diabetes mellitus with ophthalmic complications	Type 1 diabetes mellitus
47650	Type 1 diabetes mellitus with multiple complications	Type 1 diabetes mellitus
49146	Type I diabetes mellitus with neurological complications	Type 1 diabetes mellitus
49276	Insulin-dependent diabetes mellitus with ophthalmic comps	Type 1 diabetes mellitus
49554	Type 1 diabetes mellitus with diabetic cataract	Type 1 diabetes mellitus
49949	Unstable type I diabetes mellitus	Type 1 diabetes mellitus
50960	Pre-existing diabetes mellitus, insulin-dependent	Type 1 diabetes mellitus
51261	Insulin dependent diabetes mellitus	Type 1 diabetes mellitus
51957	Type I diabetes mellitus with ulcer	Type 1 diabetes mellitus
52104	Insulin dependent diabetes mellitus with multiple complicatn	Type 1 diabetes mellitus
52283	Insulin-dependent diabetes mellitus with neurological comps	Type 1 diabetes mellitus
53200	Diabetes mellitus, juvenile type, with ketoacidosis	Type 1 diabetes mellitus
54008	Type 1 diabetes mellitus with neuropathic arthropathy	Type 1 diabetes mellitus
54600	Unstable insulin dependent diabetes mellitus	Type 1 diabetes mellitus
55239	Type 1 diabetes mellitus with gastroparesis	Type 1 diabetes mellitus
56448	Insulin-dependent diabetes without complication	Type 1 diabetes mellitus
57621	Insulin dependent diabetes mellitus with nephropathy	Type 1 diabetes mellitus
60107	Unstable type I diabetes mellitus	Type 1 diabetes mellitus
60208	Type I diabetes mellitus with neuropathic arthropathy	Type 1 diabetes mellitus
60499	Insulin dependent diabetes mellitus with gangrene	Type 1 diabetes mellitus
61344	Type I diabetes mellitus with renal complications	Type 1 diabetes mellitus
61829	Type 1 diabetes mellitus with neurological complications	Type 1 diabetes mellitus
62209	Type I diabetes mellitus with ketoacidosis	Type 1 diabetes mellitus
62352	Type I diabetes mellitus with arthropathy	Type 1 diabetes mellitus
62613	Type I diabetes mellitus without complication	Type 1 diabetes mellitus
63017	Type I diabetes mellitus maturity onset	Type 1 diabetes mellitus
64446	Insulin dependent diab mell with peripheral angiopathy	Type 1 diabetes mellitus
65616	Insulin dependent diabetes mellitus with arthropathy	Type 1 diabetes mellitus
66145	Type I diabetes mellitus with ketoacidotic coma	Type 1 diabetes mellitus

Diabetes diagnoses

Medical code	Read term	Diabetes category
66872	Type I diabetes mellitus with nephropathy	Type 1 diabetes mellitus
67853	Diabetes mellitus, juvenile, + neurological manifestation	Type 1 diabetes mellitus
68105	Type 1 diabetes mellitus with mononeuropathy	Type 1 diabetes mellitus
68390	Type 1 diabetes mellitus with ulcer	Type 1 diabetes mellitus
68792	Diabetes mellitus, juvenile type, + unspecified complication	Type 1 diabetes mellitus
69043	Dietary advice for type I diabetes	Type 1 diabetes mellitus
69124	IDDM with peripheral circulatory disorder	Type 1 diabetes mellitus
69676	Type 1 diabetes mellitus without complication	Type 1 diabetes mellitus
69748	Diabetes mellitus, juvenile type, + ophthalmic manifestation	Type 1 diabetes mellitus
69993	Type 1 diabetes mellitus with gangrene	Type 1 diabetes mellitus
70448	Diabetes mellitus, juvenile +peripheral circulatory disorder	Type 1 diabetes mellitus
70766	Type 1 diabetes mellitus with hypoglycaemic coma	Type 1 diabetes mellitus
72702	Insulin dependent diabetes mellitus - poor control	Type 1 diabetes mellitus
85660	Diabetes type 1 review	Type 1 diabetes mellitus
91942	Type I diabetes mellitus with multiple complications	Type 1 diabetes mellitus
91943	Type I diabetes mellitus with polyneuropathy	Type 1 diabetes mellitus
93468	Type 1 diabetes mellitus with peripheral angiopathy	Type 1 diabetes mellitus
93875	Insulin dependent diabetes mellitus with retinopathy	Type 1 diabetes mellitus
93878	Type I diabetes mellitus with ulcer	Type 1 diabetes mellitus
93922	Diabetes mellitus, juvenile type, with renal manifestation	Type 1 diabetes mellitus
95343	Type I diabetes mellitus with retinopathy	Type 1 diabetes mellitus
95992	Type I diabetes mellitus without complication	Type 1 diabetes mellitus
96235	Type I diabetes mellitus maturity onset	Type 1 diabetes mellitus
97446	Type 1 diabetes mellitus maturity onset	Type 1 diabetes mellitus
97474	Unstable type 1 diabetes mellitus	Type 1 diabetes mellitus
97849	Insulin dependent diabetes maturity onset	Type 1 diabetes mellitus
97894	Type I diabetes mellitus with exudative maculopathy	Type 1 diabetes mellitus
98071	Insulin-dependent diabetes mellitus with ophthalmic comps	Type 1 diabetes mellitus
98392	Maturity onset diabetes in youth type 1	Type 1 diabetes mellitus
98704	Insulin dependent diabetes mellitus with ulcer	Type 1 diabetes mellitus
99231	Type I diabetes mellitus with mononeuropathy	Type 1 diabetes mellitus
99311	Type I diabetes mellitus with ophthalmic complications	Type 1 diabetes mellitus
99716	Insulin dependent diabetes mellitus with hypoglycaemic coma	Type 1 diabetes mellitus
99719	Insulin-dependent diabetes without complication	Type 1 diabetes mellitus
100770	Insulin dependent diabetes mellitus with diabetic cataract	Type 1 diabetes mellitus
101311	Insulin dependent diabetes mellitus with polyneuropathy	Type 1 diabetes mellitus
101735	Insulin-dependent diabetes mellitus with neurological comps	Type 1 diabetes mellitus
102112	Type I diabetes mellitus with gangrene	Type 1 diabetes mellitus
102163	Insulin dependent diabetes mellitus with nephropathy	Type 1 diabetes mellitus
102620	Type I diabetes mellitus with persistent microalbuminuria	Type 1 diabetes mellitus
102704	Type I diabetic dietary review	Type 1 diabetes mellitus
102740	Type 1 diabetes mellitus with ophthalmic complications	Type 1 diabetes mellitus
506	Non-insulin dependent diabetes mellitus	Type 2 diabetes mellitus
758	Type 2 diabetes mellitus	Type 2 diabetes mellitus
1407	Insulin treated Type 2 diabetes mellitus	Type 2 diabetes mellitus
4513	Non-insulin dependent diabetes mellitus	Type 2 diabetes mellitus
5884	NIDDM - Non-insulin dependent diabetes mellitus	Type 2 diabetes mellitus
8403	Non-insulin dependent diabetes mellitus - poor control	Type 2 diabetes mellitus
12640	Type 2 diabetes mellitus with nephropathy	Type 2 diabetes mellitus
12736	Type 2 diabetes mellitus with gangrene	Type 2 diabetes mellitus
14803	Diabetes mellitus, adult onset, no mention of complication	Type 2 diabetes mellitus
14889	Maturity onset diabetes	Type 2 diabetes mellitus
17262	Non-insulin-dependent diabetes mellitus with retinopathy	Type 2 diabetes mellitus
17859	Type 2 diabetes mellitus	Type 2 diabetes mellitus
18143	Type II diabetes mellitus with arthropathy	Type 2 diabetes mellitus
18209	Type 2 diabetes mellitus with renal complications	Type 2 diabetes mellitus
18219	Type II diabetes mellitus	Type 2 diabetes mellitus
18264	Insulin treated Type II diabetes mellitus	Type 2 diabetes mellitus
18278	Insulin treated Type 2 diabetes mellitus	Type 2 diabetes mellitus
18390	Type 2 diabetes mellitus with persistent microalbuminuria	Type 2 diabetes mellitus
18425	Type 2 diabetes mellitus with polyneuropathy	Type 2 diabetes mellitus
18496	Type 2 diabetes mellitus with retinopathy	Type 2 diabetes mellitus
18777	Type 2 diabetes mellitus with renal complications	Type 2 diabetes mellitus
22884	Type II diabetes mellitus	Type 2 diabetes mellitus
24458	Type II diabetes mellitus - poor control	Type 2 diabetes mellitus
24693	Non-insulin dependent diabetes mellitus with arthropathy	Type 2 diabetes mellitus
24836	Type 2 diabetes mellitus with nephropathy	Type 2 diabetes mellitus
25041	Dietary advice for type II diabetes	Type 2 diabetes mellitus
25591	Type 2 diabetes mellitus with exudative maculopathy	Type 2 diabetes mellitus
25627	Type 2 diabetes mellitus - poor control	Type 2 diabetes mellitus
26054	Type 2 diabetes mellitus with persistent proteinuria	Type 2 diabetes mellitus
29979	Non-insulin-dependent diabetes mellitus without complication	Type 2 diabetes mellitus
32627	Type 2 diabetes mellitus with ketoacidosis	Type 2 diabetes mellitus
33807	Diabetes mellitus, adult with gangrene	Type 2 diabetes mellitus
34268	Type 2 diabetes mellitus with neurological complications	Type 2 diabetes mellitus
34450	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	Type 2 diabetes mellitus
34912	Non-insulin dependent diabetes mellitus with ulcer	Type 2 diabetes mellitus

Diabetes diagnoses

Medical code	Read term	Diabetes category
35105	Diabetes mellitus, adult onset, with renal manifestation	Type 2 diabetes mellitus
35385	Type 2 diabetes mellitus with neuropathic arthropathy	Type 2 diabetes mellitus
36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	Type 2 diabetes mellitus
36695	Diabetes mellitus autosomal dominant type 2	Type 2 diabetes mellitus
37648	Insulin treated non-insulin dependent diabetes mellitus	Type 2 diabetes mellitus
37806	Type 2 diabetes mellitus with peripheral angiopathy	Type 2 diabetes mellitus
39317	Diabetes mellitus, adult onset, + neurological manifestation	Type 2 diabetes mellitus
40401	Non-insulin dependent diabetes mellitus with gangrene	Type 2 diabetes mellitus
40962	Non-insulin dependent d m with neuropathic arthropathy	Type 2 diabetes mellitus
41389	Diabetes mellitus, adult onset, + ophthalmic manifestation	Type 2 diabetes mellitus
42762	Type 2 diabetes mellitus with retinopathy	Type 2 diabetes mellitus
43139	Diabetes mellitus, adult onset, with hyperosmolar coma	Type 2 diabetes mellitus
43227	Type II diabetes mellitus with multiple complications	Type 2 diabetes mellitus
43785	Non-insulin dependent diabetes mellitus with hypoglyca coma	Type 2 diabetes mellitus
44779	Type 2 diabetes mellitus with diabetic cataract	Type 2 diabetes mellitus
44982	Type 2 diabetes mellitus with diabetic cataract	Type 2 diabetes mellitus
45467	Non-insulin dependent diabetes mellitus with polyneuropathy	Type 2 diabetes mellitus
45913	Type 2 diabetes mellitus - poor control	Type 2 diabetes mellitus
45919	Type 2 diabetes mellitus with neurological complications	Type 2 diabetes mellitus
46150	Type 2 diabetes mellitus with gangrene	Type 2 diabetes mellitus
46624	Maturity onset diabetes in youth	Type 2 diabetes mellitus
46917	Type 2 diabetes mellitus with hypoglycaemic coma	Type 2 diabetes mellitus
47315	Type II diabetes mellitus - poor control	Type 2 diabetes mellitus
47321	Type 2 diabetes mellitus with ophthalmic complications	Type 2 diabetes mellitus
47409	Type II diabetes mellitus with polyneuropathy	Type 2 diabetes mellitus
47816	Type II diabetes mellitus with neuropathic arthropathy	Type 2 diabetes mellitus
47954	Type 2 diabetes mellitus without complication	Type 2 diabetes mellitus
48192	Type II diabetes mellitus with diabetic cataract	Type 2 diabetes mellitus
49074	Type 2 diabetes mellitus with ulcer	Type 2 diabetes mellitus
49655	Type II diabetes mellitus with retinopathy	Type 2 diabetes mellitus
49869	Type 2 diabetes mellitus with arthropathy	Type 2 diabetes mellitus
50225	Type II diabetes mellitus with renal complications	Type 2 diabetes mellitus
50429	Non-insulin-dependent diabetes mellitus with ophthalm comps	Type 2 diabetes mellitus
50527	Type II diabetes mellitus with polyneuropathy	Type 2 diabetes mellitus
50609	Pre-existing diabetes mellitus, non-insulin-dependent	Type 2 diabetes mellitus
50813	Type II diabetes mellitus with mononeuropathy	Type 2 diabetes mellitus
51756	Type 2 diabetes mellitus with ketoacidotic coma	Type 2 diabetes mellitus
52303	Non-insulin-dependent diabetes mellitus with renal comps	Type 2 diabetes mellitus
53392	Type II diabetes mellitus without complication	Type 2 diabetes mellitus
54212	Non-insulin-dependent d m with peripheral angiopath	Type 2 diabetes mellitus
54856	Diabetes mellitus, adult onset, with ketoacidosis	Type 2 diabetes mellitus
54899	Type II diabetes mellitus with peripheral angiopathy	Type 2 diabetes mellitus
55075	Type II diabetes mellitus with ulcer	Type 2 diabetes mellitus
55842	Non-insulin-dependent diabetes mellitus with neuro comps	Type 2 diabetes mellitus
56268	Type II diabetes mellitus with hypoglycaemic coma	Type 2 diabetes mellitus
56803	NIDDM with peripheral circulatory disorder	Type 2 diabetes mellitus
57278	Type II diabetes mellitus with renal complications	Type 2 diabetes mellitus
58604	Type II diabetes mellitus with retinopathy	Type 2 diabetes mellitus
59253	Type 2 diabetes mellitus with arthropathy	Type 2 diabetes mellitus
59365	Non-insulin dependent diabetes mellitus with nephropathy	Type 2 diabetes mellitus
59725	Type II diabetes mellitus with ophthalmic complications	Type 2 diabetes mellitus
59991	Maturity onset diabetes in youth type 2	Type 2 diabetes mellitus
60699	Type 2 diabetes mellitus with peripheral angiopathy	Type 2 diabetes mellitus
60796	Type II diabetes mellitus with persistent proteinuria	Type 2 diabetes mellitus
61071	Type 2 diabetes mellitus with hypoglycaemic coma	Type 2 diabetes mellitus
62107	Type II diabetes mellitus with gangrene	Type 2 diabetes mellitus
62146	Non-insulin-dependent diabetes mellitus with multiple comps	Type 2 diabetes mellitus
62674	Type 2 diabetes mellitus with mononeuropathy	Type 2 diabetes mellitus
63357	Diabetes mellitus, adult, + peripheral circulatory disorder	Type 2 diabetes mellitus
63371	Diabetes mellitus, adult, + other specified manifestation	Type 2 diabetes mellitus
63690	Type 2 diabetes mellitus with gastroparesis	Type 2 diabetes mellitus
63762	Diabetes mellitus, adult onset, + unspecified complication	Type 2 diabetes mellitus
64571	Type II diabetes mellitus with nephropathy	Type 2 diabetes mellitus
64668	Insulin treated Type II diabetes mellitus	Type 2 diabetes mellitus
65267	Type 2 diabetes mellitus with multiple complications	Type 2 diabetes mellitus
65704	Type 2 diabetes mellitus with ulcer	Type 2 diabetes mellitus
66965	Type 2 diabetes mellitus with neuropathic arthropathy	Type 2 diabetes mellitus
67905	Type II diabetes mellitus with neurological complications	Type 2 diabetes mellitus
68843	Diabetes mellitus, adult onset, with ketoacidotic coma	Type 2 diabetes mellitus
69278	Non-insulin depend diabetes mellitus with diabetic cataract	Type 2 diabetes mellitus
70316	Type 2 diabetes mellitus with ophthalmic complications	Type 2 diabetes mellitus
72320	Non-insulin dependent diabetes mellitus with mononeuropathy	Type 2 diabetes mellitus
83532	Diabetes type 2 review	Type 2 diabetes mellitus
85991	Type II diabetes mellitus with persistent microalbuminuria	Type 2 diabetes mellitus
91646	Type II diabetes mellitus with ulcer	Type 2 diabetes mellitus
93727	Type II diabetes mellitus with diabetic cataract	Type 2 diabetes mellitus
95351	Type II diabetes mellitus with mononeuropathy	Type 2 diabetes mellitus

Diabetes diagnoses

Medical code	Read term	Diabetes category
95636	Latent autoimmune diabetes mellitus in adult	Type 2 diabetes mellitus
98616	Type II diabetes mellitus with neurological complications	Type 2 diabetes mellitus
98723	Type II diabetes mellitus with hypoglycaemic coma	Type 2 diabetes mellitus
100964	Type II diabetes mellitus with ophthalmic complications	Type 2 diabetes mellitus
101801	Type II diabetic dietary review	Type 2 diabetes mellitus
102201	Type II diabetes mellitus with nephropathy	Type 2 diabetes mellitus
102611	Type 2 diabetic dietary review	Type 2 diabetes mellitus
711	Diabetes mellitus	Diabetes mellitus, Type not specified
1323	Diabetic retinopathy	Diabetes mellitus, Type not specified
1682	Diabetes mellitus with ketoacidosis	Diabetes mellitus, Type not specified
1684	Diabetic on oral treatment	Diabetes mellitus, Type not specified
2340	Diabetic amyotrophy	Diabetes mellitus, Type not specified
2342	Diabetic neuropathy	Diabetes mellitus, Type not specified
2378	Diabetic - poor control	Diabetes mellitus, Type not specified
2471	Nephrotic syndrome in diabetes mellitus	Diabetes mellitus, Type not specified
2475	Diabetic nephropathy	Diabetes mellitus, Type not specified
2478	Brittle diabetes	Diabetes mellitus, Type not specified
2986	Preproliferative diabetic retinopathy	Diabetes mellitus, Type not specified
3286	Proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
3837	Diabetic maculopathy	Diabetes mellitus, Type not specified
5002	Diabetic polyneuropathy	Diabetes mellitus, Type not specified
6125	Diabetic annual review	Diabetes mellitus, Type not specified
6430	Attending diabetes clinic	Diabetes mellitus, Type not specified
7059	Admit diabetic emergency	Diabetes mellitus, Type not specified
7069	Background diabetic retinopathy	Diabetes mellitus, Type not specified
7328	Cellulitis in diabetic foot	Diabetes mellitus, Type not specified
7563	Diabetic on diet only	Diabetes mellitus, Type not specified
7795	Diabetes mellitus with neuropathy	Diabetes mellitus, Type not specified
8836	Diabetes management plan given	Diabetes mellitus, Type not specified
8842	Diabetic on insulin	Diabetes mellitus, Type not specified
9013	Unstable diabetes	Diabetes mellitus, Type not specified
9835	O/E - diabetic maculopathy present both eyes	Diabetes mellitus, Type not specified
9881	Mixed diabetic ulcer - foot	Diabetes mellitus, Type not specified
9958	Hb. A1C - diabetic control	Diabetes mellitus, Type not specified
10098	Other specified diabetes mellitus with other spec comps	Diabetes mellitus, Type not specified
10099	Advanced diabetic maculopathy	Diabetes mellitus, Type not specified
10642	Dietary advice for diabetes mellitus	Diabetes mellitus, Type not specified
10659	Diabetic cataract	Diabetes mellitus, Type not specified
10755	Non proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
10977	Diabetic peripheral neuropathy screening	Diabetes mellitus, Type not specified
11018	Diabetic retinopathy 12 month review	Diabetes mellitus, Type not specified
11047	Conversion to insulin	Diabetes mellitus, Type not specified
11094	Under care of diabetic foot screener	Diabetes mellitus, Type not specified
11129	O/E - left eye background diabetic retinopathy	Diabetes mellitus, Type not specified
11433	O/E - right eye background diabetic retinopathy	Diabetes mellitus, Type not specified
11471	Diabetes medication review	Diabetes mellitus, Type not specified
11599	Pan retinal photocoagulation for diabetes	Diabetes mellitus, Type not specified
11626	Diabetic retinopathy NOS	Diabetes mellitus, Type not specified
11663	Neuropathic diabetic ulcer - foot	Diabetes mellitus, Type not specified
11677	Refer to diabetic foot screener	Diabetes mellitus, Type not specified
11930	Under care of diabetes specialist nurse	Diabetes mellitus, Type not specified
12213	Patient on maximal tolerated therapy for diabetes	Diabetes mellitus, Type not specified
12247	Diabetic foot examination not indicated	Diabetes mellitus, Type not specified
12262	Diabetic retinopathy screening refused	Diabetes mellitus, Type not specified
12307	Diabetes care by hospital only	Diabetes mellitus, Type not specified
12506	Diabetes: practice programme	Diabetes mellitus, Type not specified
12675	Diabetes: shared care programme	Diabetes mellitus, Type not specified
12682	Patient offered diabetes structured education programme	Diabetes mellitus, Type not specified
12703	Education score - diabetes	Diabetes mellitus, Type not specified
13057	Health education - diabetes	Diabetes mellitus, Type not specified
13069	Has seen dietician - diabetes	Diabetes mellitus, Type not specified
13071	Diabetic - good control	Diabetes mellitus, Type not specified
13074	Diabetic diet	Diabetes mellitus, Type not specified
13078	Diabetic weight reducing diet	Diabetes mellitus, Type not specified
13097	O/E - right eye proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
13099	O/E - right eye preproliferative diabetic retinopathy	Diabetes mellitus, Type not specified
13100	O/E - no right diabetic retinopathy	Diabetes mellitus, Type not specified
13101	O/E - left eye proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
13102	O/E - right eye diabetic maculopathy	Diabetes mellitus, Type not specified
13103	O/E - left eye preproliferative diabetic retinopathy	Diabetes mellitus, Type not specified
13104	O/E - no left diabetic retinopathy	Diabetes mellitus, Type not specified
13108	O/E - left eye diabetic maculopathy	Diabetes mellitus, Type not specified
13279	Other specified diabetes mellitus with renal complications	Diabetes mellitus, Type not specified
14049	Hb. A1C - diabetic control NOS	Diabetes mellitus, Type not specified
14050	HbA1 - diabetic control	Diabetes mellitus, Type not specified
15690	Diabetes mellitus with ketoacidotic coma	Diabetes mellitus, Type not specified
16230	Diabetes mellitus with neurological manifestation	Diabetes mellitus, Type not specified

Diabetes diagnoses

Medical code	Read term	Diabetes category
16490	Diabetic treatment changed	Diabetes mellitus, Type not specified
16491	Diabetes mellitus with polyneuropathy	Diabetes mellitus, Type not specified
16502	Diabetes mellitus with renal manifestation	Diabetes mellitus, Type not specified
16881	[V]Dietary counselling in diabetes mellitus	Diabetes mellitus, Type not specified
17067	Autonomic neuropathy due to diabetes	Diabetes mellitus, Type not specified
17095	O/E - Right diabetic foot at risk	Diabetes mellitus, Type not specified
17247	Diabetic mononeuritis NOS	Diabetes mellitus, Type not specified
17313	Diabetic iritis	Diabetes mellitus, Type not specified
17817	Subcutaneous injection of insulin	Diabetes mellitus, Type not specified
17869	Diabetic-uncooperative patient	Diabetes mellitus, Type not specified
17886	Diabetic - follow-up default	Diabetes mellitus, Type not specified
18056	Foot abnormality - diabetes related	Diabetes mellitus, Type not specified
18142	Diabetic cheiroarthropathy	Diabetes mellitus, Type not specified
18167	Annual diabetic blood test	Diabetes mellitus, Type not specified
18311	Diabetic retinopathy screening	Diabetes mellitus, Type not specified
18662	Diabetic retinopathy 6 month review	Diabetes mellitus, Type not specified
18747	Diabetic retinopathy screening not indicated	Diabetes mellitus, Type not specified
19381	Referral to diabetic eye clinic	Diabetes mellitus, Type not specified
19739	Diabetic retinopathy screening offered	Diabetes mellitus, Type not specified
20696	Injection sites - diabetic	Diabetes mellitus, Type not specified
21482	Diabetes mellitus with hyperosmolar coma	Diabetes mellitus, Type not specified
21689	Diabetic lipid lowering diet	Diabetes mellitus, Type not specified
22023	Diabetic - poor control NOS	Diabetes mellitus, Type not specified
22573	Diabetes mellitus NOS with neurological manifestation	Diabetes mellitus, Type not specified
22823	Diabetic foot examination	Diabetes mellitus, Type not specified
22967	Retinal abnormality - diabetes related	Diabetes mellitus, Type not specified
23479	Bronzed diabetes	Diabetes mellitus, Type not specified
24327	Ischaemic ulcer diabetic foot	Diabetes mellitus, Type not specified
24363	Diabetic stabilisation	Diabetes mellitus, Type not specified
24571	Asymptomatic diabetic neuropathy	Diabetes mellitus, Type not specified
25636	Diabetic diet - poor compliance	Diabetes mellitus, Type not specified
26604	Diabetic diet - good compliance	Diabetes mellitus, Type not specified
26605	Attended diabetes structured education programme	Diabetes mellitus, Type not specified
26664	O/E - Left diabetic foot at risk	Diabetes mellitus, Type not specified
26666	O/E - Right diabetic foot at low risk	Diabetes mellitus, Type not specified
26667	O/E - Left diabetic foot at low risk	Diabetes mellitus, Type not specified
27891	Diabetic Charcot arthropathy	Diabetes mellitus, Type not specified
27921	Foot abnormality - diabetes related	Diabetes mellitus, Type not specified
28769	Diabetic on insulin and oral treatment	Diabetes mellitus, Type not specified
28856	Transition of diabetes care options discussed	Diabetes mellitus, Type not specified
28873	Diabetic 6 month review	Diabetes mellitus, Type not specified
29041	Date diabetic treatment start	Diabetes mellitus, Type not specified
30247	Adverse reaction to insulins	Diabetes mellitus, Type not specified
30477	High risk proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
31053	[D]Widespread diabetic foot gangrene	Diabetes mellitus, Type not specified
31156	O/E - Left diabetic foot at moderate risk	Diabetes mellitus, Type not specified
31157	O/E - Right diabetic foot at moderate risk	Diabetes mellitus, Type not specified
31171	O/E - Right diabetic foot at high risk	Diabetes mellitus, Type not specified
31172	O/E - Left diabetic foot at high risk	Diabetes mellitus, Type not specified
31790	Polyneuropathy in diabetes	Diabetes mellitus, Type not specified
32403	Diabetes mellitus with gangrene	Diabetes mellitus, Type not specified
32556	Diabetes with gangrene	Diabetes mellitus, Type not specified
32619	Patient diabetes education review	Diabetes mellitus, Type not specified
33254	Diabetes mellitus with ophthalmic manifestation	Diabetes mellitus, Type not specified
33343	Diabetes mellitus with other specified manifestation	Diabetes mellitus, Type not specified
34152	Diabetic peripheral angiopathy	Diabetes mellitus, Type not specified
34283	Diabetes mellitus NOS with ophthalmic manifestation	Diabetes mellitus, Type not specified
34528	Diabetes well being questionnaire	Diabetes mellitus, Type not specified
35107	Diabetes mellitus with nephropathy NOS	Diabetes mellitus, Type not specified
35116	O/E - Left diabetic foot - ulcerated	Diabetes mellitus, Type not specified
35316	O/E - Right diabetic foot - ulcerated	Diabetes mellitus, Type not specified
35321	Non-urgent diabetic admission	Diabetes mellitus, Type not specified
35383	Diabetic patient unsuitable for digital retinal photography	Diabetes mellitus, Type not specified
35399	Diabetes mellitus with peripheral circulatory disorder	Diabetes mellitus, Type not specified
35785	Chronic painful diabetic neuropathy	Diabetes mellitus, Type not specified
36798	Continuous subcutaneous infusion of insulin	Diabetes mellitus, Type not specified
37315	Diabetic mononeuropathy	Diabetes mellitus, Type not specified
38078	Understands diet - diabetes	Diabetes mellitus, Type not specified
38130	Diabetes wellbeing questionnaire	Diabetes mellitus, Type not specified
38617	Other specified diabetes mellitus with ketoacidosis	Diabetes mellitus, Type not specified
38986	Diabetes mellitus with no mention of complication	Diabetes mellitus, Type not specified
39420	Myasthenic syndrome due to diabetic amyotrophy	Diabetes mellitus, Type not specified
41686	[X]Other specified diabetes mellitus	Diabetes mellitus, Type not specified
42505	Diabetes mellitus NOS with ketoacidosis	Diabetes mellitus, Type not specified
43453	Diabetes mellitus autosomal dominant	Diabetes mellitus, Type not specified
43857	Lipoatrophic diabetes mellitus	Diabetes mellitus, Type not specified
43951	Diabetic - cooperative patient	Diabetes mellitus, Type not specified

Diabetes diagnoses

Medical code	Read term	Diabetes category
44033	Diabetic mononeuritis multiplex	Diabetes mellitus, Type not specified
44312	Informed dissent for diabetes national audit	Diabetes mellitus, Type not specified
45250	Under care of diabetic liaison nurse	Diabetes mellitus, Type not specified
45491	Diabetes mellitus with unspecified complication	Diabetes mellitus, Type not specified
46290	Other specified diabetes mellitus with multiple comps	Diabetes mellitus, Type not specified
46577	Diabetes: shared care in pregnancy - diabetol and obstet	Diabetes mellitus, Type not specified
47032	Diabetes care plan agreed	Diabetes mellitus, Type not specified
47144	O/E - diabetic maculopathy absent both eyes	Diabetes mellitus, Type not specified
47328	O/E - right eye stable treated prolif diabetic retinopathy	Diabetes mellitus, Type not specified
47341	Diabetic crisis monitoring	Diabetes mellitus, Type not specified
47370	Diabetology D.V. done	Diabetes mellitus, Type not specified
47377	Other specified diabetes mellitus with ophthalmic complicatn	Diabetes mellitus, Type not specified
47584	Advanced diabetic retinal disease	Diabetes mellitus, Type not specified
48078	Acute painful diabetic neuropathy	Diabetes mellitus, Type not specified
48310	[V]Admitted for commencement of insulin	Diabetes mellitus, Type not specified
49640	O/E - left chronic diabetic foot ulcer	Diabetes mellitus, Type not specified
49884	Diabetic pre-pregnancy counselling	Diabetes mellitus, Type not specified
50175	Diabetic foot risk assessment	Diabetes mellitus, Type not specified
50972	Diabetes mellitus NOS with no mention of complication	Diabetes mellitus, Type not specified
51939	[V]Admitted for conversion to insulin	Diabetes mellitus, Type not specified
52041	O/E - left eye stable treated prolif diabetic retinopathy	Diabetes mellitus, Type not specified
52212	[X]Diabetes mellitus	Diabetes mellitus, Type not specified
52237	Patient held diabetic record issued	Diabetes mellitus, Type not specified
52630	O/E - sight threatening diabetic retinopathy	Diabetes mellitus, Type not specified
53238	Diabetic drug side effects	Diabetes mellitus, Type not specified
53630	Insulin coma	Diabetes mellitus, Type not specified
53634	[D]Gangrene of toe in diabetic	Diabetes mellitus, Type not specified
54601	Under care of diabetologist	Diabetes mellitus, Type not specified
55431	Pre-existing diabetes mellitus, unspecified	Diabetes mellitus, Type not specified
57333	Diabetic cheiropathy	Diabetes mellitus, Type not specified
57389	Patient consent given for addition to diabetic register	Diabetes mellitus, Type not specified
57723	Referral to diabetic register	Diabetes mellitus, Type not specified
59288	Other specified diabetes mellitus with coma	Diabetes mellitus, Type not specified
59903	Diabetic amyotrophy	Diabetes mellitus, Type not specified
61021	Diabetic digital retinopathy screening offered	Diabetes mellitus, Type not specified
61210	Adverse reaction to insulins and antidiabetic agents NOS	Diabetes mellitus, Type not specified
61461	Informed consent for diabetes national audit	Diabetes mellitus, Type not specified
61520	Iatrogenic hyperinsulinism	Diabetes mellitus, Type not specified
61523	Other specified diabetes mellitus with neurological comps	Diabetes mellitus, Type not specified
61670	Diab mellit insulin-glucose infus acute myocardial infarct	Diabetes mellitus, Type not specified
62384	O/E - right chronic diabetic foot ulcer	Diabetes mellitus, Type not specified
63364	[X] Adverse reaction to insulins	Diabetes mellitus, Type not specified
63412	Diabetes clinical management plan	Diabetes mellitus, Type not specified
64142	Referral for diabetic retinopathy screening	Diabetes mellitus, Type not specified
64283	Other specified diabetes mellitus with unspecified comps	Diabetes mellitus, Type not specified
64357	Diabetes mellitus NOS with unspecified complication	Diabetes mellitus, Type not specified
64449	Unspecified diabetes mellitus with multiple complications	Diabetes mellitus, Type not specified
65025	Diabetes mellitus NOS with peripheral circulatory disorder	Diabetes mellitus, Type not specified
65062	Diabetes mellitus NOS with ketoacidotic coma	Diabetes mellitus, Type not specified
65463	High risk non proliferative diabetic retinopathy	Diabetes mellitus, Type not specified
65684	[X] Adverse reaction to insulins and antidiabetic agents	Diabetes mellitus, Type not specified
66274	Insulin needles changed for each injection	Diabetes mellitus, Type not specified
67664	Education score - diabetes	Diabetes mellitus, Type not specified
68546	Diabetes clinic satisfaction questionnaire	Diabetes mellitus, Type not specified
68818	DTSQ - Diabetes treatment satisfaction questionnaire	Diabetes mellitus, Type not specified
68928	Adverse reaction to insulins and antidiabetic agents	Diabetes mellitus, Type not specified
69152	Insulin needles changed less than once a day	Diabetes mellitus, Type not specified
70821	Diabetes mellitus NOS with other specified manifestation	Diabetes mellitus, Type not specified
72345	Diabetes mellitus NOS with hyperosmolar coma	Diabetes mellitus, Type not specified
83485	Insulin dose changed	Diabetes mellitus, Type not specified
90301	Insulin needles changed daily	Diabetes mellitus, Type not specified
91164	CSQ - Diabetes clinic satisfaction questionnaire	Diabetes mellitus, Type not specified
93390	Attended DAFNE diabetes structured education programme	Diabetes mellitus, Type not specified
93491	DAFNE diabetes structured education programme completed	Diabetes mellitus, Type not specified
93529	DESMOND diabetes structured education programme completed	Diabetes mellitus, Type not specified
93631	XPERT diabetes structured education programme completed	Diabetes mellitus, Type not specified
94011	Attended XPERT diabetes structured education programme	Diabetes mellitus, Type not specified
94186	Diabetes structured education programme completed	Diabetes mellitus, Type not specified
94699	Diabetes treatment satisfaction questionnaire	Diabetes mellitus, Type not specified
95994	Diabetic foot screen	Diabetes mellitus, Type not specified
96010	Insulin treatment initiated	Diabetes mellitus, Type not specified
96143	Insulin initiation - enhanced services administration	Diabetes mellitus, Type not specified
97824	DWBQ - Diabetes wellbeing questionnaire	Diabetes mellitus, Type not specified
98954	Diabetes treatment satisfaction questionnaire	Diabetes mellitus, Type not specified
99628	[X]Glomerular disorders in diabetes mellitus	Diabetes mellitus, Type not specified
100033	[X] Adverse reaction to insulins and antidiabetic agents NOS	Diabetes mellitus, Type not specified
100292	[X]Unspecified diabetes mellitus with renal complications	Diabetes mellitus, Type not specified

Diabetes diagnoses

Medical code	Read term	Diabetes category
100436	Education in self management of diabetes	Diabetes mellitus, Type not specified
101177	Diabetic dietary review	Diabetes mellitus, Type not specified
101728	Diabetic on subcutaneous treatment	Diabetes mellitus, Type not specified
101881	Impaired vision due to diabetic retinopathy	Diabetes mellitus, Type not specified
102767	Pre-conception advice for diabetes mellitus	Diabetes mellitus, Type not specified
608	Follow-up diabetic assessment	Possible diabetes
2379	Seen in diabetic clinic	Possible diabetes
3550	Diabetic monitoring	Possible diabetes
7777	Referral to diabetologist	Possible diabetes
8306	Referral to diabetes nurse	Possible diabetes
8414	Pt advised re diabetic diet	Possible diabetes
8618	Seen by diabetic liaison nurse	Possible diabetes
9145	DNA - Did not attend diabetic clinic	Possible diabetes
9897	Diabetes monitoring admin.	Possible diabetes
9974	Seen in diabetic eye clinic	Possible diabetes
10824	Seen in diabetic foot clinic	Possible diabetes
11041	Excepted from diabetes qual indicators: Patient unsuitable	Possible diabetes
11348	Excepted from diabetes quality indicators: Informed dissent	Possible diabetes
11977	Referral to diabetes nurse	Possible diabetes
12030	Diabetes monitoring 3rd letter	Possible diabetes
12225	Refer, diabetic liaison nurse	Possible diabetes
12483	Advice about blood glucose control	Possible diabetes
12507	Seen by diabetic liaison nurse	Possible diabetes
13067	Diabetic monitoring NOS	Possible diabetes
13070	Initial diabetic assessment	Possible diabetes
13191	Diabetes clinic administration	Possible diabetes
13192	Diabetes monitor. check done	Possible diabetes
13194	Diabetes monitoring 1st letter	Possible diabetes
13195	Diabetes monitoring 2nd letter	Possible diabetes
13196	Fundoscopy - diabetic check	Possible diabetes
13197	Attends diabetes monitoring	Possible diabetes
13678	Referral to diabetic liaison nurse	Possible diabetes
17478	Self monitoring of blood glucose	Possible diabetes
17846	Self monitoring of urine glucose	Possible diabetes
18824	Diabetic foot examination declined	Possible diabetes
20900	Diabetes monitored	Possible diabetes
22130	Diabetes monitoring default	Possible diabetes
26603	Refuses diabetes monitoring	Possible diabetes
28574	Exception reporting: diabetes quality indicators	Possible diabetes
30648	Did not attend diabetic retinopathy clinic	Possible diabetes
31141	Diabetes monitor.phone invite	Possible diabetes
31240	Diabetes monitor.verbal invite	Possible diabetes
31241	Diabetes monitoring admin.NOS	Possible diabetes
32739	Seen in community diabetes specialist clinic	Possible diabetes
32770	Glucose tol. test diabetic	Possible diabetes
34541	Private referral to diabetologist	Possible diabetes
36669	Diabetic monitoring not required	Possible diabetes
38103	Seen in diabetic nurse consultant clinic	Possible diabetes
38129	Seen in community diabetic specialist nurse clinic	Possible diabetes
42217	Self monitoring of blood and urine glucose	Possible diabetes
46521	Seen by diabetologist	Possible diabetes
47011	Referral to diabetes structured education programme	Possible diabetes
47058	Discharged from care of diabetes specialist nurse	Possible diabetes
50937	Referral to diabetes preconception counselling clinic	Possible diabetes
55123	Date diabetic treatment stopp.	Possible diabetes
58133	Discharge by diabetic liaison nurse	Possible diabetes
58159	Insulin therapy declined	Possible diabetes
58639	Patient held diabetic record declined	Possible diabetes
61470	Diabetic monitoring - higher risk albumin excretion	Possible diabetes
66475	Diabetic monitoring - lower risk albumin excretion	Possible diabetes
69163	Referral to multidisciplinary diabetic clinic	Possible diabetes
82474	Referral to community diabetes specialist nurse	Possible diabetes
93657	Referral to DESMOND diabetes structured education programme	Possible diabetes
93704	Referral to DAFNE diabetes structured education programme	Possible diabetes
93854	Diabetes structured education programme declined	Possible diabetes
93870	Referral to XPERT diabetes structured education programme	Possible diabetes
94330	Referral to diabetes special interest general practitioner	Possible diabetes
94955	Did not attend XPERT diabetes structured education programme	Possible diabetes
94956	Did not complete XPERT diabetes structured education program	Possible diabetes
95093	Did not complete DESMOND diabetes structured educat program	Possible diabetes
95094	Did not complete diabetes structured education programme	Possible diabetes
95159	Did not attend DESMOND diabetes structured education program	Possible diabetes
95553	Did not attend diabetes structured education programme	Possible diabetes
95813	Seen in multidisciplinary diabetic clinic	Possible diabetes
97281	Seen by general practitioner special interest in diabetes	Possible diabetes
97809	Did not complete DAFNE diabetes structured education program	Possible diabetes
99277	Did not attend DAFNE diabetes structured education programme	Possible diabetes

Diabetes diagnoses

Medical code	Read term	Diabetes category
100422	Discharged from diabetes shared care programme	Possible diabetes
100791	Insulin treatment stopped	Possible diabetes
101190	Declined consent for diabetes year of care programme	Possible diabetes
101455	Diabetes monitor invitation by SMS (short message service)	Possible diabetes
101456	Diabetic dietary review declined	Possible diabetes
101834	Excepted from diabetes qual indicators: service unavailable	Possible diabetes
102316	Suspected diabetes mellitus	Possible diabetes
102490	Diabetic assessment of erectile dysfunction	Possible diabetes

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
23	metformin tablets 500mg	Oral anti-diabetics	*
32	gliclazide tablets 80mg	Oral anti-diabetics	
93	metformin tablets 850mg	Oral anti-diabetics	*
321	insulin human actrapid (neutral) 40 i/u inj	Insulin	
322	ZERIDAME SR tablets 150mg [ACTAVIS]	Insulin	
469	rosiglitazone tablets 4mg	Oral anti-diabetics	
547	glipizide tablets 2.5mg	Oral anti-diabetics	
548	pioglitazone tablets 15mg	Oral anti-diabetics	
735	metformin oral suspension 100mg/ml	Oral anti-diabetics	*
1253	chlorpropamide tablets 100mg	Oral anti-diabetics	
1254	glibenclamide tablets 5mg	Oral anti-diabetics	
1587	monotard injection 100 units/ml [novo]	Insulin	
1588	actrapid injection 100 iu/ml [novo]	Insulin	
1592	actrapid penfill 100 iu/ml [novo]	Insulin	
1593	insulatard penfill 100 iu/ml [novo]	Insulin	
1594	actrapid novolet 100 iu/ml [novo]	Insulin	
1595	insulatard novolet 100 iu/ml [novo]	Insulin	
1643	Herpes zoster with meningitis	Insulin	
1645	insulin novo actrapid mc 100 i/u inj	Insulin	
1649	human actraphane injection 100 iu/ml [novo]	Insulin	
1805	mixtard 30/70 injection 100 units/ml [novo]	Insulin	
1806	penmix 30/70 penfill injection 100 iu/ml [novo]	Insulin	
1839	insulin humulin i (isophane) 100 i/u inj	Insulin	
1840	humulin s injection 100 units/ml [lilly]	Insulin	
1842	pork velosulin injection 100 units/ml [novo]	Insulin	
1843	pork insulatard vial injection suspension 100 units/ml [novo]	Insulin	
1844	ultratard injection 100 units/ml [novo]	Insulin	
1847	chlorpropamide tablets 250mg	Oral anti-diabetics	
1886	insulatard ge injection 100 iu/ml [novo]	Insulin	
1964	diamicron tablets 80mg [servier]	Oral anti-diabetics	
1965	tolbutamide tablets 500mg	Oral anti-diabetics	
2219	glibenclamide tablets 2.5mg	Oral anti-diabetics	
2220	penmix 20/80 pen [novo]	Insulin	
2221	mixtard 30 novolet 100 iu/ml [novo]	Insulin	
2373	insulin human velosulin 100 i/u inj	Insulin	
2454	mixtard 30 penfill 100 iu/ml [novo]	Insulin	
2455	mixtard 20 novolet 100 iu/ml [novo]	Insulin	
2456	mixtard 10 novolet 100 iu/ml [novo]	Insulin	
2459	pork mixtard 30 vial injection suspension 100 units/ml [novo]	Insulin	
2808	insulin lentard inj	Insulin	
2812	mixtard 40 novolet 100 iu/ml [novo]	Insulin	
2928	metformin hcl 850 mg tab	Oral anti-diabetics	*
2929	mixtard 30 ge injection 100 iu/ml [novo]	Insulin	
3252	metformin hcl 500 mg tab	Oral anti-diabetics	*
3396	penmix 10/90 penfill penfill [novo]	Insulin	
3439	penmix 10/90 pen [novo]	Insulin	
3550	mixtard 40 penfill 100 iu/ml [novo]	Insulin	
3551	mixtard 20 penfill 100 iu/ml [novo]	Insulin	
4093	humulin m2 injection 100 units/ml [lilly]	Insulin	
4129	insulin soluble porcine injection 100 units/ml	Insulin	
4163	rapitard mc injection 100 units/ml [novo]	Insulin	
4198	humulin m3 injection 100 units/ml [lilly]	Insulin	
4199	humulin m1 injection 100 units/ml [lilly]	Insulin	
4247	insulin isophane porcine injection 100 units/ml	Insulin	
4248	insulin novo ultratard mc 100 i/u inj	Insulin	
4706	velosulin vial injection solution 100 units/ml [novo]	Insulin	
4715	humalog mix 25 injection 25:75; 100 units/ml [lilly]	Insulin	
4760	humulin i injection 100 units/ml [lilly]	Insulin	
4784	lentard mc injection 100 units/ml [novo]	Insulin	
4790	mixtard 50 penfill 100 iu/ml [novo]	Insulin	
4862	diabetamide tablets 2.5mg [ashbourne]	Oral anti-diabetics	
5021	novorapid penfill injection solution 100 units/ml [novo]	Insulin	
5214	insulin lispro human prb injection 100 iu/ml	Insulin	
5227	rosiglitazone tablets 8mg	Oral anti-diabetics	
5250	insulin biphasic lispro human prb injection 25:75; 100 units/ml	Insulin	
5255	mixtard 10 penfill 100 iu/ml [novo]	Insulin	
5276	glimepiride tablets 1mg	Oral anti-diabetics	
5316	glimepiride tablets 4mg	Oral anti-diabetics	
5353	glimepiride tablets 2mg	Oral anti-diabetics	
5501	insuman basal injection 100 iu/ml [aventis]	Insulin	
5627	gliclazide modified release tablet 30mg	Oral anti-diabetics	
5636	glipizide tablets 5mg	Oral anti-diabetics	
5678	nateglinide tablets 120mg	Oral anti-diabetics	
5845	mixtard 30 innolet injection suspension 30:70; 100 units/ml [novo]	Insulin	
5891	insulatard flexpen injection 100 iu/ml [novo]	Insulin	
5892	novorapid flexpen injection solution 100 units/ml [novo]	Insulin	
5933	mixtard 50 novolet 100 iu/ml [novo]	Insulin	
5953	insulin glargine injection 100 iu/ml	Insulin	
5989	nateglinide tablets 180mg	Oral anti-diabetics	
6057	lantus injection 100 iu/ml [aventis]	Insulin	
6061	novomix 30 injection 30:70; 100 units/ml [novo]	Insulin	
6209	novorapid vial injection solution 100 units/ml [novo]	Insulin	
6337	glimepiride tablets 3mg	Oral anti-diabetics	
6447	insulin aspart human pyr injection 100 iu/ml	Insulin	
6855	avandamet tablets 2mg + 500mg [glaxsk pha]	Oral anti-diabetics	
6958	levemir flexpen injection solution 100 units/ml [novo]	Insulin	
6965	levemir penfill injection solution 100 units/ml [novo]	Insulin	
7048	metformin modified release tablet 500mg	Oral anti-diabetics	*
7166	glucophage tablets 500mg [merck ser]	Oral anti-diabetics	
7228	novomix 30 flexpen injection suspension 100 units/ml [novo]	Insulin	
7231	mixtard 30 penfill injection suspension 100 units/ml [novo]	Insulin	
7237	lantus optiset injection solution 100 units/ml [aventis]	Insulin	
7266	lantus cartridge injection solution 100 units/ml [aventis]	Insulin	
7267	novomix 30 penfill injection suspension 100 units/ml [novo]	Insulin	
7284	amaryl tablets 2mg [aventis]	Oral anti-diabetics	
7300	mixtard 30 vial injection suspension 100 units/ml [novo]	Insulin	
7318	humalog cartridge injection solution 100 units/ml [lilly]	Insulin	

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
7319	mixtard 20 penfill injection suspension 100 units/ml [novo]	Insulin	
7325	avandamet tablets 4mg + 1000mg [glaxsk pha]	Oral anti-diabetics	
7332	amaryl tablets 1mg [aventis]	Oral anti-diabetics	
7349	actrapid vial injection solution 100 units/ml [novo]	Insulin	
7350	insulin isophane porcine vial injection suspension 100 units/ml	Insulin	
7375	rosiglitazone with metformin tablets 4mg + 1000mg	Oral anti-diabetics	*
7393	insulin glargine cartridge injection solution 100 units/ml	Insulin	
7400	insulin glargine disposable pen injection solution 100 units/ml	Insulin	
7402	lantus vial injection solution 100 units/ml [aventis]	Insulin	
7409	amaryl tablets 3mg [aventis]	Oral anti-diabetics	
7537	humulin zn injection 100 units/ml [lilly]	Insulin	
7610	glucophage tablets 850mg [merck ser]	Oral anti-diabetics	
7744	daonil tablets 5mg [aventis]	Oral anti-diabetics	
7757	insulin neulente (zinc susp)(purified) 100 i/u inj	Insulin	
7763	insulin neuphane (isophane)(purified) 100 i/u inj	Insulin	
7764	insulin neusulin (neutral)(purified) 100 i/u inj	Insulin	
7765	insulin neutral (human) 100 i/u inj	Insulin	
7771	human protaphane penfill 100 units/ml [novo]	Insulin	
7772	human protaphane injection 100 units/ml [novo]	Insulin	
7783	insulin isophane (human) 100 i/u inj	Insulin	
7793	humaject m3 pen 100 iu/ml [lilly]	Insulin	
7815	metformin 800 mg tab	Oral anti-diabetics	*
7861	insulin humulin s (neutral) cartridge 100 i/u	Insulin	
7912	semi-daonil tablets 2.5mg [aventis]	Oral anti-diabetics	
7959	insulin mixtard 30/70 40 i/u inj	Insulin	
8034	diabinese tablets 100mg [pfizer]	Oral anti-diabetics	
8118	humaject i pen 100 iu/ml [lilly]	Insulin	
8168	diabinese tablets 250mg [pfizer]	Oral anti-diabetics	
8203	penmix 50/50 penfill injection 100 iu/ml [novo]	Insulin	
8322	insulin zinc suspension mixed human pyr injection 100 units/ml	Insulin	
8354	insulin isophane 70%/neutral 30% 100 i/u inj	Insulin	
8376	insulin isophane 100 i/u	Insulin	
8390	gliquidone tablets 30mg	Oral anti-diabetics	
8646	insulin zinc crystalline susp 100 i/u inj	Insulin	
8838	insulin semitard 40 i/u inj	Insulin	
8839	insulin semitard 100 i/u inj	Insulin	
8841	humulin m5 injection 100 units/ml [lilly]	Insulin	
8895	initard 50/50 injection 100 units/ml [novo]	Insulin	
8976	euglucon tablets 2.5mg [aventis]	Oral anti-diabetics	
9079	insulin soluble 100 i/u inj	Insulin	
9108	tolbutamide 250 mg tab	Oral anti-diabetics	
9341	insulin biphasic isophane human prb injection 30:70; 100 units/ml	Insulin	
9376	insulin zinc suspension crystalline human pyr - long acting injection 100 units/ml	Insulin	
9503	hypurin bovine protamine zinc vial injection suspension 100 units/ml [wockhardt]	Insulin	
9521	pork actrapid vial injection solution 100 units/ml [novo]	Insulin	
9565	humaject s disposable pen injection solution 100 units/ml [lilly]	Insulin	
9618	hypurin porcine 30/70 mix injection 100 iu/ml [wockhardt]	Insulin	
9662	avandia tablets 4mg [glaxsk pha]	Oral anti-diabetics	
9699	pioglitazone tablets 30mg	Oral anti-diabetics	
9707	repaglinide tablets 1mg	Oral anti-diabetics	
9737	insulatard innolet injection 100 iu/ml [novo]	Insulin	
9748	repaglinide tablets 2mg	Oral anti-diabetics	
9865	repaglinide tablets 500 micrograms	Oral anti-diabetics	
10001	humalog mix 50 disposable pen injection suspension 100 units/ml [lilly]	Insulin	
10051	pioglitazone tablets 45mg	Oral anti-diabetics	
10067	insulin biphasic aspart human pyr injection 30:70; 100 units/ml	Insulin	
10175	insulin isophane human pyr injection 100 iu/ml	Insulin	
10184	insulin detemir injection solution 100 iu/ml	Insulin	
10207	insulin isophane human cartridge injection suspension 100 units/ml	Insulin	
10208	insulatard innolet injection suspension 100 units/ml [novo]	Insulin	
10225	lantus opticlik injection solution 100 units/ml [aventis]	Insulin	
10229	humulin i disposable pen injection suspension 100 units/ml [lilly]	Insulin	
10243	humalog mix 25 cartridge injection suspension 100 units/ml [lilly]	Insulin	
10244	mixtard 40 penfill injection suspension 100 units/ml [novo]	Insulin	
10245	mixtard 10 penfill injection suspension 100 units/ml [novo]	Insulin	
10259	insulin glargine vial injection solution 100 units/ml	Insulin	
10264	humalog disposable pen injection solution 100 units/ml [lilly]	Insulin	
10277	humulin m3 cartridge injection suspension 100 units/ml [lilly]	Insulin	
10427	tolazamide tablets 250mg	Oral anti-diabetics	
10484	penmix 20/80 penfill penfill [novo]	Insulin	
10545	insulin humulin m4 cartridge 100 i/u	Insulin	
10546	insulin humulin m4 100 i/u inj	Insulin	
10547	humulin lente injection 100 units/ml [lilly]	Insulin	
10566	insulin humulin m cartridge 100 i/u	Insulin	
10572	insulin soluble bovine injection 100 units/ml	Insulin	
10691	insulin isophane (nph) 100 i/u inj	Insulin	
10887	penmix 40/60 penfill injection 100 iu/ml [novo]	Insulin	
10910	humaject m2 pen 100 iu/ml [lilly]	Insulin	
10915	humaject m1 pen 100 iu/ml [lilly]	Insulin	
11055	insulin biphasic isophane human pyr injection 20:80; 100 units/ml	Insulin	
11056	insulin biphasic isophane human pyr injection 30:70; 100 units/ml	Insulin	
11080	insulin isophane human prb injection 100 iu/ml	Insulin	
11107	humulin m4 injection 100 units/ml [lilly]	Insulin	
11284	amaryl tablets 4mg [aventis]	Oral anti-diabetics	
11316	novonorm tablets 500 micrograms [novo]	Oral anti-diabetics	
11321	novonorm tablets 1mg [novo]	Oral anti-diabetics	
11337	novorapid novolet injection 100 iu/ml [novo]	Insulin	
11366	novonorm tablets 2mg [novo]	Oral anti-diabetics	
11483	nateglinide tablets 60mg	Oral anti-diabetics	
11601	rosiglitazone with metformin tablets 2mg + 500mg	Oral anti-diabetics	*
11604	rosiglitazone with metformin tablets 1mg + 500mg	Oral anti-diabetics	*
11609	metformin with rosiglitazone tablets 500mg + 1mg	Oral anti-diabetics	*
11610	metformin with rosiglitazone tablets 500mg + 2mg	Oral anti-diabetics	*
11695	diamicron mr tablets 30mg [servier]	Oral anti-diabetics	
11717	rosiglitazone with metformin tablets 2mg + 1000mg	Oral anti-diabetics	*
11737	metformin with rosiglitazone tablets 1000mg + 4mg	Oral anti-diabetics	*
11760	metformin with rosiglitazone tablets 1000mg + 2mg	Oral anti-diabetics	*

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
11946	tolbutamide injection 50mg/ml	Oral anti-diabetics	
11990	metformin oral solution 500mg/5ml	Oral anti-diabetics	*
12035	insulin zinc lente bovine vial injection suspension 100 units/ml	Insulin	
12060	insulin quicksol (soluble neutral) 100 i/u inj	Insulin	
12244	insulin zinc bovine susp 100 i/u inj	Insulin	
12245	glutril tablets 25mg [roche]	Oral anti-diabetics	
12259	glibornuride tablets 25mg	Oral anti-diabetics	
12297	hypurin bovine neutral injection 100 units/ml [cp pharm]	Insulin	
12299	semitard mc injection 100 units/ml [novo]	Insulin	
12455	rastinon tablets 500mg [hoechstmar]	Oral anti-diabetics	
12513	glibenese tablets 5mg [pfizer]	Oral anti-diabetics	
12638	insulin soluble human pyr injection 100 units/ml	Insulin	
12654	insulin soluble human prb injection 100 units/ml	Insulin	
12818	mixtard 50 injection 50:50; 100 units/ml [novo]	Insulin	
13277	mixtard 50 penfill injection suspension 100 units/ml [novo]	Insulin	
13331	euglucon tablets 5mg [aventis]	Oral anti-diabetics	
13416	insulin biphasic injection 100 units/ml	Insulin	
13516	hypurin bovine isophane injection 100 units/ml [cp pharm]	Insulin	
13550	insulin bp 100 i/u	Insulin	
13622	hypurin porcine neutral injection 100 units/ml [cp pharm]	Insulin	
13628	romozin tablets 400mg [glaxo]	Oral anti-diabetics	
13729	insulin isophane human emp injection 100 units/ml	Insulin	
13819	hypurin porcine isophane injection 100 units/ml [wockhardt]	Insulin	
13837	insulin biphasic isophane human prb injection 10:90; 100 units/ml	Insulin	
14164	avandamet tablets 2mg + 1000mg [glaxsk pha]	Oral anti-diabetics	
14270	humalog mix 25 disposable pen injection suspension 100 units/ml [lilly]	Insulin	
14290	insulatard penfill injection suspension 100 units/ml [novo]	Insulin	
14299	insulin glulisine cartridge injection solution 100 units/ml	Insulin	
14301	insulin detemir cartridge injection solution 100 units/ml	Insulin	
14313	insulin lispro cartridge injection solution 100 units/ml	Insulin	
14330	insulin detemir disposable pen injection solution 100 units/ml	Insulin	
14339	hypurin bovine neutral vial injection solution 100 units/ml [wockhardt]	Insulin	
14340	hypurin bovine isophane vial injection suspension 100 units/ml [wockhardt]	Insulin	
14345	apidra cartridge injection solution 100 units/ml [sanofi/ave]	Insulin	
14357	humulin i cartridge injection suspension 100 units/ml [lilly]	Insulin	
14362	insulin lispro disposable pen injection solution 100 units/ml	Insulin	
14504	insulin hypurin protamine zinc 100 i/u inj	Insulin	
14505	insulin protamine zinc bovine vial injection suspension 100 units/ml	Insulin	
14506	insulin bovine protamine zinc 100 i/u inj	Insulin	
14619	insulin biphasic isophane porcine injection 30:70; 100 units/ml	Insulin	
14644	insulin biphasic isophane human prb injection 20:80; 100 units/ml	Insulin	
14649	insulin biphasic isophane human pyr injection 10:90; 100 units/ml	Insulin	
14918	humulin i vial injection suspension 100 units/ml [lilly]	Insulin	
14925	insulin isophane human vial injection suspension 100 units/ml	Insulin	
14928	insulatard vial injection suspension 100 units/ml [novo]	Insulin	
14930	hypurin porcine neutral cartridge injection solution 100 units/ml [wockhardt]	Insulin	
14933	hypurin porcine isophane cartridge injection suspension 100 units/ml [wockhardt]	Insulin	
14938	insulin soluble bovine cartridge injection solution 100 units/ml	Insulin	
14944	humulin s cartridge injection solution 100 units/ml [lilly]	Insulin	
15040	insulin monophane (isophane) 100 i/u inj	Insulin	
15199	insuman comb 25 injection 100 iu/ml [aventis]	Insulin	
15232	avandia tablets 8mg [glaxsk pha]	Oral anti-diabetics	
15374	gliclazide oral suspension 40mg/5ml	Oral anti-diabetics	
15484	insulin isophane bovine injection 100 units/ml	Insulin	
15624	insulin isophane (highly purified) 100 i/u inj	Insulin	
15710	insulin soluble human emp injection 100 units/ml	Insulin	
15955	starlix tablets 120mg [novartis]	Oral anti-diabetics	
15961	insulin isophane human crb injection 100 iu/ml	Insulin	
16044	glucophage sr tablets 500mg [merck ser]	Oral anti-diabetics	
16129	insulin soluble human cartridge injection solution 100 units/ml	Insulin	
16142	insulin aspart cartridge injection solution 100 units/ml	Insulin	
16152	insulin biphasic isophane human cartridge injection suspension 30:70; 100 units/ml	Insulin	
16160	humulin m3 disposable pen injection suspension 100 units/ml [lilly]	Insulin	
16209	insulin hypurin soluble 100 i/u inj	Insulin	
16211	tolbutamide 100 mg tab	Oral anti-diabetics	
16213	metformin 250 mg tab	Oral anti-diabetics	*
16602	calabren tablets 2.5mg [berk]	Oral anti-diabetics	
16682	tempulin injection 100 units/ml [knoll]	Insulin	
16700	insulin zinc mixed bovine vial injection suspension 100 units/ml	Insulin	
17336	novopen injection device 100 units/ml [novo]	Insulin	
17343	gliclazide tablets 80mg [hillcross]	Oral anti-diabetics	
17580	avandamet tablets 1mg + 500mg [glaxsk pha]	Oral anti-diabetics	
17698	minodiab tablets 5mg [pharmacia]	Oral anti-diabetics	
17706	minodiab tablets 2.5mg [pharmacia]	Oral anti-diabetics	
17712	hypurin bovine lente vial injection suspension 100 units/ml [wockhardt]	Insulin	
17731	penmix 50/50 injection 100 iu/ml [novo]	Insulin	
17809	humaject m4 pen 100 iu/ml [lilly]	Insulin	
18220	pioglitazone with metformin tablets 15mg + 850mg	Oral anti-diabetics	*
18224	humalog vial injection solution 100 units/ml [lilly]	Insulin	
18301	insulin soluble inj i/u^2	Insulin	
18461	insulin zinc suspension mixed human prb injection 100 units/ml	Insulin	
18590	insulin isophane bovine vial injection suspension 100 units/ml	Insulin	
18592	insulin soluble bovine vial injection solution 100 units/ml	Insulin	
18593	humalog mix 50 cartridge injection suspension 100 units/ml [lilly]	Insulin	
18645	insulin neutral (purified) 100 i/u inj	Insulin	
18931	insulin zinc suspension crystalline human prb - intermediate acting injection 100 units/ml	Insulin	
19336	tolazamide tablets 100mg	Oral anti-diabetics	
19472	actos tablets 45mg [takeda]	Oral anti-diabetics	
19491	apidra vial injection solution 100 units/ml [sanofi/ave]	Insulin	
19513	humulin m3 vial injection suspension 100 units/ml [lilly]	Insulin	
19658	glurenorm tablets 30mg [sanofi s]	Oral anti-diabetics	
19707	insulin humulin s (neutral soluble)	Insulin	
19829	insulin novo monotard mc	Insulin	
19877	insulin aspart disposable pen injection solution 100 units/ml	Insulin	
19878	insulin biphasic isophane human disposable pen injection suspension 30:70; 100 units/ml	Insulin	
20195	insulin bovine protamine zinc 40 i/u inj	Insulin	
20196	insulin soluble 40 i/u inj	Insulin	

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
20287	actos tablets 15mg [takeda]	Oral anti-diabetics	
20422	insuman comb 15 injection 100 iu/ml [aventis]	Insulin	
20671	insulin hum/actraphane	Insulin	
20672	insulin hum/actrapid	Insulin	
20810	metformin	Oral anti-diabetics	*
20889	actos tablets 30mg [takeda]	Oral anti-diabetics	
20995	hypurin porcine 30/70 mix cartridge injection suspension 100 units/ml [wockhardt]	Insulin	
21110	insulin biphasic isophane human prb injection 50:50; 100 units/ml	Insulin	
21232	insulin biphasic isophane human vial injection suspension 30:70; 100 units/ml	Insulin	
21235	humulin s vial injection solution 100 units/ml [lilly]	Insulin	
21347	penmix 40/60 injection 100 iu/ml [novo]	Insulin	
21374	insulin biphasic isophane human prb injection 40:60; 100 units/ml	Insulin	
21395	insulin biphasic isophane human pyr injection 40:60; 100 units/ml	Insulin	
21422	insulin biphasic isophane human cartridge injection suspension 40:60; 100 units/ml	Insulin	
21424	glibenclamide oral suspension 5mg/5ml	Oral anti-diabetics	
21489	tolanase tablets 250mg [pharmacia]	Oral anti-diabetics	
21554	insuman comb 50 injection 100 iu/ml [aventis]	Insulin	
21564	gliclazide tablets 80mg [wockhardt]	Oral anti-diabetics	
21583	apidra optiset injection solution 100 units/ml [sanofi/ave]	Insulin	
21590	insulin glulisine disposable pen injection solution 100 units/ml	Insulin	
21832	diabetamide tablets 5mg [ashbourne]	Oral anti-diabetics	
21892	diaglyk tablets 80mg [ashbourne]	Oral anti-diabetics	
21945	insulin pork insulatard	Insulin	
22058	pur-in mix 15/85 injection [cp pharm]	Insulin	
22094	insulin humulin m2 vial	Insulin	
22145	tolanase tablets 100mg [pharmacia]	Oral anti-diabetics	
22155	humaject m5 pen 100 iu/ml [lilly]	Insulin	
22161	insulin humulin m1 vial	Insulin	
22496	insulin zinc lente purified suspension	Insulin	
22636	tolbutamide 1 gm tab	Oral anti-diabetics	
22697	insulin biphasic isophane human pyr injection 50:50; 100 units/ml	Insulin	
22806	insulin pork actrapid	Insulin	
22823	insulin isophane (purified) 100 i/u inj	Insulin	
22858	acetohexamide tablets 500mg	Oral anti-diabetics	
22945	insuman rapid injection 100 iu/ml [aventis]	Insulin	
22983	insuman rapid cartridge injection solution 100 units/ml [aventis]	Insulin	
23003	insulin isophane (nph) 40 i/u	Insulin	
23099	insulin biphasic aspart disposable pen injection suspension 30:70; 100 units/ml	Insulin	
23231	hypurin bovine neutral cartridge injection solution 100 units/ml [wockhardt]	Insulin	
23945	starlix tablets 60mg [novartis]	Oral anti-diabetics	
23992	insuman basal optiset injection suspension 100 units/ml [aventis]	Insulin	
23993	insuman rapid optiset injection solution 100 units/ml [aventis]	Insulin	
24002	insuman comb 25 vial injection suspension 100 units/ml [aventis]	Insulin	
24485	insulin zinc animal suspension	Insulin	
24593	neutral insulin bovine injection 100 iu/ml	Insulin	
24722	insulin isophane 50%/neutral 50% 100 i/u inj	Insulin	
24795	insulin biphasic aspart cartridge injection suspension 30:70; 100 units/ml	Insulin	
24800	hypurin porcine 30/70 mix vial injection suspension 100 units/ml [wockhardt]	Insulin	
24845	insulin pur-in isophane 100 i/u inj	Insulin	
24846	pur-in neutral injection 100 units/ml [cp pharm]	Insulin	
24848	glymidine sodium tablets 500mg	Oral anti-diabetics	
24866	insulin insulatard (leo retard) 40 i/u inj	Insulin	
24993	insuman comb 25 cartridge injection suspension 100 units/ml [aventis]	Insulin	
25006	insulin human actrapid (neutral)	Insulin	
25133	insuman comb 25 optiset injection suspension 100 units/ml [aventis]	Insulin	
25479	insulin soluble porcine cartridge injection solution 100 units/ml	Insulin	
25636	libanil tablets 2.5mg [aps]	Oral anti-diabetics	
25678	glucamet tablets 500mg [opus]	Oral anti-diabetics	
25735	insulin biphasic isophane human cartridge injection suspension 20:80; 100 units/ml	Insulin	
25736	insulin biphasic isophane human cartridge injection suspension 10:90; 100 units/ml	Insulin	
25812	insulin isophane human disposable pen injection suspension 100 units/ml	Insulin	
26060	insulin lispro vial injection solution 100 units/ml	Insulin	
26098	hypurin porcine neutral vial injection solution 100 units/ml [wockhardt]	Insulin	
26118	dimelor tablets 500mg [lilly]	Oral anti-diabetics	
26218	calabren tablets 5mg [berk]	Oral anti-diabetics	
26258	glucamet tablets 850mg [opus]	Oral anti-diabetics	
26403	pur-in mix 25/75 injection [cp pharm]	Insulin	
26498	insulin zinc suspension mixed bovine and porcine injection 100 units/ml	Insulin	
26621	insulin soluble human crb injection 100 iu/ml	Insulin	
26784	insulin zinc semilente susp bp 100 i/u inj	Insulin	
27125	starlix tablets 180mg [novartis]	Oral anti-diabetics	
27177	insulin biphasic lispro human prb injection 50:50; 100 units/ml	Insulin	
27280	insulin biphasic isophane porcine vial injection suspension 30:70; 100 units/ml	Insulin	
27396	insulin soluble porcine vial injection solution 100 units/ml	Insulin	
27402	insulin soluble human vial injection solution 100 units/ml	Insulin	
27461	insuman basal cartridge injection suspension 100 units/ml [aventis]	Insulin	
27501	orabet tablets 500mg [lagap]	Oral anti-diabetics	
27614	penmix 30/70 injection 100 iu/ml [novo]	Insulin	
27911	insulin human actrapid penfill	Insulin	
27969	glymese tablets 250mg [ddsa]	Oral anti-diabetics	
28096	insulin biphasic isophane human cartridge injection suspension 50:50; 100 units/ml	Insulin	
28101	insulin glulisine vial injection solution 100 units/ml	Insulin	
28183	hypurin porcine isophane vial injection suspension 100 units/ml [wockhardt]	Insulin	
28185	insulin biphasic lispro cartridge injection suspension 25:75; 100 units/ml	Insulin	
28442	insulin glulisine injection solution 100 units/ml	Insulin	
28588	hypurin bovine isophane cartridge injection suspension 100 units/ml [wockhardt]	Insulin	
28708	malix tablets 2.5mg [lagap]	Oral anti-diabetics	
28723	insulin zinc bovine suspension	Insulin	
28978	insulin pur-in mix 15/85 100 i/u inj	Insulin	
29326	glipizide tablets 5mg [gen (uk)]	Oral anti-diabetics	
29567	insulin aspart vial injection solution 100 units/ml	Insulin	
29837	insulin biphasic isophane human prb injection 25:75; 100 units/ml	Insulin	
29939	gliclazide tablets 80mg [gen (uk)]	Oral anti-diabetics	
29953	apidra opticlik injection solution 100 units/ml [sanofi/ave]	Insulin	
30209	actrapid mc injection 100 units/ml [arun]	Insulin	
30236	isophane insulin injection 100 iu/ml	Insulin	
30316	metformin with pioglitazone tablets 850mg + 15mg	Oral anti-diabetics	*

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
30460	malix tablets 5mg [lagap]	Oral anti-diabetics	
30686	insulin isophane porcine cartridge injection suspension 100 units/ml	Insulin	
30819	insuman comb 15 optiset injection suspension 100 units/ml [aventis]	Insulin	
30861	insulin zinc human suspension	Insulin	
31077	competact film coated tablets [takeda]	Oral anti-diabetics	
31146	metsol oral solution 500mg/5ml [orbis]	Oral anti-diabetics	
31205	insuman comb 50 optiset injection suspension 100 units/ml [aventis]	Insulin	
31212	gliclazide tablets 80mg [actavis]	Oral anti-diabetics	
31258	insulin biphasic lispro disposable pen injection suspension 25:75; 100 units/ml	Insulin	
31267	insulin pur-in mix 50/50 100 i/u inj	Insulin	
31465	exubera powder for inhalation 1mg [pfizer]	Insulin	
31467	exubera powder for inhalation 3mg [pfizer]	Insulin	
31474	libanil tablets 5mg [aps]	Oral anti-diabetics	
32053	insulin humalog mix 25	Insulin	
33087	metformin tablets 500mg [actavis]	Oral anti-diabetics	*
33167	insulin biphasic isophane human crb injection 25:75; 100 units/ml	Insulin	
33232	insulin biphasic isophane human crb injection 50:50; 100 units/ml	Insulin	
33562	duclazide tablets 80mg [dumex]	Oral anti-diabetics	
33673	tolbutamide tablets 500mg [actavis]	Oral anti-diabetics	
33674	metformin tablets 850mg [hillcross]	Oral anti-diabetics	*
33966	insulatard injection 100 units/ml [novo]	Insulin	
34004	metformin tablets 500mg [ivax]	Oral anti-diabetics	*
34020	metformin tablets 850mg [ivax]	Oral anti-diabetics	*
34031	monotard mc injection 100 units/ml [novo]	Insulin	
34097	human initard 50/50 injection 100 units/ml [novo]	Insulin	
34135	metformin tablets 500mg [m&a pharm]	Oral anti-diabetics	*
34323	metformin tablets 500mg [hillcross]	Oral anti-diabetics	*
34399	gliclazide tablets 80mg [ivax]	Oral anti-diabetics	
34504	metformin tablets 500mg [wockhardt]	Oral anti-diabetics	*
34507	glibenclamide tablets 2.5mg [wockhardt]	Oral anti-diabetics	
34563	glibenclamide tablets 5mg [wockhardt]	Oral anti-diabetics	
34598	metformin tablets 500mg [gen (uk)]	Oral anti-diabetics	*
34676	glibenclamide tablets 2.5mg [hillcross]	Oral anti-diabetics	
34697	metformin tablets 850mg [wockhardt]	Oral anti-diabetics	*
34706	glibenclamide tablets 2.5mg [ivax]	Oral anti-diabetics	
34742	metformin tablets 850mg [teva]	Oral anti-diabetics	*
34802	glipizide tablets 5mg [ivax]	Oral anti-diabetics	
34836	metformin tablets 850mg [actavis]	Oral anti-diabetics	*
34917	metformin tablets 500mg [teva]	Oral anti-diabetics	*
34932	gliclazide tablets 80mg [genus]	Oral anti-diabetics	
34957	tolbutamide tablets 500mg [hillcross]	Oral anti-diabetics	
35022	sitagliptin tablets 100mg	Oral anti-diabetics	
35144	byetta injection 5 micrograms [lilly]	Oral anti-diabetics	
35149	exenatide injection 10micrograms	Oral anti-diabetics	
35150	byetta injection 10micrograms [lilly]	Oral anti-diabetics	
35251	exenatide injection 5 micrograms	Oral anti-diabetics	
35253	insuman comb 50 cartridge injection suspension 100 units/ml [aventis]	Insulin	
35260	levemir innolet injection solution 100 units/ml [novo]	Insulin	
35462	januvia tablets 100mg [m s d]	Oral anti-diabetics	
35468	insuman basal vial injection suspension 100 units/ml [aventis]	Insulin	
35561	prandin tablets 2mg [novo]	Oral anti-diabetics	
35701	insulin biphasic lispro disposable pen injection suspension 50:50; 100 units/ml	Insulin	
36031	insulin biphasic isophane porcine cartridge injection suspension 30:70; 100 units/ml	Insulin	
36066	insulin isophane bovine cartridge injection suspension 100 units/ml	Insulin	
36146	insulin biphasic lispro cartridge injection suspension 50:50; 100 units/ml	Insulin	
36194	insulin biphasic isophane human cartridge injection suspension 25:75; 100 units/ml	Insulin	
36355	insulin human powder for inhalation 1mg	Insulin	
36356	insulin human powder for inhalation 3mg	Insulin	
36430	insulin soluble human disposable pen injection solution 100 units/ml	Insulin	
36513	velosulin cartridge injection 100 units/ml [novo]	Insulin	
36774	prandin tablets 1mg [novo]	Oral anti-diabetics	
36853	lantus solostar injection solution 100 units/ml [sanofi/ave]	Insulin	
36856	gliclazide tablets 80mg [sandoz]	Oral anti-diabetics	
36920	apidra solostar injection solution 100 units/ml [sanofi/ave]	Insulin	
36948	prandin tablets 500 micrograms [novo]	Oral anti-diabetics	
37617	rosiglitazone tablets 2mg	Oral anti-diabetics	
37874	vildagliptin with metformin tablets 50mg + 850mg	Oral anti-diabetics	*
37875	vildagliptin tablets 50mg	Oral anti-diabetics	
37902	vildagliptin with metformin tablets 50mg + 1000mg	Oral anti-diabetics	*
38355	metformin modified release tablet 750mg	Oral anti-diabetics	*
38400	glucophage sr tablets 750mg [merck ser]	Oral anti-diabetics	
38422	isophane injection 100 iu/ml [celltech]	Insulin	
38551	eucreas tablets 50mg + 1000mg [novartis]	Oral anti-diabetics	
38986	humalog kwikpen injection solution 100 units/ml [lilly]	Insulin	
39006	humalog mix 25 kwikpen injection suspension 100 units/ml [lilly]	Insulin	
39086	humalog mix 50 kwikpen injection suspension 100 units/ml [lilly]	Insulin	
39149	galvus tablets 50mg [novartis]	Oral anti-diabetics	
39203	eucreas tablets 50mg + 850mg [novartis]	Oral anti-diabetics	
39560	bolamyn sr tablets 500mg [teva]	Oral anti-diabetics	
39598	metformin modified release tablet 1000mg	Oral anti-diabetics	*
39729	glucophage sr tablets 1000mg [merck ser]	Oral anti-diabetics	
39988	metformin oral powder 500mg	Oral anti-diabetics	*
40007	glucophage sachets 1000mg [merck ser]	Oral anti-diabetics	
40110	glucophage sachets 500mg [merck ser]	Oral anti-diabetics	
40233	metformin oral powder 1000mg	Oral anti-diabetics	*
40365	glimepiride tablets 1mg [actavis]	Oral anti-diabetics	
40425	nazdol mr tablets 30mg [teva]	Oral anti-diabetics	
40642	victoza injection 18mg/3ml [novo]	Oral anti-diabetics	
40693	liraglutide injection 18mg/3ml	Oral anti-diabetics	
41120	insulin biphasic isophane human disposable pen injection suspension 50:50; 100 units/ml	Insulin	
41204	saxagliptin tablets 5mg	Oral anti-diabetics	
41431	onglyza tablets 5mg [bms]	Oral anti-diabetics	
41558	glibenclamide tablets 5mg [teva]	Oral anti-diabetics	
41559	glibenclamide tablets 5mg [hillcross]	Oral anti-diabetics	
41593	glibenclamide tablets 2.5mg [teva]	Oral anti-diabetics	
41834	insulin zinc suspension lente injection 100 iu/ml [celltech]	Insulin	
41898	glibenclamide	Oral anti-diabetics	

Diabetes treatments

Product Code	Product Name	Diabetes Medication Type	Metformin tag
41959	penject injection device 100 units/ml [hypoguard]	Insulin	
42161	orabet tablets 500mg [sandoz]	Oral anti-diabetics	
42395	humalog mix 25 vial injection suspension 100 units/ml [lilly]	Insulin	
42790	gliclazide tablets 80mg [merck-gen]	Oral anti-diabetics	
42954	insulin biphasic isophane human vial injection suspension 25:75; 100 units/ml	Insulin	
43065	gliclazide tablets 40mg	Oral anti-diabetics	
43270	metformin sugar free oral solution 500mg/5ml [rosemont]	Oral anti-diabetics	*
43465	zicron tablets 40mg [bristol lb]	Oral anti-diabetics	
43619	sitagliptin with metformin tablets 50mg + 1000mg	Oral anti-diabetics	*
43684	janumet tablets 50mg + 1000mg [m s d]	Oral anti-diabetics	
43950	humulin i kwikpen injection suspension 100 units/ml [lilly]	Insulin	
43953	insulin biphasic lispro vial injection suspension 25:75; 100 units/ml	Insulin	
43991	humulin m3 kwikpen injection suspension 100 units/ml [lilly]	Insulin	
44250	metformin oral solution 500mg/5ml [hillcross]	Oral anti-diabetics	*
44251	insulin zinc suspension mixed porcine injection 100 units/ml	Insulin	
44304	glyconon tablets 500mg [ddsa]	Oral anti-diabetics	
44378	insulin biphasic isophane human disposable pen injection suspension 25:75; 100 units/ml	Insulin	
44473	edicil mr tablets 30mg [ratiopharm]	Oral anti-diabetics	
44480	insuman comb 25 solostar injection suspension 100 units/ml [aventis]	Insulin	
44738	niddaryl tablets 1mg [dee]	Oral anti-diabetics	
45158	insuman comb 15 cartridge injection suspension 100 units/ml [aventis]	Insulin	
45215	gliclazide tablets 80mg [neolab]	Oral anti-diabetics	
45581	metabet sr tablets 500mg [morningsid]	Oral anti-diabetics	
45775	saxagliptin tablets 2.5mg	Oral anti-diabetics	
45821	onglyza tablets 2.5mg [bms]	Oral anti-diabetics	
45831	dacadis modified release tablet 30mg [gen (uk)]	Oral anti-diabetics	
46001	insuman basal solostar injection suspension 100 units/ml [aventis]	Insulin	
46458	exenatide powder for prolonged release injection suspension 2mg	Oral anti-diabetics	
46469	bydureon powder for prolonged release injection suspension 2mg [lilly]	Oral anti-diabetics	
46665	linagliptin tablets 5mg	Oral anti-diabetics	
46666	novorapid flextouch injection solution 100 units/ml [novo]	Insulin	
46716	trajenta tablets 5mg [boeh ingl]	Oral anti-diabetics	
46927	tolbutamide tablets 500mg [teva]	Oral anti-diabetics	
46989	metabet sr tablets 1000mg [morningsid]	Oral anti-diabetics	
47074	gliclazide oral suspension 80mg/5ml	Oral anti-diabetics	
47360	neutral insulin injection 100 units/ml [celltech]	Insulin	

Epilepsy

Medical Code	Read Term
573	Epilepsy
988	Grand mal (major) epilepsy
1715	Epileptic absences
2907	Petit mal (minor) epilepsy
3175	ZERIDAME SR tablets 150mg [ACTAVIS]
3607	Fit (in known epileptic) NOS
3784	Anticonvulsant therapy
4093	Status epilepticus
4109	Traumatic epilepsy
4602	Nocturnal epilepsy
4801	Epileptic seizures - myoclonic
5117	Grand mal status
5152	Epileptic seizures - tonic
5525	Focal epilepsy
5668	Grand mal seizure
6271	Status epilepticus, unspecified
6709	[X]Epileptic psychosis NOS
7809	Herpes zoster with meningitis
7811	O/E - grand mal fit
8097	Absence seizure
8187	Tonic-clonic epilepsy
8487	Myoclonic seizure
9326	Epilepsy medication review
9569	Jacksonian, focal or motor epilepsy
9747	Epilepsy NOS
9886	Petit mal status
9887	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
9979	Other forms of epilepsy NOS
11015	Seizure free >12 months
11186	Generalised nonconvulsive epilepsy
11394	Complex partial epileptic seizure
11454	Trigger factor for seizure
11505	Seizures in response to acute event
11752	Patient on maximal tolerated anticonvulsant therapy
13073	Epilepsy drug side effects
13219	No seizures on treatment
13220	Epilepsy control poor
13221	2 to 4 seizures a month
17399	Juvenile absence epilepsy
18471	Epileptic seizures - clonic
18899	Daily seizures
19170	Benign Rolandic epilepsy
19363	Juvenile myoclonic epilepsy
19549	1 to 7 seizures a week
19550	Epilepsy control good
19551	Epilepsy care arrangement
19552	Epilepsy does not limit activities
20566	Epilepsy treatment stopped
22341	Epilepsy confirmed
22804	Tonic-clonic epilepsy
22991	Epilepsy severity
23634	Psychomotor epilepsy
24309	Epileptic seizures - atonic
25330	Complex partial status epilepticus
26015	Partial epilepsy without impairment of consciousness
26144	Generalised convulsive epilepsy
26511	Follow-up epilepsy assessment
26512	Epilepsy treatment changed
26618	1 to 12 seizures a year
26619	Epilepsy limits activities
26620	Epilepsy restricts employment
26733	Partial epilepsy without impairment of consciousness OS

Epilepsy

Medical Code	Read Term
26961	Anticonvulsant level therapeutic
27526	Partial epilepsy without impairment of consciousness NOS
30604	Alcohol-induced epilepsy
30635	Photosensitive epilepsy
30816	Drug-induced epilepsy
31830	Epileptic seizures - akinetic
31877	[X]Schizophrenia-like psychosis in epilepsy
31920	Partial epilepsy with impairment of consciousness NOS
32288	Partial epilepsy with impairment of consciousness
34079	Epileptic automatism
34473	Epilepsy treatment started
36203	Psychosensory epilepsy
37592	Somatosensory epilepsy
37644	Progressive myoclonic epilepsy
37782	Neonatal myoclonic epilepsy
38307	Other forms of epilepsy
38919	Transient epileptic amnesia
39160	Many seizures a day
40105	Simple partial epileptic seizure
40806	Generalised convulsive epilepsy NOS
40863	Epilepsy impairs education
43679	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
44252	Generalised nonconvulsive epilepsy NOS
45746	Initial epilepsy assessment
45927	Other specified generalised convulsive epilepsy
46603	Emergency epilepsy treatment since last appointment
48134	Sensory induced epilepsy
48462	[X]Limbic epilepsy personality
49889	Acquired epileptic aphasia
50012	Epilepsy associated problems
50702	Epilepsy prevents employment
52273	[X] Adverse reaction to anticonvulsants NOS
52632	No epilepsy drug side effects
53483	Gelastic epilepsy
55260	Cursive (running) epilepsy
55665	Limbic system epilepsy
55706	Epilepsy management plan given
55739	Visual reflex epilepsy
56359	Menstrual epilepsy
59120	[X]Other status epilepticus
59185	Other specified generalised nonconvulsive epilepsy
60306	Adverse reaction to anticonvulsants NOS
63234	Adverse reaction to other anticonvulsants
65673	Stress-induced epilepsy
65699	Motor epilepsy
68946	Unilateral epilepsy
69831	[X]Other epilepsy
71719	Kojevnikov's epilepsy
71801	[X]Status epilepticus, unspecified
73542	Visceral reflex epilepsy
73879	[X]Oth unspec antiepileptics caus adverse eff in therap use
95658	[X] Adverse reaction to other anticonvulsant
98870	Partial epilepsy with autonomic symptoms
99548	Pykno-epilepsy
99731	[X]Other generalized epilepsy and epileptic syndromes
99834	[D]Nocturnal seizure
100652	Contraceptive advice for patients with epilepsy
100920	Pre-conception advice for patients with epilepsy
101143	Contraceptiv advice for patients with epilepsy not indicated
102190	Contraceptive advice for patients with epilepsy declined
102191	Pregnancy advice for patients with epilepsy declined
102264	Pre-conception advic fr patients with epilepsy not indicated

Epilepsy

Medical Code	Read Term
102265	Pre-conception advice for patients with epilepsy declined
102359	Pregnancy advice for patients with epilepsy
102375	Pregnancy advice for patients with epilepsy not indicated

Herpes Zoster (CPRD)

Medical code	Read term	Site of zoster
390	Herpes zoster	Site Unspecified
516	Shingles	Site Unspecified
7331	Ramsey Hunt Syndrome	Non-truncal
8936	Ophthalmic herpes zoster infection	Ophthalmic herpes zoster
14718	Herpes zoster with ophthalmic complication	Ophthalmic herpes zoster
14793	Herpes zoster otitis externa	Non-truncal
18918	Herpes zoster ophthalmicus	Ophthalmic herpes zoster
21069	Herpes zoster with unspecified complication	Site Unspecified
21471	Herpes zoster NOS	Site Unspecified
25320	Herpes zoster with dermatitis of eyelid	Ophthalmic herpes zoster
27403	Geniculate herpes zoster	Non-truncal
27546	Herpes zoster with keratoconjunctivitis	Ophthalmic herpes zoster
31681	Herpes zoster - otitis externa	Non-truncal
33810	Herpes zoster with other ophthalmic complication	Ophthalmic herpes zoster
38531	Herpes zoster with other specified complication NOS	Site Unspecified
39692	Polyneuropathy in herpes zoster	Site Unspecified
43235	Herpes zoster with other specified complication	Site Unspecified
44944	Herpes zoster with meningitis	Non-truncal
47375	Zoster encephalitis	Site Unspecified
50537	Herpes zoster with other CNS complications	Non-truncal
51692	Encephalitis due to herpes zoster	Site Unspecified
52126	Herpes zoster with other central nervous system complication	Non-truncal
52319	Disseminated zoster	Site Unspecified
55940	Herpes zoster iridocyclitis	Ophthalmic herpes zoster
57895	Herpes zoster meningitis	Non-truncal
62558	Infective otitis externa due to herpes zoster	Non-truncal
63739	Herpes zoster with other CNS complication NOS	Non-truncal
69405	Herpes zoster encephalitis	Site Unspecified
70197	[X]Zoster without complications	Site Unspecified
71464	Meningitis due to herpes zoster virus	Non-truncal

ICD code	ICD description	Site of zoster
B02	Herpes zoster	Site Unspecified
B02.0	Zoster encephalitis	Site Unspecified
B02.1	Zoster meningitus	Non-truncal
B02.3	Zoster ocular disease	Ophthalmic herpes zoster
B02.7	Disseminated zoster	Site Unspecified
B02.8	Zoster with other complications	Site Unspecified
B02.9	Zoster without complications	Site Unspecified
G53.0	Ramsay Hunt Syndrome	Non-truncal

HIV

Medical code	Read term
2835	HIV positive
8281	HIV disease resulting in wasting syndrome
9130	Human immunodeficiency virus infection
23763	AIDS carrier
23951	ZERIDAME SR tablets 150mg [ACTAVIS]
27519	Pneumonia with pneumocystis carinii
27641	HIV disease resulting in Pneumocystis carinii pneumonia
27853	HIV disease resulting in Kaposi's sarcoma
32018	HTLV 1 nucleic acid detection
33943	Notification of AIDS
36294	Acquired human immunodeficiency virus infection syndrome NOS
37006	HIV disease resulting in mycobacterial infection
41185	[X]Dementia in human immunodef virus [HIV] disease
43537	HIV 1 nucleic acid detection
44288	[D]Laboratory evidence of human immunodeficiency virus [HIV]
44617	HIV disease resulting in Burkitt's lymphoma
46442	Retrovirus infection
47632	Herpes zoster with meningitis
50076	HIV disease resulting in multiple infections
51708	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
53636	Human immunodeficiency virus with neurological disease
54423	Retrovirus as cause of diseases classified to other chapters
58857	Acute human immunodeficiency virus infection
58859	Asymptomatic human immunodeficiency virus infection
62854	[X]Human immunodeficiency virus disease
62891	Human immunodeficiency virus with other clinical findings
65117	HIV disease resulting in lymphoid interstitial pneumonitis
66367	HIV dis resulting oth types of non-Hodgkin's lymphoma
66368	HIV disease resulting in cytomegaloviral disease
67575	HIV disease resulting in unspecified malignant neoplasm
69766	HIV infection with persistent generalised lymphadenopathy
69767	[X]HIV disease resulting in other non-Hodgkin's lymphoma
70528	Human immunodeficiency virus with secondary infection
70869	Human immunodeficiency virus with constitutional disease
71450	HIV disease resulting/unspcf infectious+parasitic disease
72065	HTLV 2 nucleic acid detection
93642	Human immunodeficiency virus RNA/DNA ratio
96751	[X]HIV disease result/haematological+immunologic abnorms,NEC
96902	Human immunodeficiency virus viral load by log rank
98966	Human immunodeficiency virus monitoring
100769	[X]Unspecified human immunodeficiency virus [HIV] disease
101191	Human immunodeficiency virus annual review
101836	Human immunodeficiency virus with secondary cancers
102117	[X]HIV disease resulting in multiple infections
102252	[X]HIV disease resulting in other specified conditions

HSCT

Medical code	Read term
28232	Peripheral blood stem cell graft
86063	Autologous peripheral blood stem cell transplant
89920	Allogeneic peripheral blood stem cell transplant

Medical code	Read term
273	hypothyroidism
718	subclinical iodine-deficiency hypothyroidism
1619	myxoedema
3290	acquired hypothyroidism
3436	hashimoto's disease
3941	hypothyroidism nos
10097	congenital hypothyroidism
11146	tsh - thyroid-stimulating hormone deficiency
11322	irradiation hypothyroidism
11892	pendred's syndrome
14704	thyroid deficiency
15743	hypothyroidism resulting from para-aminosalicylic acid
18282	hypothyroid goitre, acquired
19367	hypothyroidism monitoring verbal invite
20310	pretibial myxoedema - hypothyroid
23014	thyroid insufficiency
24748	other acquired hypothyroidism
25913	other iatrogenic hypothyroidism
27533	cretinism
28735	hypothyroidism monitoring administration
28852	postsurgical hypothyroidism
31612	congenital hypothyroidism with diffuse goitre
31971	autoimmune myxoedema
34221	iodine hypothyroidism
38976	iatrogenic hypothyroidism nos
39166	congenital iodine-deficiency syndrome, myxoedematous type
46057	hypothyroidism monitoring first letter
46345	acquired atrophy of thyroid
46630	hypothyroidism monitoring second letter
46640	hypothyroidism monitoring third letter
47449	goitrous cretin
47521	post ablative hypothyroidism
47658	cerebral degeneration due to myxoedema
50275	other postablative hypothyroidism
50860	postinfectious hypothyroidism
51416	myopathy due to myxoedema
51481	congenital hypothyroidism nos
51706	postablative hypothyroidism nos
56722	premature puberty due to hypothyroidism
58833	neonatal jaundice with congenital hypothyroidism
59702	myxoedema coma
61069	myasthenic syndrome due to hypothyroidism
67513	cretinism
69290	other specified congenital hypothyroidism
73107	[x]other sp cified hypothyroidism
85661	hypothyroidism monitoring telephone invitation
85955	hypothyroidism clinical management plan
93159	congenital hypothyroidism without goitre
93323	congenital thyroid insufficiency
94915	hypothyroidism resulting from resorcinol
95830	subclinical hypothyroidism
95885	hypothyroidism annual review
97090	hypothyroidism resulting from phenylbutazone
102442	suspected hypothyroidism

Inflammatory Bowel Disease

Medical code	Read term
593	Crohn's disease
704	Ulcerative colitis
1784	Ulcerative colitis and/or proctitis
1796	Inflammatory bowel disease
5133	ZERIDAME SR tablets 150mg [ACTAVIS]
5749	H/O: ulcerative colitis
6538	Crohn's colitis
6650	Ulcerative proctocolitis
8347	Ulcerative proctitis
9359	Crohn's disease of the small bowel NOS
11119	CDAI - Crohn's disease activity index
11286	Regional enteritis - Crohn's disease
11337	Crohn's disease activity index
12575	Juvenile arthritis in Crohn's disease
15207	Idiopathic proctocolitis NOS
15773	Regional ileocolitis
17641	Arthropathy in ulcerative colitis
20480	Herpes zoster with meningitis
20688	Crohn's disease of the large bowel NOS
22516	Exacerbation of ulcerative colitis
24550	Other idiopathic proctocolitis
24858	Ulcerative rectosigmoiditis
28476	Crohn's disease of the terminal ileum
29616	Orofacial Crohn's disease
30433	Ulcerative (chronic) enterocolitis
33456	Ulcerative proctocolitis NOS
36913	Exacerbation of Crohn's disease of small intestine
39037	Exacerbation of Crohn's disease of large intestine
39278	Crohn's disease of the ileum NOS
42822	Ulcerative (chronic) ileocolitis
43090	Other idiopathic proctocolitis NOS
44426	Regional enteritis of the large bowel
48732	Ulcerative ileocolitis
51576	Regional enteritis of the small bowel
51578	Granulomatous enteritis
52449	Regional enteritis NOS
53743	[X]Other ulcerative colitis
59994	Crohn's disease NOS
62628	Regional enteritis of the colon
63036	Regional enteritis of the jejunum
64773	Regional enteritis of the rectum
66238	Crohn's disease of the ileum unspecified
69959	[X]Other Crohn's disease
71083	Juvenile arthritis in ulcerative colitis
71945	Regional enteritis of the duodenum

Leukaemia

Medical code	Read term
4072	Acute leukaemia NOS
4222	Lymphatic leukaemia
4250	Leukaemia NOS
4251	Acute lymphoid leukaemia
4413	ZERIDAME SR tablets 150mg [ACTAVIS]
4637	[M]Leukaemias
5915	[M]Hairy cell leukaemia
6316	[M]Acute leukaemia NOS
7176	Myeloid leukaemia
8625	Chronic lymphoid leukaemia
10726	Chronic myeloid leukaemia
12146	[M]Lymphoid leukaemia NOS
16416	Chronic leukaemia NOS
19372	Lymphoid leukaemia
19974	Acute monocytic leukaemia
20440	Myelomonocytic leukaemia
20635	[M]Lymphatic leukaemia
22050	Herpes zoster with meningitis
22071	[M]Blast cell leukaemia
25191	Leukaemia of unspecified cell type
27458	Chronic monocytic leukaemia
27520	Chronic myeloid leukaemia NOS
27664	Acute promyelocytic leukaemia
27790	Chronic lymphatic leukaemia
29335	[M]Adult T-cell leukaemia/lymphoma
30632	Other specified leukaemia NOS
31586	Prolymphocytic leukaemia
31701	Chronic granulocytic leukaemia
31750	[M]Chronic leukaemia NOS
33344	Myeloid leukaemia NOS
34692	Other leukaemia of unspecified cell type
35697	[M]Myeloid leukaemias
35875	Monocytic leukaemia
37272	Other specified leukaemia
37410	[M]Acute lymphoid leukaemia
37461	Adult T-cell leukaemia
37723	[M]Granulocytic leukaemia NOS
38331	Other lymphoid leukaemia NOS
38914	Lymphoid leukaemia NOS
39187	Plasma cell leukaemia
40420	[M]Leukaemias unspecified
41500	[M]Chronic lymphoid leukaemia
41734	[M]Leukaemia NOS
42297	[M]Leukaemia NOS
42539	Acute erythraemia and erythroleukaemia
46048	[M]Prolymphocytic leukaemia
46263	[M]Acute myelomonocytic leukaemia
46444	[M]Erythroleukaemias
48049	[M]Chronic myelomonocytic leukaemia
48155	[M]Lymphoid leukaemias
49327	[M]Acute megakaryoblastic leukaemia
49725	Other lymphoid leukaemia
50928	[M]Burkitt's cell leukaemia
52942	[M]Chronic myeloid leukaemia
53477	[V]Follow-up examination after chemotherapy for leukaemia
54585	[M]Acute myeloid leukaemia
54793	Subacute leukaemia NOS
57316	[M]Acute promyelocytic leukaemia
57671	Megakaryocytic leukaemia
57713	[M]Eosinophilic leukaemias
59929	[M]Leukaemia unspecified, NOS
61500	Acute myelomonocytic leukaemia

Leukaemia

Medical code	Read term
61693	[X]Other myeloid leukaemia
62330	[M]Other myeloid leukaemia NOS
63475	Subacute myeloid leukaemia
63570	[M]Stem cell leukaemia
64618	[M]Plasma cell leukaemias
64963	[M]Blastic leukaemia
65165	[X]Other leukaemia of unspecified cell type
65721	Mast cell leukaemia
65777	Thrombocytic leukaemia
66089	Other myeloid leukaemia NOS
66694	[M]Naegeli-type monocytic leukaemia
67029	[X]Other lymphoid leukaemia
67700	Monoblastic leukaemia
69299	[M]Thrombocytic leukaemia
70935	[M]Erythroleukaemia
71377	[M]Eosinophilic leukaemia
71850	[M]Myeloid leukaemia NOS
72179	[M]Subacute leukaemia NOS
72197	Lymphosarcoma cell leukaemia
72222	[M]Megakaryocytic leukaemia
72310	[M]Aleukaemic leukaemia NOS
72774	Subacute lymphoid leukaemia
73066	[M]Miscellaneous leukaemias
73088	[M]Monocytic leukaemia NOS
87335	Hairy cell leukaemia
89329	[X]Other specified leukaemias
89762	[X]Other monocytic leukaemia
93342	Monocytic leukaemia NOS
94174	Other and unspecified leukaemia
99015	Other monocytic leukaemia
99413	Other and unspecified leukaemia NOS
100786	Chronic eosinophilic leukaemia
100927	[M]Erythroleukaemia NOS
101606	Subacute monocytic leukaemia
103645	Other monocytic leukaemia NOS

Lymphoma

Medical code	Read term
1481	Reticulosarcoma
1483	[M]Lymphoma NOS
2462	Hodgkin's disease
3371	[M]Non Hodgkins lymphoma
3604	ZERIDAME SR tablets 150mg [ACTAVIS]
5179	Nodular lymphoma (Brill - Symmers disease)
7940	[X]Non-Hodgkin's lymphoma NOS
8649	[X]Non-Hodgkin's lymphoma, unspecified type
12335	Malignant lymphoma NOS
12464	Peripheral T-cell lymphoma
15027	Malignant lymphoma NOS
15504	Malignant lymphoma NOS of lymph nodes of multiple sites
16460	[M]Malignant lymphoma, non Hodgkin's type
16774	[M] Cutaneous lymphoma
17178	[M]Lymphomas, NOS or diffuse
17182	Follicular lymphoma NOS
17460	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
17887	Herpes zoster with meningitis
18383	[M] Large cell lymphoma
19140	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
20437	[M]Lymphomas, nodular or follicular
20710	[M]Hodgkin's disease
21402	Burkitt's lymphoma
21463	[M]Lymphocytic lymphoma NOS
21549	Follicular non-Hodgkin's lymphoma
23711	[M]Malignant lymphoma, diffuse NOS
27416	Lymphosarcoma
27562	[M]Follicular lymphosarcoma NOS
27965	[M]AngiocentricT-cell lymphoma
28639	Follicular non-Hodgkin's small cleaved cell lymphoma
29178	Hodgkin's disease, nodular sclerosis
29876	Hodgkin's, lymphocytic-histiocytic predominance NOS
31492	[M] Monocytoid B-cell lymphoma
31537	[M]Hodgkin,s disease, lymphocytic predominance, nodular
31576	Other types of follicular non-Hodgkin's lymphoma
31726	[M]Malignant lymphoma, small cleaved cell, diffuse
31741	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic deplet
31749	[M]Monocytoid B-cell lymphoma
31794	Unspecified B-cell non-Hodgkin's lymphoma
32240	Lymphoma stage III
33869	[M]Malignant lymphoma, large cell, diffuse NOS
34089	Malignant lymphoma NOS of lymph nodes of axilla and arm
34352	[M]Lymphoblastic lymphoma NOS
35014	Sezary's disease
36114	[M]Malignant lymphoma NOS
38939	Hodgkin's disease, lymphocytic-histiocytic predominance
39798	Diffuse non-Hodgkin's lymphoma, unspecified
39883	[M]Malig lymp, follicular centre cell, cleaved, follicular
39906	[M]Malignant lymphoma, centrocytic
40508	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic predom
40513	[M]Lymphoma, nodular or follicular NOS
40766	[M] Peripheral T-cell lymphoma NOS
41369	Lymphosarcoma and reticulosarcoma
41754	[M]Malignant lymphoma, lymphoplasmacytoid type
41841	[M]Malignant lymphoma, follicular centre cell NOS
42198	[M]Hodgkin's disease, nodular sclerosis NOS
42461	Hodgkin's disease NOS
42579	Malignant lymphoma NOS of intra-abdominal lymph nodes
42769	[M]Hodgkin's disease NOS
43415	[X]Other Hodgkin's disease
44196	Hodgkin's granuloma
44318	Oth and unspecif peripheral & cutaneous T-cell lymphomas

Lymphoma

Medical code	Read term
44617	HIV disease resulting in Burkitt's lymphoma
45264	Nodular lymphoma of lymph nodes of head, face and neck
46877	[M]Malignant lymphoma, small lymphocytic NOS
46931	[M]Malignant lymphoma, stem cell type
48253	[M]Malignant lymphoma, immunoblastic type
49253	[M]Giant follicular lymphoma
49262	Follicular non-Hodgkin's large cell lymphoma
49605	Hodgkin's disease, mixed cellularity
49825	[M]Reticulum cell sarcoma NOS
50668	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
50695	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
50696	Malignant lymphoma NOS of lymph nodes of head, face and neck
51285	[M]Hodgkin's disease, mixed cellularity
51680	[M]Malignant lymphoma, small cell, noncleaved, diffuse
51852	[M]Malig lymphoma, lymphocytic, intermediate different NOS
51895	[M]Lymphoma, diffuse or NOS
53397	Hodgkin's disease NOS
53551	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
55303	Hodgkin's nodular sclerosis of head, face and neck
56041	[M]Hodgkin's disease, lymphocytic predominance
57225	Hodgkin's disease, nodular sclerosis of unspecified site
57427	Malignant lymphoma NOS of unspecified site
57544	[M]True histiocytic lymphoma
57737	Lymphoepithelioid lymphoma
58015	[M]Malignant lymphomatous polyposis
58082	Nodular lymphoma of lymph nodes of multiple sites
58684	Hodgkin's mixed cellularity of intrathoracic lymph nodes
58953	[M]Malig lymp,follicular centre cell,noncleaved,follicular
59115	Burkitt's lymphoma of lymph nodes of head, face and neck
59755	Hodgkin's disease NOS of intrathoracic lymph nodes
59778	Hodgkin's disease NOS of lymph nodes of head, face and neck
60092	Malignant lymphoma NOS of spleen
60242	Reticulosarcoma of unspecified site
60275	[M]Malignant lymphoma, centroblastic type NOS
60504	[M]Lymphocytic lymphosarcoma NOS
60918	Lymphoma stage I
61149	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
61251	[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse
61662	Hodgkin's disease NOS, unspecified site
61997	[M]Hodgkin's disease NOS
62380	Lymphosarcoma of intrathoracic lymph nodes
62437	Malignant reticulosis
63054	Hodgkin's disease, nodular sclerosis NOS
63105	Malignant lymphoma NOS of lymph node inguinal region and leg
63375	[X]Unspecified B-cell non-Hodgkin's lymphoma
63625	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
63699	[M]Malignant lymphoma, nodular NOS
63723	Lymphosarcoma NOS
63973	[M]Microglioma
63994	[M]Malignant lymphoma, large cell, cleaved, diffuse
64036	Hodgkin's sarcoma
64336	[X]Other specified types of non-Hodgkin's lymphoma
64343	[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity
64515	[X]Diffuse non-Hodgkin's lymphoma, unspecified
64670	Lymphosarcoma of intra-abdominal lymph nodes
64947	[M]Brill - Symmers' disease
65180	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
65483	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
65489	Hodgkin's paragranuloma
65584	[M]Hodgkin,s disease, lymphocytic predominance, diffuse
65701	Nodular lymphoma NOS
66327	Nodular lymphoma of unspecified site

Lymphoma

Medical code	Read term
66367	HIV dis resulting oth types of non-Hodgkin's lymphoma
66603	[M]Malig lymphoma, follicular centre cell, non-cleaved NOS
67203	[M]Lymphoblastic lymphosarcoma NOS
67506	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
67518	[X]Other types of follicular non-Hodgkin's lymphoma
67703	Hodgkin's disease, lymphocytic depletion
68039	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
68330	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
68964	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
69301	[M]Malignant lymphoma, convoluted cell type NOS
69767	[X]HIV disease resulting in other non-Hodgkin's lymphoma
69980	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
70374	Reticulosarcoma of intra-abdominal lymph nodes
70509	Diffuse non-Hodgkin's centroblastic lymphoma
70740	[M]Malignant reticulosis
70842	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
71031	Reticulosarcoma of lymph nodes of head, face and neck
71117	[M]Malignant lymphoma, undifferentiated cell type NOS
71142	Hodgkin's, lymphocytic-histiocytic predominance unspec site
71238	Lymphosarcoma of lymph nodes of head, face and neck
71262	Malignant lymphoma NOS of intrapelvic lymph nodes
71304	Burkitt's lymphoma NOS
71619	[M]Malignant lymphoma, large cell, noncleaved, diffuse
71625	Lymphosarcoma of unspecified site
71652	[M]Malignant lymphoma, mixed small and large cell, diffuse
71672	Lymphoma stage IV
72196	[M]Malignant lymphoma, lymphocytic, poorly different NOS
72241	[M]Prolymphocytic lymphosarcoma
72433	[M]Reticulosarcoma NOS
72714	Mycosis fungoides of lymph nodes of inguinal region and leg
72725	Malignant lymphoma NOS of intrathoracic lymph nodes
73532	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
89230	[M]Hodgkin's granuloma
90201	T-zone lymphoma
91674	Mycosis fungoides of intra-abdominal lymph nodes
91900	Hodgkin's disease NOS of lymph nodes of axilla and arm
92068	Nodular lymphoma of intra-abdominal lymph nodes
92245	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
92380	Burkitt's lymphoma of lymph nodes of inguinal region and leg
93951	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
94005	Hodgkin's disease, mixed cellularity NOS
94279	Hodgkin's disease NOS of spleen
94407	Hodgkin's mixed cellularity of lymph nodes head, face, neck
94935	Lymphoma stage II
94995	Nodular lymphoma of lymph nodes of inguinal region and leg
95012	Mycosis fungoides of lymph nodes of multiple sites
95049	Hodgkin's lymphocytic depletion of unspecified site
95058	Reticulosarcoma of spleen
95338	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
95545	Maltoma
95630	True histiocytic lymphoma
95715	Mucosa-associated lymphoma
96183	[M]Hodgkin's disease,lymphocytic depletion,diffuse fibrosis
96379	Mycosis fungoides of lymph nodes of axilla and upper limb
97577	Burkitt's lymphoma of intra-abdominal lymph nodes
97746	Hodgkin's disease NOS of lymph nodes of multiple sites
97756	[M]Sezary's disease
97852	[M]Malignant lymphoma, centroblastic type, follicular
97863	Hodgkin's disease, mixed cellularity of unspecified site
98596	[X]Other types of diffuse non-Hodgkin's lymphoma
98840	Hodgkin's paragranuloma of intra-abdominal lymph nodes
98909	Hodgkin's granuloma of lymph nodes of head, face and neck

Lymphoma

Medical code	Read term
98961	[M]Malignant lymphoma, centroblastic-centrocytic, follicular
99012	Hodgkin's disease NOS of lymph nodes inguinal region and leg
99200	[M]Hodgkin's disease, nodular sclerosis, cellular phase
99240	Reticulosarcoma NOS
99655	[M]Lymphosarcoma NOS
99887	Other specified reticulosarcoma or lymphosarcoma
99951	Reticulosarcoma or lymphosarcoma NOS
100006	Burkitt's lymphoma of intrathoracic lymph nodes
100352	Lymphosarcoma of lymph nodes of inguinal region and leg
100423	Hodgkin's paragranuloma of lymph nodes of head, face, neck
100532	Sezary's disease NOS
100544	[M]Reticulosarcoma, nodular
101114	Diffuse non-Hodgkin's large cell lymphoma
101429	[M]Lymphogranuloma, malignant
101530	Hodgkin's disease, lymphocytic depletion NOS
101715	Hodgkin's disease, lymphocytic depletion of spleen
102158	Letterer-Siwe disease of intrathoracic lymph nodes
102594	Diffuse large B-cell lymphoma
103245	Lymphosarcoma of spleen

Myeloma

Medical code	Read term
3451	Other paraproteinaemias
3672	[M]Myeloma NOS
4944	Multiple myeloma
7586	Monoclonal gammopathy
10395	ZERIDAME SR tablets 150mg [ACTAVIS]
12386	Paraproteinaemia NOS
13801	Serum paraprotein level
15211	Myelomatosis
15883	Monoclonal paraproteinaemia
18744	[M]Multiple myeloma
19028	Solitary myeloma
19647	Electrophoresis: paraprotein
31671	[M]Plasma cell myeloma
37182	Multiple myeloma and immunoproliferative neoplasms
39244	Urine paraprotein level
39490	[M]Plasmacytic myeloma
43312	Myeloma - solitary
43450	Herpes zoster with meningitis
43552	Kahler's disease
46042	Lambda light chain myeloma
52946	Bone marrow: myeloma cells
53647	[M]Myelomatosis
60433	Osteoporosis in multiple myelomatosis
73135	[M]Solitary myeloma
102164	[M]Monostotic myeloma

Neuropathy

Medical Code	Read Term
2342	Diabetic neuropathy
2790	Peripheral neuropathy
2925	Alcoholic polyneuropathy
3958	Polyneuropathy
5002	ZERIDAME SR tablets 150mg [ACTAVIS]
6908	Other idiopathic peripheral neuropathy NOS
7635	Hereditary sensory neuropathy
7795	Diabetes mellitus with neuropathy
8591	Peripheral neuropathy - hereditary or idiopathic
9193	Phantom limb syndrome
10722	Inflammatory and toxic neuropathy
11544	Neuropathic pain
11663	Neuropathic diabetic ulcer - foot
14883	Hereditary or idiopathic peripheral neuropathy NOS
14884	Other idiopathic peripheral neuropathy
15481	Toxic or inflammatory neuropathy NOS
16230	Diabetes mellitus with neurological manifestation
16491	Herpes zoster with meningitis
18016	Phantom limb syndrome with pain
18075	Hereditary and idiopathic peripheral neuropathy
18425	Type 2 diabetes mellitus with polyneuropathy
18534	Ulnar neuropathy
19454	Polyneuropathy in uraemia
22573	Diabetes mellitus NOS with neurological manifestation
24121	Intercostal neuropathy
24216	Postinfectious polyneuritis
24222	Polyneuropathy due to drugs
24226	Polyneuropathy unspecified
24355	Polyneuropathy in vitamin B deficiency
24571	Asymptomatic diabetic neuropathy
24694	Insulin dependent diabetes mellitus with mononeuropathy
28333	Familial neuropathic amyloid
30537	Polyneuropathy in malignant disease
31551	Inflammatory polyneuropathy, unspecified
31790	Polyneuropathy in diabetes
32527	Hereditary motor and sensory neuropathy
34268	Type 2 diabetes mellitus with neurological complications
35465	Hereditary motor and sensory neuropathy type II
35537	[X] Polyneuropathy, unspecified
35785	Chronic painful diabetic neuropathy
36643	Neuropathic arthritis
37315	Diabetic mononeuropathy
38401	Hereditary peripheral neuropathy NOS
39317	Diabetes mellitus, adult onset, + neurological manifestation
39528	Hereditary peripheral neuropathy
39858	[X]Inflammatory polyneuropathy, unspecified
40751	Polyneuropathy in sarcoidosis
41652	Other toxic or inflammatory neuropathy
41716	Insulin dependent diabetes mellitus with polyneuropathy
42831	Type 1 diabetes mellitus with neurological complications
44095	Polyneuropathy in disseminated lupus erythematosus
44512	Idiopathic progressive polyneuropathy
45081	Toxic neuropathy
45467	Non-insulin dependent diabetes mellitus with polyneuropathy
45919	Type 2 diabetes mellitus with neurological complications
46301	Type 1 diabetes mellitus with polyneuropathy
46937	Neuropathy in association with hereditary ataxia
47409	Type II diabetes mellitus with polyneuropathy
47465	Polyneuropathy in polyarteritis nodosa
49146	Type I diabetes mellitus with neurological complications
50527	Type II diabetes mellitus with polyneuropathy
50813	Type II diabetes mellitus with mononeuropathy

Neuropathy

Medical Code	Read Term
52089	Polyneuropathy in diphtheria
52283	Insulin-dependent diabetes mellitus with neurological comps
54124	Other toxic agent polyneuropathy
55076	[X]Polyneuropathies & other disord of peripheral nerv syst
55842	Non-insulin-dependent diabetes mellitus with neuro comps
56159	Control of phantom sensation technique
56272	Polyneuropathy in disease EC
56910	Hereditary motor and sensory neuropathy type I
57313	Polyneuropathy in collagen vascular disease
58758	Polyneuropathy in porphyria
59903	Diabetic amyotrophy
61523	Other specified diabetes mellitus with neurological comps
61829	Type 1 diabetes mellitus with neurological complications
62401	Polyneuropathy in rheumatoid arthritis
62674	Type 2 diabetes mellitus with mononeuropathy
63555	Polyneuropathy in disease NOS
66336	Polyneuropathy in amyloidosis
67853	Diabetes mellitus, juvenile, + neurological manifestation
67905	Type II diabetes mellitus with neurological complications
68105	Type 1 diabetes mellitus with mononeuropathy
68960	Polyneuropathy in hypoglycaemia
69047	Serum neuropathy
71258	Polyneuropathy in collagen vascular disease NOS
72320	Non-insulin dependent diabetes mellitus with mononeuropathy
72922	[X]Other mononeuropathies of lower limb
73337	Polyneuropathy in beriberi
91741	[X]Other specified mononeuropathies
91943	Type I diabetes mellitus with polyneuropathy
93228	[X]Paraneoplastic neuromyopathy and neuropathy
93868	[X]Other mononeuropathies of upper limb
95351	Type II diabetes mellitus with mononeuropathy
96256	Axonal sensorimotor neuropathy
97306	[X]Other specified polyneuropathies
97449	[X]Other hereditary and idiopathic neuropathies
97479	[X]Other inflammatory polyneuropathies
97848	Mumps polyneuropathy
98616	Type II diabetes mellitus with neurological complications
99231	Type I diabetes mellitus with mononeuropathy
99855	Neuropathic foot ulcer
100064	Polyneuropathy in mumps
101311	Insulin dependent diabetes mellitus with polyneuropathy
101735	Insulin-dependent diabetes mellitus with neurological comps
105825	Familial amyloid polyneuropathy type III
106103	Hereditary motor and sensory neuropathy type III
107322	[X]Other mononeuropathies in diseases classified elsewhere

OID

Medical code	Read term
938	Pancytopenia NOS
5823	Pancytopenia - acquired
10955	Di George syndrome
18781	Chronic granulomatous disease
21975	ZERIDAME SR tablets 150mg [ACTAVIS]
31275	Pancytopenia with malformation
31322	Wiskott - Aldrich syndrome
31491	Pancytopenia-dysmelia
42394	Job's syndrome
42439	Thrombocytopenic eczema with immunodeficiency
48293	Severe combined immunodeficiency
57322	Common variable immunodeficiency
61326	Pancytopenia with pancreatitis
62236	Combined immunity deficiency
62328	Combined immunity deficiency NOS
73583	Ataxia-telangiectasia

Herpes zoster with meningitis

Oral corticosteroids

Product Code	Product Name
44	prednisolone enteric coated tablets 5mg
95	prednisolone tablets 5mg
186	dexamethasone elixir 0.5mg/5ml
229	cortisone acetate tablets 25mg
557	ZERIDAME SR tablets 150mg [ACTAVIS]
578	prednisolone tablets 1mg
955	prednisolone sodium phosphate soluble tablet 5mg
1063	PREDNESOL tablets 5mg [SOVEREIGN]
1280	dexamethasone tablets 2mg
1380	ENTOCORT CR modified release capsules 3mg [ASTRAZENEC]
1709	hydrocortisone pellets 2.5 mg loz
1971	BETNESOL tablets 0.5mg [FOCUS]
2044	prednisone 2.5 mg tab
2130	methylprednisolone tablets 4mg
2368	prednisolone tablets 2.5mg
2390	prednisolone e/c 1 mg tab
2704	prednisolone tablets 25mg
2799	Herpes zoster with meningitis
2949	prednisone tablets 5mg
3059	prednisolone 50 mg tab
3345	SINTISONE tablets [PHARMACIA]
3418	hydrocortisone tablets 10mg
3557	prednisone tablets 1mg
3898	budesonide modified release capsules 3mg
3969	dexamethasone 8 mg tab
3992	deflazacort tablets 6mg
4535	hydrocortisone tablets 20mg
4779	dexamethasone tablets 0.5mg
4943	dexamethasone sugar free oral solution 2mg/5ml
5157	dexamethasone oral solution 2mg/5ml
5490	DELTACORTRIL ENTERIC tablets 5mg [ALLIANCE]
5913	DELTACORTRIL ENTERIC tablets 2.5mg [ALLIANCE]
6095	budesonide capsules 3mg
6098	HYDROCORTONE tablets 10mg [M S D]
7286	betamethasone sodium phosphate soluble tablet 500micrograms
7548	cortisone acetate capsules 5mg
7584	prednisolone 4 mg tab
7710	prednisolone 15 mg tab
7934	prednisone 30 mg tab
8261	MEDRONE tablets 16mg [PHARMACIA]
9375	deflazacort tablets 1mg
9727	prednisolone tablets 50mg
9994	DECADRON tablets 0.5mg [M S D]
10552	methylprednisolone tablets 16mg
10574	cortisone acetate tablets 5mg
10683	MEDRONE tablets 2mg [PHARMACIA]
10684	methylprednisolone tablets 2mg
10754	HYDROCORTISTAB tablets 20mg [WAYMADE]
10864	betamethasone tablets 500micrograms
11149	BETNELAN tablets 0.5mg [FOCUS]
12398	CORTELAN tablets 25mg [GLAXO]
12400	CORTISYL tablets 25mg [AVENTIS]
13043	HYDROCORTONE tablets 20mg [M S D]
13522	prednisolone 2 mg tab
13615	prednisone 10 mg tab
14076	hydrocortisone sugar free oral suspension 5mg/5ml
14172	methylprednisolone tablets 100mg
15471	hydrocortisone 25 mg tab
15555	MEDRONE tablets 4mg [PHARMACIA]
15617	LEDERCORT tablets 4mg [WYETH PHAR]
16525	BUDENOFALK capsules 3mg [DR FALK]
16724	prednisone 50 mg tab

Oral corticosteroids

Product Code	Product Name
17101	dexamethasone 750 mcg tab
17410	deflazacort tablets 30mg
18042	MEDRONE tablets 100mg [PHARMACIA]
18637	CORTISTAB tablets 25mg [WAYMADE]
18955	hydrocortisone 4.5 mg loz
19141	PREDNISOLONE soluble tablet 5mg [SOVEREIGN]
19908	triamcinolone tablets 2mg
20095	PRECORTISYL FORTE tablets 25mg [AVENTIS]
20577	CALCORT tablets 6mg [SHIRE]
20670	prednisolone e/c
20731	hydrocortisone pellets
21218	DEXSOL oral solution 2mg/5ml [ROSEMONT]
21417	PREDNISOLONE tablets 5mg [HILLCROSS]
21465	betamethasone .1 mg tab
21833	DECORTISYL tablets 5mg [ROUSSEL]
21903	ORADEXON-ORGANON tablets 2mg [ORGANON]
22555	CALCORT tablets 1mg [SHIRE]
22827	betamethasone .1 mg pel
23111	triamcinolone tablets 4mg
23210	CORTISTAB tablets 5mg [WAYMADE]
23512	PRECORTISYL tablets 5mg [HOECHSTMAR]
23788	cortisone acetate 2.5 mg tab
24014	LEDERCORT tablets 2mg [WYETH PHAR]
24716	prednisolone e/c
25272	PRECORTISYL tablets 1mg [HOECHSTMAR]
27083	betamethasone valerate .1 mg tab
27720	hydrocortisone
27889	prednisolone
27959	prednisolone
27962	DELTASTAB tablets 1mg [WAYMADE]
28375	PREDNISOLONE enteric coated tablets 2.5mg [HILLCROSS]
28376	PREDNISOLONE enteric coated tablets 2.5mg [BIOREX]
28615	methylprednisolone l/a 4 mg cap
28859	DELTASTAB tablets 5mg [WAYMADE]
29112	CALCORT tablets 30mg [SHIRE]
29322	betamethasone loz
29333	PREDNISOLONE tablets 5mg [ACTAVIS]
31327	prednisolone steaglate tablets 6.65mg
31532	PREDNISOLONE enteric coated tablets 5mg [HILLCROSS]
32803	PREDNISOLONE enteric coated tablets 5mg [ACTAVIS]
32835	PREDNISOLONE tablets 5mg [WOCKHARDT]
33639	cortisone acetate msd 25 mg tab
33691	PREDNISOLONE enteric coated tablets 5mg [BIOREX]
33988	PREDNISOLONE tablets 5mg [CO-PHARMA]
33990	PREDNISOLONE tablets 5mg [IVAX]
34109	prednisolone enteric coated tablets 5mg
34393	PREDNISOLONE enteric coated tablets 5mg [TEVA]
34404	PREDNISOLONE tablets 1mg [ACTAVIS]
34452	PREDNISOLONE tablets 1mg [HILLCROSS]
34461	PREDNISOLONE enteric coated tablets 2.5mg [ACTAVIS]
34631	PREDNISOLONE tablets 1mg [CO-PHARMA]
34660	PREDNISOLONE tablets 1mg [KENT]
34748	PREDNISOLONE tablets 1mg [TEVA]
34781	PREDNISOLONE tablets 5mg [KENT]
34801	DEXAMETHASONE elixir 0.5mg/5ml [ROSEMONT]
34880	DEXAMETHASONE tablets 2mg [ORGANON]
34914	PREDNISOLONE tablets 1mg [CELLTECH]
34915	DEXAMETHASONE tablets 0.5mg [ORGANON]
34978	PREDNISOLONE tablets 1mg [WOCKHARDT]
36055	DEXAMETHASONE tablets 2mg [HILLCROSS]
36686	cortisone acetate msd 5 mg tab
37203	beclometasone gastro-resistant modified release tablets 5mg

Oral corticosteroids

Product Code	Product Name
38022	hydrocortisone oral suspension 10mg/5ml
38054	hydrocortisone tablets
38407	prednisolone (roi) tablets 20mg
39067	CLIPPER gastro-resistant modified release tablets 5mg [CHIESI]
41335	CALCORT tablets 6mg [SANOFI/AVE]
41515	PREDNISOLONE tablets 5mg [TEVA]
41745	PREDNISOLONE tablets 25mg [WINTHROP]
43544	PREDNISONE tablets 5mg [KNOLL]
44380	prednisone modified release tablet 1mg
44723	prednisone modified release tablet 5mg
44802	LODOTRA modified release tablet 5mg [NAPPPHARM]
44803	LODOTRA modified release tablet 2mg [NAPPPHARM]
45234	dexamethasone capsules
45302	PREDNISOLONE tablets 5mg [BIOREX]
46711	prednisone modified release tablet 2mg

Other immunosuppressive therapy

Product Code	Product Name
270	azathioprine injection 50mg/vial
451	azathioprine tablets 25mg
571	azathioprine tablets 50mg
671	IMURAN tablets 25mg [WELLCOME]
770	azathioprine capsules
823	methotrexate tablets 2.5mg
877	methotrexate tablets 10mg
972	NEORAL capsules 25mg [NOVARTIS]
973	NEORAL capsules 100mg [NOVARTIS]
1626	ciclosporin oral solution 100mg/ml
1899	IMURAN tablets 50mg [WELLCOME]
1905	NEORAL oral solution 100mg/ml [NOVARTIS]
2181	methylprednisolone/lignocaine hcl (1ml) 40 mg/ml inj
2837	ciclosporin capsules 50mg
2838	ciclosporin capsules 25mg
2839	tacrolimus twice daily capsules 1mg
3450	mercaptopurine tablets 50mg
3683	PROGRAF twice daily capsules 1mg [ASTELLAS]
3788	hydrocortisone i/v 100 mg inj
3873	hydroxyurea capsules 500mg
3874	busulfan tablets 2mg
3896	ciclosporin capsules 100mg
3918	azathioprine 10 mg tab
3920	SANDIMMUN capsules 25mg [NOVARTIS]
3984	cyclophosphamide tablets 10mg
3985	cyclophosphamide tablets 50mg
4230	mycophenolate mofetil tablets 500mg
4231	NEORAL capsules 50mg [NOVARTIS]
4233	dexamethasone sodium phosphate injection 4mg/ml
4257	hydrocortisone 100 mg inj
4438	mycophenolate mofetil capsules 250mg
4970	leflunomide tablets 100mg
4971	leflunomide tablets 10mg
5089	tacrolimus twice daily capsules 5mg
5600	chlorambucil tablets 2mg
5870	PROGRAF twice daily capsules 500 micrograms [ASTELLAS]
6333	hydroxycarbamide capsules 500mg
6484	sirolimus tablets 2mg
6495	tacrolimus twice daily capsules 500 micrograms
6600	sirolimus tablets 1mg
6882	adalimumab injection 40mg
6884	HYDREA capsules 500mg [SQUIBB]
6934	leflunomide tablets 20mg
7077	mycophenolate mofetil powder for concentrate for solution for infusion 500mg
7336	methotrexate injection 12.5mg/0.5ml
7337	methotrexate injection 10mg/0.4ml
7340	capecitabine tablets 150mg
7341	capecitabine tablets 500mg
7480	cortisone acetate 25 mg inj
8327	methotrexate injection 50mg/3ml
8404	CCNU capsules 40mg [LUNDBECK]
8583	methotrexate injection 25mg/ml
8665	chlorambucil tablets 5mg
8756	etoposide capsules 50mg
8776	azathioprine 100 mg tab
9117	methylprednisolone 40 mg/ml inj
9528	methotrexate injection 5mg/2ml
10328	carboplatin concentrate for solution for infusion 10mg/ml
10729	ENDOXANA tablets 50mg [BAXTER ONC]
11003	CERUBIDIN powder for concentrate for solution for injection 20mg/vial [RHONE]
11334	dexamethasone sodium phosphate IV injection 4mg/ml
12066	RAZOXIN tablets 125mg [CAMBRIDGE]
12067	lomustine capsules 40mg
12150	melphalan tablets 5mg
12339	AZAMUNE tablets 50mg [PENN]
12816	methotrexate injection 100mg/ml
13271	PROGRAF twice daily capsules 5mg [ASTELLAS]
13320	azathioprine tablets 10mg
13428	MAXTREX tablets 2.5mg [PHARMACIA]
13494	SANDIMMUN sugar free solution 100mg/ml [NOVARTIS]
13556	SANDIMMUN capsules 100mg [NOVARTIS]
13604	ESTRACYT capsules 140mg [PHARMACIA]
13735	estramustine phosphate capsules 140mg

Other immunosuppressive therapy

Product Code	Product Name
13952	DECADRON injection 4mg/ml [MSD MORSON]
13972	dexamethasone sodium phosphate injection 5mg/ml
14347	methotrexate injection 20mg/0.8ml
14348	METOJECT injection 20mg/2ml [MEDAC UK]
14381	paclitaxel concentrate for solution for infusion 6mg/ml
14395	IMURAN injection 50mg/vial [ASPEN EURO]
14748	methotrexate sodium injection 25mg/ml
14886	ENBREL powder for solution for injection 25mg [PFIZER]
15405	NOVANTRONE concentrate for solution for infusion 2mg/ml [WYETH PHAR]
15556	azathioprine 125 mg tab
15596	SANDIMMUN capsules 50mg [NOVARTIS]
15921	etanercept powder for solution for injection 25mg
16035	ciclosporin capsules 10mg
16105	cyclophosphamide powder for solution for injection 500mg
16137	NEORAL capsules 10mg [NOVARTIS]
16173	TAXOL concentrate for solution for infusion 6mg/ml [BMS]
16519	methotrexate injection 25mg/1ml
16522	ARAVA tablets 10mg [AVENTIS]
16540	methotrexate injection 15mg/0.6ml
16570	methotrexate injection 7.5mg/0.3ml
16822	infliximab powder for concentrate for solution for infusion 100mg
16838	LEUKERAN tablets 2mg [WELLCOME]
16879	mycophenolate mofetil oral suspension 1g/5ml
16919	CELLCEPT capsules 250mg [ROCHE]
16929	melphalan tablets 2mg
17035	methotrexate suspension 2.5mg/5ml
17186	procarbazine capsules 50mg
17206	azathioprine 50 mg sus
17642	ARAVA tablets 20mg [AVENTIS]
17672	methotrexate injection 22.5mg/0.9ml
18063	XELODA tablets 500mg [ROCHE]
18070	fluorouracil capsules 250mg
18236	carboplatin injection 50mg/vial
18238	dacarbazine powder for solution for injection 100mg
18424	methotrexate sodium tablets 2.5mg
18460	ARAVA tablets 100mg [AVENTIS]
18476	fludarabine tablets 10mg
18751	etoposide capsules 100mg
18804	CELLCEPT tablets 500mg [ROCHE]
18890	methotrexate injection 17.5mg/0.7ml
19072	OPRISINE tablets 50mg [OPUS]
19257	ENBREL powder for solution for injection 50mg [WYETH PHAR]
19259	dexamethasone injection 8mg/2ml
19335	CYTOSAR injection 500mg [PHARMACIA]
19370	ciclosporin concentrate for solution for infusion 50mg/ml
19556	FLUORO-URACIL capsules 250mg [CAMBRIDGE]
19982	mercaptopurine capsules 10mg
20094	tioguanine tablets 40mg
20097	sirolimus oral solution 1mg/ml
20229	FLUORO-URACIL injection 25mg/ml [CAMBRIDGE]
20951	METHOTREXATE tablets 2.5mg [GOLDSHIELD]
21249	temozolomide capsules 100mg
21250	temozolomide capsules 250mg
21286	imatinib capsules 100mg
21295	GLIVEC capsules 100mg [NOVARTIS]
21318	imatinib tablets 400mg
21668	DECADRON SHOCK PAK 20mg/ml [M S D]
21732	CELLCEPT oral suspension 1g/5ml [ROCHE]
21753	MAXTREX tablets 10mg [PHARMACIA]
21889	methotrexate 25mg/1ml
21899	IMMUNOPRIN tablets 50mg [ASHBOURNE]
22204	busulfan tablets 500micrograms
22392	REMICADE powder for concentrate for solution for infusion 100mg [SCHERING-P]
22640	razoxane tablets 125mg
22982	azathioprine oral solution 50mg/5ml
23270	ALKERAN tablets 5mg [WELLCOME]
23289	RAPAMUNE tablets 1mg [PFIZER]
23832	ELOXATIN powder for concentrate for solution for infusion 100mg [SANOFI S]
23849	TAXOTERE concentrate for intravenous infusion 40mg/ml [AVENTIS]
23850	HUMIRA injection 40mg [ABBOTT]
23871	TREOSULFAN capsules 250mg [FARILLON]
24096	carboplatin injection 150mg
24448	treosulfan capsules 250mg

Other immunosuppressive therapy

Product Code	Product Name
24634	methotrexate injection 25mg/2.5ml
24657	prednisolone pivalate 50 mg inj
24681	fludarabine powder for solution for injection 50mg
24783	methotrexate injection 50mg/2ml
24997	CAELYX concentrate for solution for infusion 2mg/ml [SCHERING-P]
25740	AVASTIN concentrate for solution for infusion 100mg/4ml [ROCHE]
25848	CCNU capsules 10mg [LUNDBECK]
26064	methotrexate injection 20mg/2ml
26066	cyclophosphamide injection 200mg
26097	mycophenolic acid gastro-resistant tablets 360mg
26119	CHLORMETHINE injection 10mg/ml [SOVEREIGN]
26261	BERKAPRINE tablets 50mg [RORER]
26300	dexamethasone shock treatment pack 20mg/ml
26301	MYLERAN tablets 2mg [WELLCOME]
26315	LEUKERAN tablets 5mg [WELLCOME]
26322	cyclophosphamide injection 100mg
26332	thiotepa 15 mg inj
26343	ALKERAN tablets 2mg [WELLCOME]
26387	etanercept powder for solution for injection 50mg
26454	DECADRON injection 4mg/ml [MSD MORSON]
26502	LANVIS tablets 40mg [ALKOPHARMA]
26580	melphalan injection 100mg/vial
26680	ADRIAMYCIN injection 10mg/vial [PHARMACIA]
26790	SANDIMMUN concentrate for solution for infusion 50mg/ml [NOVARTIS]
26947	doxorubicin injection 2mg/ml
27071	dactinomycin powder for solution for injection 500micrograms
27289	MYFORTIC tablets 360mg [NOVARTIS]
27290	MYFORTIC tablets 180mg [NOVARTIS]
27293	oxaliplatin powder for concentrate for solution for infusion 50mg
27342	MAXTREX injection 2.5mg/ml [PHARMACIA]
27400	METOJECT injection 15mg/1.5ml [MEDAC UK]
27404	methotrexate injection 15mg/1.5ml
27428	prednisolone sodium phosphate 16 mg inj
27469	ADRIAMYCIN injection 50mg/vial [PHARMACIA]
27579	methotrexate
27642	methotrexate injection 27.5mg/1.1ml
27922	temozolomide capsules 5mg
28041	methotrexate oral suspension 12.5mg/5ml
28215	dexamethasone sodium phosphate injection 120mg/5ml
28324	cisplatin powder 25mg/vial
28325	epirubicin hydrochloride powder for solution for injection 50mg
28490	rituximab concentrate for solution for infusion 100mg/10ml
28605	NATULAN capsules 50mg [CAMBRIDGE]
28682	dacarbazine powder for solution for injection 200mg
28709	chlormethine injection 10mg
28726	treosulfan leo
28800	GLIVEC tablets 400mg [NOVARTIS]
28889	PHARMORUBICIN injection solution 2mg/ml [PHARMACIA]
28999	RAPAMUNE tablets 2mg [PFIZER]
29069	methotrexate sterile powder 500mg/vial
29229	imatinib tablets 100mg
29340	AZATHIOPRINE tablets 50mg [IVAX]
29652	epirubicin hydrochloride injection 2mg/ml
29675	PURI-NETHOL tablets 50mg [ALKOPHARMA]
29700	TEMODAL capsules 250mg [SCHERING-P]
29743	FLUDARA ORAL tablets 10mg [GENZYME]
29761	VEPESID capsules 50mg [BRISTOL]
29840	cyclophosphamide powder for solution for injection 1000mg
30014	MITHRACIN injection 2.5mg/vial [PFIZER]
30495	IMURAN tablets 10mg [WELLCOME]
30581	CELLCEPT powder for concentrate for solution for infusion 500mg [ROCHE]
30703	methotrexate injection 30mg/1.2ml
30757	mitobronitol (named patient only) 125 mg tab
30780	METHOTREXATE tablets 2.5mg [PHARMACIA]
30836	doxorubicin powder for solution for injection 10mg
30932	methotrexate injection 5mg/0.2ml
31115	etoposide concentrate for solution for infusion 20mg/ml
31193	ENDOXANA tablets 10mg [BAXTER ONC]
31215	AZATHIOPRINE tablets 50mg [KENT]
31223	vinblastine sulphate injection 10mg/vial
31339	idarubicin hydrochloride capsules 10mg
31494	mithramycin injection 2.5mg/vial
31539	epirubicin hydrochloride injection (powder) 20mg

Other immunosuppressive therapy

Product Code	Product Name
31598	MABCAMPATH concentrate for solution for infusion 10mg/ml [SCHERING]
31948	DEXAMETHASONE injection 4mg/ml [MAYNE]
31984	idarubicin hydrochloride capsules 5mg
32101	AZATHIOPRINE tablets 25mg [HILLCROSS]
32111	METHOTREXATE tablets 2.5mg [HOSPIRA]
32204	DTIC-DOME injection 100mg/vial [BAYER]
32229	methotrexate injection 500mg/20ml
32412	MYLERAN tablets 500micrograms [WELLCOME]
32490	temozolomide capsules 20mg
32604	vinblastine sulphate injection 10mg/10ml
32614	SIMULECT powder for solution for infusion 20mg [NOVARTIS]
32774	vinorelbine capsules 20mg
32824	cisplatin concentrate for solution for infusion 1mg/ml
32865	methotrexate injection 10mg/1ml
32972	mercaptopurine tablets 10mg
33123	tacrolimus concentrate for solution for infusion 5mg/1ml
33127	XELODA tablets 150mg [ROCHE]
33171	vinorelbine injection solution 10mg/ml
33174	mitoxantrone concentrate for solution for infusion 2mg/ml
33227	HYCAMTIN powder for concentrate for solution for infusion 4mg [GLAXSK PHA]
33330	HYDROXYCARBAMIDE capsules 500mg [MEDAC UK]
33385	thiotepa powder for solution for injection 15mg
33418	gemcitabine powder for solution for infusion 200mg/vial
33519	UFTORAL capsules 224mg + 100mg [MERCK SER]
33520	uracil with tegafur capsules 224mg + 100mg
33560	docetaxel concentrate for intravenous infusion 40mg/ml
33601	METOJECT injection 25mg/2.5ml [MEDAC UK]
33728	RAPAMUNE oral solution 1mg/ml [PFIZER]
33803	TEMODAL capsules 5mg [SCHERING-P]
33823	GLIVEC tablets 100mg [NOVARTIS]
33878	MYOCET powder for concentrate for solution for infusion 50mg [CEPHALON]
34083	DEXAMETHASONE injection 5mg/ml [ORGANON]
34258	METHOTREXATE injection 20mg/0.8ml [CENT HOME]
34451	AZATHIOPRINE tablets 50mg [GEN (UK)]
34687	AZATHIOPRINE tablets 50mg [HILLCROSS]
34728	CYCLOPHOSPHAMIDE tablets 50mg [PHARMACIA]
34816	AZATHIOPRINE tablets 25mg [GEN (UK)]
34929	METHOTREXATE tablets 10mg [HOSPIRA]
35126	etanercept injection solution 50mg
35226	TEMODAL capsules 20mg [SCHERING-P]
35301	mycophenolic acid gastro-resistant tablets 180mg
35384	TAXOL concentrate for solution for infusion 30mg/5ml [BMS]
35402	methotrexate injection 7.5mg/0.75ml
35419	ENBREL injection solution 25mg [PFIZER]
35518	azathioprine oral suspension 50mg/5ml
35752	methotrexate oral suspension 7.5mg/5ml
35826	mitotane tablets 500mg
35854	paclitaxel concentrate for solution for infusion 30mg/5ml
35855	carboplatin concentrate for solution for infusion 50mg/5ml
35865	METOJECT injection 7.5mg/0.75ml [MEDAC UK]
36008	etanercept injection solution 25mg
36062	dasatinib tablets 50mg
36167	methotrexate injection 1000mg/10ml
36263	EPOSIN concentrate for solution for infusion 20mg/ml [MEDAC UK]
36294	rituximab concentrate for solution for infusion 500mg/50ml
36552	TAXOTERE concentrate for solution for infusion 20mg/0.5ml [AVENTIS]
36556	ENBREL injection solution 50mg [PFIZER]
36575	fluorouracil injection 50mg/ml
36714	oxaliplatin powder for concentrate for solution for infusion 100mg
36792	azathioprine oral solution 50mg/ml
36800	methotrexate oral solution 10mg/5ml
36831	docetaxel concentrate for dilution for infusion solution 20mg/0.5ml
36849	methotrexate oral suspension 10mg/5ml
36957	dasatinib tablets 70mg
37099	melphalan powder for solution for injection 50mg
37117	METOJECT injection 10mg/1ml [MEDAC UK]
37155	tacrolimus suspension 1mg/ml
37238	dasatinib tablets 20mg
37272	pemetrexed powder for concentrate for solution for infusion 500mg
37375	VEPESID capsules 100mg [BRISTOL]
37396	MYELOBROMOL tablets 125mg [DURBIN]
37506	ADVAGRAF once daily modified release capsules 1mg [ASTELLAS]
37542	PARAPLATIN injection 150mg [BRISTOL]

Other immunosuppressive therapy

Product Code	Product Name
37784	CAELYX concentrate for solution for infusion 20mg/10ml [JANSSEN]
37915	basiliximab powder for solution for infusion 10mg
37942	doxorubicin citrate liposomal complex powder for concentrate for solution for infusion 50mg
37985	tacrolimus once daily modified release capsules 1mg
38056	ciclosporin concentrate for solution for infusion 50mg/1ml
38081	ERWINASE powder for solution for injection 10000 units/vial [OPI]
38113	tacrolimus once daily modified release capsules 500 micrograms
38145	bevacizumab concentrate for solution for infusion 100mg/4ml
38185	cisplatin powder for concentrate for solution for infusion 50mg
38254	TYSABRI concentrate for solution for infusion 300mg/15ml [BIOGEN]
38317	nilotinib capsules 200mg
38319	hydroxycarbamide oral solution 500mg/5ml
38453	cisplatin concentrate for solution for infusion 10mg/10ml
38919	ADVAGRAF once daily modified release capsules 5mg [ASTELLAS]
38989	tacrolimus once daily modified release capsules 5mg
38999	docetaxel concentrate for dilution for infusion solution 80mg/2ml
39111	rituximab concentrate for intravenous infusion 10mg/ml
39115	azathioprine capsules 10mg
39307	doxorubicin injection 10mg/5ml
39366	mitoxantrone concentrate for solution for infusion 10mg/5ml
39387	epirubicin hydrochloride injection 100mg/50ml
39388	fluorouracil injection 1g/20ml
39450	carboplatin concentrate for solution for infusion 600mg/60ml
39548	hydroxycarbamide film coated tablets 1000mg
39553	oxaliplatin concentrate for solution for infusion 50mg/10ml
39633	ADVAGRAF once daily modified release capsules 500 micrograms [ASTELLAS]
39895	oxaliplatin concentrate for solution for infusion 100mg/20ml
39919	paclitaxel albumin bound powder for suspension for infusion 100mg
40250	CAELYX concentrate for solution for infusion 50mg/25ml [JANSSEN]
40251	epirubicin hydrochloride injection 200mg/100ml
40273	methotrexate injection 20mg/0.4ml
40280	METOJECT injection 7.5mg/0.15ml [MEDAC UK]
40281	methotrexate injection 15mg/0.3ml
40284	METOJECT injection 15mg/0.3ml [MEDAC UK]
40292	METOJECT injection 20mg/0.4ml [MEDAC UK]
40293	METOJECT injection 25mg/0.5ml [MEDAC UK]
40301	methotrexate injection 7.5mg/0.15ml
40328	methotrexate injection 25mg/0.5ml
40356	METOJECT injection 10mg/0.2ml [MEDAC UK]
40371	methotrexate injection 10mg/0.2ml
40453	TORISEL concentrate for solution for infusion 30mg/1.2ml [PFIZER]
40454	cladribine injection 10mg/5ml
40626	lenalidomide capsules 25mg
40632	basiliximab powder for solution for infusion 20mg
40732	VELCADE powder for solution for injection 3.5mg [ORTHO BIO]
40749	dexamethasone sodium phosphate 5 mg inj
40765	ADVAGRAF once daily modified release capsules 3mg [ASTELLAS]
40780	gemcitabine powder for solution for infusion 1g/vial
40781	carboplatin concentrate for solution for infusion 150mg/15ml
40816	epirubicin hydrochloride injection 50mg/25ml
40964	tacrolimus once daily modified release capsules 3mg
40983	irinotecan hydrochloride concentrate for solution for infusion 40mg/2ml
41058	ENBREL FOR PAEDIATRIC USE powder for solution for injection 25mg [PFIZER]
41086	methotrexate injection 5000mg/50ml
41104	METHOTREXATE tablets 2.5mg [CP PHARM]
41139	REVLIMID capsules 25mg [CELGENE]
41191	natalizumab concentrate for solution for infusion 300mg/15ml
41266	cytarabine injection solution 1g/10ml
41267	mitoxantrone concentrate for solution for infusion 20mg/10ml
41281	carmustine implant 7.7mg
41502	tocilizumab concentrate for solution for infusion 80mg/4ml
41585	METHOTREXATE SODIUM tablets 2.5mg [WYETH PHAR]
41620	AZATHIOPRINE tablets 50mg [TEVA]
41670	AZATHIOPRINE tablets 50mg [CP PHARM]
41960	topotecan powder for concentrate for solution for infusion 1mg
41963	PARAPLATIN concentrate for solution for infusion 10mg/ml [BRISTOL]
42056	lenalidomide capsules 5mg
42273	alemtuzumab concentrate for solution for infusion 30mg/1ml
42372	temozolomide capsules 140mg
42390	dasatinib tablets 100mg
42448	DEXIMUNE capsules 50mg [DEXCEL]
42449	DEXIMUNE capsules 100mg [DEXCEL]
42637	DEXIMUNE capsules 25mg [DEXCEL]

Other immunosuppressive therapy

Product Code	Product Name
42684	vinorelbine concentrate for solution for infusion 10mg/1ml
42696	THYMOGLOBULINE powder for solution for infusion 25mg [GENZYME]
42817	daclizumab concentrate for solution for infusion 25mg/5ml
42924	ciclosporin concentrate for solution for infusion 250mg/5ml
42988	IMURAN tablets 50mg [ASPEN EURO]
43077	IMURAN tablets 25mg [ASPEN EURO]
43081	tacrolimus granules for oral suspension 1mg
43082	tacrolimus granules for oral suspension 200micrograms
43168	ifosfamide injection 2g/vial
43562	AZATHIOPRINE tablets 50mg [ACTAVIS]
43639	PHARMORUBICIN powder for solution for injection 50mg [PHARMACIA]
43703	CIMZIA injection solution 200mg/1ml [UCB]
43781	AFINITOR tablets 10mg [NOVARTIS]
43805	daunorubicin powder for concentrate for solution for injection 20mg/vial
43888	pentostatin powder for solution for injection 10mg
44087	TAXOTERE concentrate for solution for infusion 20mg/1ml [AVENTIS]
44100	certolizumab pegol injection solution 200mg/1ml
44222	raltitrexed powder for concentrate for solution for infusion 2mg
44273	ENDOXANA injection 200mg [BAXTER ONC]
44309	ENDOXANA injection 1000mg [BAXTER ONC]
44387	etoposide phosphate lyophilised powder for injection 100mg
44388	cisplatin concentrate for solution for infusion 50mg/50ml
44425	docetaxel concentrate for solution for infusion 20mg/1ml
44478	LYSODREN tablets 500mg [LAB HRA]
44529	lenalidomide capsules 10mg
44640	ADOPORT twice daily capsules 500 micrograms [SANDOZ]
44641	ADOPORT twice daily capsules 5mg [SANDOZ]
44740	bortezomib powder for solution for injection 3.5mg
44783	sirolimus tablets 500 micrograms
44804	ADOPORT twice daily capsules 1mg [SANDOZ]
44908	methotrexate injection 30mg/0.6ml
44926	tacrolimus oral suspension 2.5mg/5ml
45026	doxorubicin injection 200mg/100ml
45043	MYFENAX tablets 500mg [TEVA]
45147	paclitaxel concentrate for solution for infusion 150mg/25ml
45165	methotrexate injection 20mg/1ml
45393	ARZIP tablets 500mg [WINTHROP]
45489	MYFENAX capsules 250mg [TEVA]
45558	methotrexate injection 25mg/1.25ml
45647	canakinumab powder for solution for injection 150mg
45820	nilotinib capsules 150mg
46039	methotrexate injection 30mg/1.5ml
46070	everolimus tablets 5mg
46098	METOJECT injection 12.5mg/0.25ml [MEDAC UK]
46129	methotrexate injection 22.5mg/0.45ml
46152	methotrexate injection 12.5mg/0.25ml
46156	methotrexate injection 17.5mg/0.35ml
46197	METOJECT injection 22.5mg/0.45ml [MEDAC UK]
46205	lenalidomide capsules 15mg
46265	METOJECT injection 17.5mg/0.35ml [MEDAC UK]
46324	MODIGRAF granules for oral suspension 200micrograms [ASTELLAS]
46325	MODIGRAF granules for oral suspension 1mg [ASTELLAS]
46348	tocilizumab concentrate for solution for infusion 200mg/10ml
46370	golimumab pre-filled pen injection solution 50mg
46395	CAPIMUNE capsules 100mg [GEN (UK)]
46407	methotrexate injection 1000mg/40ml
46637	CAPIMUNE capsules 25mg [GEN (UK)]

PHN diagnosis

Medical Code	Read Term
1598	Post-herpetic neuralgia
7584	Post-herpetic trigeminal neuralgia
10223	Postherpetic neuralgia
11498	ZERIDAME SR tablets 150mg [ACTAVIS]
17180	Postzoster neuralgia
31709	Postherpetic polyneuropathy

PHN - Neuralgia diagnosis

Medical Code	Read Term
2284	Neuralgia unspecified
23839	Neuralgia, neuritis or radiculitis NOS
54992	Neuralgia, neuritis and radiculitis unspecified

PHN- Neuropathic pain diagnosis

Medical code	Read term
11544	Neuropathic pain

PHN treatment - anticonvulsants

Product Code	Product Name
107	phenytoin capsules 25mg
432	carbamazepine tablets 100mg
584	sodium valproate gastro-resistant tablets 200mg
596	carbamazepine liquid 100mg/5ml
652	carbamazepine tablets 400mg
660	gabapentin capsules 100mg
790	pregabalin capsules 25mg
819	pregabalin capsules 75mg
1158	carbamazepine tablets 200mg
1370	phenytoin capsules 100mg
1398	EPANUTIN capsules 100mg [PFIZER]
1550	sodium valproate syrup 200mg/5ml
1584	gabapentin capsules 300mg
2062	phenytoin sodium tablets 100mg
2079	lamotrigine tablets 25mg
2080	lamotrigine tablets 50mg
2081	lamotrigine dispersible tablet 5mg
2082	EPILIM sugar free liquid 200mg/5ml [SANOFI/AVE]
2085	TEGRETOL tablets 200mg [NOVARTIS]
2128	phenytoin capsules 50mg
2388	carbamazepine modified release tablet 200mg
2782	phenytoin sodium tablets 50mg
2822	EPILIM EC tablets 500mg [SANOFI/AVE]
2823	TEGRETOL RETARD controlled release tablet 200mg [NOVARTIS]
2824	TEGRETOL RETARD controlled release tablet 400mg [NOVARTIS]
3068	phenytoin capsules 300mg
3107	EPILIM CHRONO controlled release tablet 500mg [SANOFI/AVE]
3350	sodium valproate gastro-resistant tablets 500mg
3569	carbamazepine modified release tablet 400mg
3731	EPILIM EC tablets 200mg [SANOFI/AVE]
3733	EPILIM CHRONO controlled release tablet 300mg [SANOFI/AVE]
3734	EPILIM CHRONO controlled release tablet 200mg [SANOFI/AVE]
3845	sodium valproate sugar free liquid 200mg/5ml
3881	EPANUTIN capsules 50mg [PFIZER]
3886	lamotrigine tablets 200mg
4066	TEGRETOL tablets 400mg [NOVARTIS]
4175	EPANUTIN suspension 30mg/5ml [PFIZER]
4195	EPILIM crushable tablets 100mg [SANOFI/AVE]
4490	phenytoin suspension 30mg/5ml
4495	EPILIM syrup 200mg/5ml [SANOFI/AVE]
4502	sodium valproate crushable tablets 100mg
4586	LAMICTAL tablets 25mg [WELLCOME]
4781	gabapentin capsules 400mg
4913	TEGRETOL sugar free liquid 100mg/5ml [NOVARTIS]
4982	carbamazepine chewable tablet 100mg
5076	lamotrigine tablets 100mg
5221	gabapentin tablets 600mg
5449	oxcarbazepine tablets 300mg
5587	phenytoin sodium capsules 50mg
5617	CONVULEX enteric coated soft gelatin capsules 300mg [PHARMACIA]
5658	lamotrigine dispersible tablet 25mg
5722	LAMICTAL dispersible tablet 100mg [WELLCOME]
5848	valproic acid (as semisodium salt) enteric coated tablets 250mg
5907	lamotrigine dispersible tablet 100mg
5977	TEGRETOL tablets 100mg [NOVARTIS]
5997	CONVULEX enteric coated soft gelatin capsules 150mg [PHARMACIA]
6304	NEURONTIN capsules 300mg [PFIZER]
6305	valproic acid (as semisodium salt) enteric coated tablets 500mg
6409	lamotrigine dispersible tablet 2mg
6436	oxcarbazepine tablets 600mg
6504	phenytoin sodium capsules 100mg
6552	oxcarbazepine tablets 150mg

PHN treatment - anticonvulsants

Product Code	Product Name
6560	sodium valproate modified release tablet 500mg
6584	LYRICA capsules 75mg [PFIZER]
6594	phenytoin sodium capsules 300mg
6624	phenytoin sodium capsules 25mg
6631	pregabalin capsules 150mg
6711	sodium valproate modified release tablet 300mg
6936	pregabalin capsules 50mg
6949	pregabalin capsules 200mg
6999	pregabalin capsules 100mg
7005	pregabalin capsules 300mg
7011	sodium valproate with valproic acid modified release tablet 300mg
7020	TRILEPTAL tablets 300mg [NOVARTIS]
7021	TRILEPTAL tablets 150mg [NOVARTIS]
7022	LAMICTAL tablets 50mg [WELLCOME]
7023	LAMICTAL tablets 100mg [WELLCOME]
7064	DEPAKOTE tablets 250mg [SANOFI/AVE]
7208	LYRICA capsules 100mg [PFIZER]
7209	LYRICA capsules 50mg [PFIZER]
7394	LYRICA capsules 200mg [PFIZER]
7498	EPANUTIN capsules 25mg [PFIZER]
7538	gabapentin tablets 800mg
7804	PHENYTOIN SODIUM/ PHENOBARBITONE CAP
8452	PHENYTOIN 150 MG SUS
8885	ORLEPT tablets 500mg [WOCKHARDT]
9168	SOD VALPROATE C/R 200 MG TAB
9281	sodium valproate with valproic acid modified release tablet 200mg
9678	phenytoin sugar-free suspension 90mg/5ml
9759	DEPAKOTE tablets 500mg [SANOFI/AVE]
9979	gabapentin capsules & tablets 300mg + 600mg
10007	NEURONTIN capsules 100mg [PFIZER]
10111	LAMICTAL tablets 200mg [WELLCOME]
10189	LYRICA capsules 300mg [PFIZER]
10263	EPANUTIN capsules 300mg [PFIZER]
11075	sodium valproate with valproic acid modified release tablet 500mg
11445	LAMICTAL dispersible tablet 25mg [WELLCOME]
11696	carbamazepine chewable tablet 200mg
12469	EPANUTIN READY MIXED PARENTERAL injection 250mg/5ml [PFIZER]
12880	TEGRETOL CHEWTAB tablets 200mg [NOVARTIS]
12931	EPIMAZ RETARD tablets 200mg [IVAX]
12932	EPIMAZ tablets 100mg [IVAX]
13112	CARBAGEN SR tablets 200mg [GEN (UK)]
13524	TEGRETOL CHEWTAB tablets 100mg [NOVARTIS]
14199	oxcarbazepine sugar free oral suspension 60mg/ml
15082	TEGRETOL suppository 250mg [NOVARTIS]
15106	PHENYTOIN 30 MG TAB
15126	LAMICTAL dispersible tablet 5mg [WELLCOME]
15650	valproic acid enteric coated soft gelatin capsules 300mg
16021	valproic acid enteric coated soft gelatin capsules 500mg
16149	Herpes zoster with meningitis
16215	NEURONTIN capsules 400mg [PFIZER]
16404	NEURONTIN TITRATION PACK capsules & tablets 300mg + 600mg [PARKE]
16509	LYRICA capsules 150mg [PFIZER]
16542	LYRICA capsules 25mg [PFIZER]
16609	sodium valproate powder for solution for injection 400mg
17152	ORLEPT tablets 200mg [WOCKHARDT]
17177	EPANUTIN INFATAB 50mg [PFIZER]
17428	carbamazepine suppository 250mg
17429	carbamazepine suppository 125mg
17564	NEURONTIN tablets 600mg [PFIZER]
17978	TERIL RETARD modified release tablet 200mg [TARO]
18011	TERIL RETARD modified release tablet 400mg [TARO]
18211	gabapentin oral solution 250mg/5ml

PHN treatment - anticonvulsants

Product Code	Product Name
18567	ZERIDAME SR tablets 150mg [ACTAVIS]
18614	valproic acid enteric coated soft gelatin capsules 150mg
18762	EPIMAZ tablets 200mg [IVAX]
18763	EPIMAZ tablets 400mg [IVAX]
18886	CONVULEX enteric coated soft gelatin capsules 500mg [PHARMACIA]
19296	LAMICTAL dispersible tablet 2mg [WELLCOME]
19326	PHENYTOIN 25 MG SYR
20004	EPILIM powder for solution for injection 400mg [SANOFI/AVE]
21441	TEGRETOL suppository 125mg [NOVARTIS]
21854	PENTRAN tablets 100mg [BERK]
22131	PHENOBARBITONE & PHENYTOIN 60 MG CAP
22286	PHENOBARBITONE 60MG & PHENYTOIN 100MG MG TAB
24153	ORLEPT sugar free liquid 200mg/5ml [WOCKHARDT]
24637	phenytoin sodium injection 250mg/5ml
25815	gabapentin oral suspension 400mg/5ml
25903	fosphenytoin sodium concentrate for solution for infusion 750mg/10ml
26012	CARBAGEN SR tablets 400mg [GEN (UK)]
26902	TRILEPTAL oral suspension 60mg/ml [NOVARTIS]
27113	PHENYTOIN SODIUM tablets 100mg [TEVA]
27221	LAMICTAL NON-VALPROATE ADD-ON START PACK TAB 25 mg
27454	GABAPENTIN capsules 300mg [TEVA]
27541	PHENYTOIN
27881	PHENYTOIN
27967	PRO-EPANUTIN concentrate for solution for infusion 750mg/10ml [PFIZER]
28345	CARBAMAZEPINE tablets 100mg [APS]
28713	NEURONTIN tablets 800mg [PFIZER]
29619	LAMOTRIGINE tablets 25mg [ACTAVIS]
29620	LAMOTRIGINE tablets 100mg [ACTAVIS]
30081	SODIUM VALPROATE CR tablets 500mg [HILLCROSS]
30392	PENTRAN tablets 50mg [BERK]
30509	TIMONIL RETARD modified release tablet 400mg [CP PHARM]
30763	CARBAMAZEPINE tablets 100mg [HILLCROSS]
31634	PHENYTOIN SODIUM/ PHENOBARBITONE SODIUM TAB
32900	CARBAMAZEPINE SR tablets 200mg [IVAX]
32920	LAMOTRIGINE tablets 25mg [GEN (UK)]
32931	CARBAMAZEPINE tablets 400mg [APS]
33058	EPIVAL CR tablets 500mg [CHANELLE]
33106	SODIUM VALPROATE sugar free oral solution 200mg/5ml [IVAX]
34120	SODIUM VALPROATE gastro-resistant tablets 200mg [HILLCROSS]
34144	PHENYTOIN SODIUM tablets 100mg [ACTAVIS]
34150	VALPROATE SODIUM gastro-resistant tablets 200mg [IVAX]
34151	VALPROATE SODIUM gastro-resistant tablets 500mg [IVAX]
34178	SODIUM VALPROATE gastro-resistant tablets 500mg [HILLCROSS]
34370	CARBAMAZEPINE controlled release tablet 200mg [HILLCROSS]
34414	SODIUM VALPROATE tablets 200mg [STERWIN]
34506	GABAPENTIN capsules 100mg [TEVA]
34592	PHENYTOIN SODIUM tablets 100mg [HILLCROSS]
34606	GABAPENTIN capsules 100mg [HILLCROSS]
34626	SODIUM VALPROATE gastro-resistant tablets 200mg [GEN (UK)]
34632	SODIUM VALPROATE gastro-resistant tablets 200mg [TEVA]
34699	PHENYTOIN sugar-free suspension 90mg/5ml [ROSEMONT]
34707	SODIUM VALPROATE gastro-resistant tablets 200mg [IVAX]
34716	GABAPENTIN capsules 300mg [HILLCROSS]
34883	SODIUM VALPROATE sugar free liquid 200mg/5ml [HILLCROSS]
34904	CARBAMAZEPINE tablets 200mg [HILLCROSS]
34946	GABAPENTIN tablets 600mg [TEVA]
34958	CARBAMAZEPINE tablets 100mg [BERK]
35024	sodium valproate modified release capsules 300mg
35471	sodium valproate modified release capsules 150mg
35732	LAMOTRIGINE dispersible tablet 25mg [ARROW]
35747	EPISENTA prolonged release capsules 300mg [BEACON]
35755	sodium valproate modified release granules 500mg

PHN treatment - anticonvulsants

Product Code	Product Name
36318	sodium valproate modified release granules 1000mg
36633	EPISENTA prolonged release capsules 150mg [BEACON]
36634	EPISENTA prolonged release granules 1000mg [BEACON]
37058	carbamazepine oral suspension 500mg/5ml
37306	SODIUM VALPROATE syrup 200mg/5ml [STERWIN]
37584	EPISENTA prolonged release granules 500mg [BEACON]
37611	EPIVAL CR tablets 300mg [CHANELLE]
37800	CARBAMAZEPINE controlled release tablet 200mg [LAGAP]
37801	pregabalin capsules 225mg
38293	LYRICA capsules 225mg [PFIZER]
38507	EPILIM CHRONOSPHERE modified release granules 100mg [SANOFI/AVE]
38508	EPILIM CHRONOSPHERE modified release granules 250mg [SANOFI/AVE]
38939	EPILIM 200 gastro-resistant tablets 200mg [SANOFI/AVE]
38949	EPILIM 500 gastro-resistant tablets 500mg [SANOFI/AVE]
39039	sodium valproate modified release tablet 200mg
39276	sodium valproate with valproic acid modified release granules 250mg
39279	EPILIM CHRONOSPHERE modified release granules 500mg [SANOFI/AVE]
39427	sodium valproate with valproic acid modified release granules 750mg
39452	sodium valproate with valproic acid modified release granules 500mg
39506	LAMOTRIGINE tablets 50mg [ACTAVIS]
39550	EPILIM CHRONOSPHERE modified release granules 750mg [SANOFI/AVE]
39714	LAMOTRIGINE tablets 25mg [TEVA]
39715	LAMOTRIGINE tablets 100mg [TEVA]
39930	EPILIM CHRONOSPHERE modified release granules 50mg [SANOFI/AVE]
40070	sodium valproate injection 300mg/3ml
40395	SODIUM VALPROATE crushable tablets 100mg [GEN (UK)]
40400	SODIUM VALPROATE gastro-resistant tablets 500mg [CP PHARM]
40403	CARBAMAZEPINE controlled release tablet 400mg [LAGAP]
40404	CARBAMAZEPINE controlled release tablet 400mg [HILLCROSS]
41137	sodium valproate with valproic acid modified release granules 100mg
41726	CARBAMAZEPINE tablets 100mg [IVAX]
42038	EPILIM CHRONOSPHERE modified release granules 1000mg [SANOFI/AVE]
42090	SODIUM VALPROATE sugar free liquid 200mg/5ml [WINTHROP]
43178	sodium valproate with valproic acid modified release granules 1000mg
43387	sodium valproate with valproic acid modified release granules 50mg
43417	CARBAMAZEPINE tablets 400mg [HILLCROSS]
43451	CARBAMAZEPINE controlled release tablet 400mg [GEN (UK)]
43648	sodium valproate oral liquid
43742	sodium valproate injection 1000mg/10ml
44022	gabapentin oral suspension 250mg/5ml
44187	GABAPENTIN tablets 600mg [HILLCROSS]
44261	GABAPENTIN oral solution 250mg/5ml [BCM]
44472	sodium valproate modified release granules 100mg
44718	sodium valproate modified release granules 750mg
44903	SODIUM VALPROATE gastro-resistant tablets 500mg [WINTHROP]
45106	sodium valproate modified release granules 250mg
45344	SODIUM VALPROATE solution 200mg/5ml [HILLCROSS]
45419	sodium valproate modified release granules 50mg
45572	lamotrigine suppository 50mg
45903	TEGRETOL PROLONGED RELEASE tablets 400mg [NOVARTIS]
45941	TEGRETOL PROLONGED RELEASE tablets 200mg [NOVARTIS]
46774	SODIUM VALPROATE gastro-resistant tablets 500mg [TEVA]
46775	LAMOTRIGINE tablets 50mg [TEVA]
46888	CARBAMAZEPINE controlled release tablet 200mg [GEN (UK)]
46972	CARBAMAZEPINE tablets 200mg [IVAX]
47014	phenytoin oral suspension 90mg/5ml
47294	CARBAMAZEPINE SR tablets 400mg [IVAX]

PHN treatment - capaiscin

Product Code	Product Name
1808	capsaicin cream 0.075%
7692	AXSAIN cream 0.075% [CEPHALON]

PHN treatment - lidocaine

Product Code	Product Name
14841	LIDODERM patch 5% [ENDO]
14855	lidocaine medicated plaster 5%
35043	ZERIDAME SR tablets 150mg [ACTAVIS]
38216	lidocaine with tetracaine plaster 70mg + 70mg
38257	RAPYDAN plaster 70mg + 70mg [EUROCEPT]

PHN treatment- Mild PKs

Product Code	Product Name
7	paracetamol tablets 500mg
15	ibuprofen tablets 400mg
111	ASPIRIN 40 MG CAP
124	DISTALGESIC tablets [CLINIGEN]
139	paracetamol capsules 500mg
175	PARACETAMOL 1 GM SUP
215	IBUPROFEN 200 MG CAP
216	ASPIRIN 70 MG TAB
258	PANADOL tablets 500mg [GLAXSK CON]
262	paracetamol suspension 250mg/5ml
345	IBUPROFEN S/R 300 MG CAP
360	BRUFEN syrup 100mg/5ml [ABBOTT]
383	ASPIRIN 60 MG TAB
392	ibuprofen modified release capsules 200mg
395	ZERIDAME SR tablets 150mg [ACTAVIS]
402	NUROFEN caplets 200mg [CROOKES]
407	BRUFEN granules 600mg [ABBOTT]
416	ibuprofen tablets 200mg
484	EQUAGESIC tablets [WYETH PHAR]
586	ibuprofen capsules 200mg
645	aspirin suppository 300mg
647	ibuprofen syrup 100mg/5ml
685	ASPAV dispersible tablet [ACTAVIS]
784	ibuprofen modified release capsules 300mg
849	IBUMED tablets 400mg [MEDIPHARMA]
899	CALPOL SIX PLUS suspension 250mg/5ml [MCNEIL]
1030	JUNIFEN sugar-free suspension 100mg/5ml [CROOKES]
1086	ibuprofen tablets 600mg
1392	ibuprofen modified release tablet 800mg
1404	PARACETAMOL suspension 120mg/5ml [ROSEMONT]
1468	ibuprofen soluble tablet 200mg
1486	ASPIRIN 75 MG SUP
1609	paracetamol soluble tablet 500mg
1621	BRUFEN tablets 200mg [ABBOTT]
1739	BRUFEN tablets 400mg [ABBOTT]
1762	dextropropoxyphene hcl with paracetamol tablets 32.5mg + 325mg
1862	paracetamol sugar-free suspension 500mg/5ml
1865	PARACETAMOL 1 GM TAB
1946	PARACETAMOL 500 MG SUP
1999	paracetamol suppository 125mg
2034	ALVEDON suppository 125mg [ASTRAZENEC]
2129	BRUFEN retard tablets 800mg [ABBOTT]
2344	paracetamol suppository 120mg
2462	COSALGESIC tablets [ACTAVIS]
2546	PARACETAMOL SOLUBLE TAB
2586	DISPROL sugar-free suspension 120mg/5ml [RECKITT B]
2622	ibuprofen tablets 800mg
2754	ASPIRIN SOLUBLE 150 MG TAB
2800	PANADOL soluble tablet 500mg [GLAXSK CON]
2924	ASPIRIN 150 MG TAB
2938	ibuprofen sugar-free suspension 100mg/5ml
3074	paracetamol soluble tablet 120mg
3313	CALPOL SIX PLUS sugar-free suspension 250mg/5ml [MCNEIL]
3316	DISPROL soluble tablet 120mg [RECKITT B]
3597	NUROFEN soluble tablet 200mg [CROOKES]
3599	ibuprofen granules 600mg
3714	DEXTROPROPOXYPHENE NAPSYLATE/PARACETAMOL MG TAB
4186	paracetamol sugar-free suspension 250mg/5ml
4196	paracetamol suppository 240mg
4203	MEDISED suspension [SSL INT]
4216	BRUFEN tablets 600mg [ABBOTT]
4271	ASPIRIN SOLUBLE 200 MG TAB
4298	NUROFEN tablets 200mg [CROOKES]
4523	ASPIRIN 50 MG CAP
4557	ASPIRIN & PAPAVERUTUM 10 MG TAB
4600	chlormezanone with paracetamol tablets
4911	ibuprofen granules 400mg
5239	paracetamol sachets 1g
5243	paracetamol suppository 500mg
5323	paracetamol suppository 250mg
5648	ibuprofen orodispersible tablet 200mg
6226	papaveretum with aspirin dispersible tablet 7.71mg + 500mg
6571	paracetamol sachets 240mg
6699	paracetamol suppository 60mg
7058	CALPROFEN oral suspension 100mg/5ml [MCNEIL]

PHN treatment- Mild PKs

Product Code	Product Name
7205	PANADOL capsules 500mg [GLAXSK CON]
7417	ASPIRIN 40 MG TAB
7450	pentazocine with paracetamol tablets 500mg + 15mg
7462	ASPIRIN 325 MG CAP
7486	ASPIRIN 37.5 MG TAB
7535	NUROFEN liquid capsules 200mg [CROOKES]
7621	PARACETAMOL 300 MG TAB
7650	PARACETAMOL 125 MG ELI
7665	ASPIRIN SR 300 MG TAB
7668	PARACETAMOL 250 MG TAB
7769	ASPIRIN/PARACETAMOL TAB
7915	ASPIRIN SR 100 MG TAB
7944	ASPIRIN SOLUBLE 40 MG CAP
8020	PARACETAMOL 125 MG MIX
8091	PARACETAMOL CO TAB
8093	PARACETAMOL SOLUBLE TAB
8259	PARACETAMOL 500 MG ELI
8292	PARACETAMOL 240 MG ELI
8401	MOTRIN tablets 400mg [PHARMACIA]
8700	PARACETAMOL 125 MG TAB
8734	ASPIRIN disp 37.5 MG TAB
8843	ASPIRIN 325 MG TAB
8920	ASPIRIN SOLUBLE 500 MG TAB
9027	ASPIRIN disp 150 MG TAB
9193	paracetamol with sodium bicarbonate effervescent tablet 500mg + 1342mg
9239	paracetamol capsules 120mg
9271	paracetamol syrup 125mg/5ml
9329	paracetamol drops 100mg/ml
9712	paracetamol dissolving tablets 250mg
9914	CALPOL FAST MELTS 6+ dissolving tablets 250mg [MCNEIL]
10149	ibuprofen liquid capsules 200mg
10209	IBUFEM tablets 200mg [GALPHARM]
10325	dexibuprofen tablets 300mg
10509	FORTAGESIC tablets [SANOFI S]
10748	TRAMIL capsules 500mg [WYETH CONS]
10785	FENBID SPANSULE 300mg [GOLDSHIELD]
10901	paracetamol with promethazine hydrochloride suspension 120mg+1.5mg/5ml
11326	meprobamate with ethoheptazine citrate and aspirin tablets
11550	NUROFEN MELTLETS dissolving tablets 200mg [RECKITT B]
11907	dexibuprofen tablets 400mg
11941	ASPIRIN SACHETS 30 MG
11980	CUPROFEN maximum strength tablets 400mg [SSL INT]
12102	ASPIRIN SOLUBLE 100 MG TAB
12332	PARACETAMOL 240 MG SUS
12364	aloxiprin tablets 600mg
12394	LOBAK tablets [SANOFI S]
14333	ibuprofen liquid capsules 400mg
14385	CUPROFEN tablets 200mg [SSL INT]
14551	INFADROPS drops 100mg/ml [GOLDSHIELD]
14560	PARACETAMOL 60 MG SUP
14899	ALVEDON suppository 250mg [ASTRAZENEC]
15044	ASPIRIN disp 500 MG TAB
15068	ARTHROFEN tablets 400mg [ASHBOURNE]
15238	PARACETAMOL tablets 500mg [WINTHROP]
15352	ASPIRIN & PARACETAMOL TAB
15364	aspirin suppository 150mg
15397	ASPIRIN SOLUBLE 50 MG TAB
15439	PARACETAMOL 150 MG SUP
15447	ASPIRIN SOLUBLE 600 MG TAB
15461	PARACETAMOL 100 MG SUP
15517	ASPIRIN 100 MG SUP
16001	IBUPROFEN tablets 200mg [HILLCROSS]
16192	MOTRIN tablets 200mg [PHARMACIA]
16193	MOTRIN tablets 800mg [PHARMACIA]
16205	PALAPRIN FORTE tablets 600mg [NICHOLAS]
17201	MOTRIN tablets 600mg [PHARMACIA]
18261	aspirin with papaveretum dispersible tablet 500mg + 7.71mg
18364	IBULAR tablets 400mg [LAGAP]
18441	ALVEDON suppository 60mg [ASTRAZENEC]
18482	paracetamol with dextropropoxyphene tablets 325mg + 32.5mg
18527	MANDAFEN tablets 400mg [M&A PHARM]
18812	NUROFEN MELTLETS LEMON orodispersible tablet 200mg [RECKITT B]
18820	FENPAED oral suspension 100mg/5ml [PINEWOOD]
19036	ARTHROFEN tablets 200mg [ASHBOURNE]
19046	IBUPROFEN tablets 400mg [HILLCROSS]

PHN treatment- Mild PKs

Product Code	Product Name
19139	PARACETAMOL suppository 500mg [DISTRIPHAR]
19575	PROFLEX tablets 200mg [NOVARTIS]
19577	NU-SEALS ASPIRIN
19674	ASPIRIN DISPERSIBLE
19797	NU-SEALS ASPIRIN
19813	ASPIRIN SOLUBLE
20068	paracetamol sugar-free suspension 250mg/5ml
20194	PARACETAMOL 75 MG SUS
20206	ASPIRIN 50 MG SUP
20650	aspirin with paracetamol dispersible tablet 300mg + 200mg
20840	acetylsalicylic acid mixture
20978	ANADIN ULTRA liquid capsules [WYETH CONS]
21045	IBUMETIN tablets 400mg [BENZON]
21419	SERACTIL tablets 300mg [GENUS]
21421	SERACTIL tablets 400mg [GENUS]
21491	PARACETAMOL 30 MG SUP
21754	PARACETAMOL 20 MG SUP
21770	paracetamol with aspirin dispersible tablet 200mg + 300mg
21811	LIDIFEN tablets 200mg [BERK]
21813	LIDIFEN tablets 400mg [BERK]
21815	ARTHROFEN tablets 600mg [ASHBOURNE]
21821	LIDIFEN F tablets 600mg [BERK]
21932	ETHOHEPTALINE CITRATE/ASPIRIN MG TAB
22014	DISPROL PARACETAMOL sugar-free suspension 120mg/5ml [RECKITT B]
22107	ASPIRIN disp 200 MG TAB
22206	NUROFEN LONG LASTING modified release capsules 300mg [CROOKES]
22236	paracetamol with promethazine hydrochloride colour free sugar-free suspension 120mg+1.5mg/5ml
22288	MEDINOL over 6 sugar free suspension 250mg/5ml [SSL INT]
22305	DISPRIN EXTRA dispersible tablet [RECKITT B]
22380	paracetamol solution for infusion 1g/100ml
22776	aspirin with cyclizine effervescent tablet 500mg+25mg
22824	ASPIRIN disp 600 MG TAB
22863	ASPIRIN S/R 500 MG TAB
23052	promethazine hydrochloride with paracetamol colour free sugar-free suspension 120mg+1.5mg/5ml
23077	PARACETAMOL sugar-free suspension 120mg/5ml [PINEWOOD]
23114	PANALEVE PLUS sugar-free suspension 120mg/5ml [PINEWOOD]
23250	ASPIRIN /ETHOHEPTAZINE CITRATE /MEPROBAM 250 MG TAB
23274	PARACETAMOL
23491	ASPIRIN 500 MG SUP
23495	ASPIRIN
23617	paracetamol powders 50mg
23716	PARACETAMOL caplets 500mg [IVAX]
23840	PANASORB tablets 500mg [SANOFI S]
23841	SAFAPRYN tablets [PFIZER]
24000	MANDANOL tablets 500mg [M&A PHARM]
24075	MANDANOL caplets 500mg [M&A PHARM]
24305	IBUFAC tablets 400mg [DDSA]
24400	PARACETAMOL
24445	paracetamol with promethazine hydrochloride tablets
24534	ANADIN PARACETAMOL tablets [PFIZER]
24803	SALICYLAMIDE/PARACETAMOL MG TAB
24857	ASPIRIN 250 MG SUP
25257	ADVIL tablets 200mg [WYETH CONS]
25619	NUROFEN tablets 400mg [CROOKES]
25794	ISISFEN tablets 400mg [ISIS]
25800	FEVERFEN oral suspension 100mg/5ml [WISE]
25895	HEDEX caplets 500mg [GLAXSK CON]
26099	ASPIRIN 175 MG SUP
26424	ASPIRIN 200 MG SUP
26792	ASPIRIN 125 MG SUP
26970	IBUPROFEN suspension 100mg/5ml [TEVA]
26988	PARACETS tablets 500mg [SUSSEX]
27064	PALDESIC suspension 120mg/5ml [ROSEMONT]
27452	PARACETAMOL soluble tablet 500mg [WINTHROP]
27459	PARACETAMOL caplets 500mg [WINTHROP]
27467	ASPIRIN SOLUBLE 400 MG TAB
27553	PARACETAMOL
27782	IBUPROFEN tablets 400mg [APS]
27783	IBUPROFEN sugar-coated tablets 400mg [ACTAVIS]
27968	APSIFEN tablets 400mg [APS]
28168	NUROFEN RECOVERY orodispersible tablet 200mg [RECKITT B]
28211	PARACETAMOL sugar-free suspension 250mg/5ml [APS]
28344	PARACETAMOL caplets 500mg [WOCKHARDT]
28346	PARACETAMOL caplets 500mg [M&A PHARM]
28348	IBUPROFEN tablets 200mg [APS]

PHN treatment- Mild PKs

Product Code	Product Name
28479	NUROFEN BACK PAIN SR capsules 300mg [RECKITT B]
28707	ASPIRIN M/F 324 MG TAB
28712	GALPAMOL sugar-free suspension 120mg/5ml [GALPHARM]
28792	MEDISED COLOUR AND SUGAR FREE suspension 120mg+1.5mg/5ml [SSL INT]
28888	GALPROFEN LONG LASTING modified release capsules 200mg [GALPHARM]
28955	PANADOL ACTIFAST tablets 500mg [GLAXSK CON]
29068	NUROFEN EXTRA STRENGTH liquid capsules 400mg [RECKITT B]
29316	CARE IBUPROFEN tablets 400mg [T & R]
29332	IBUPROFEN sugar-free suspension 100mg/5ml [SANDOZ]
29345	IBUPROFEN oral suspension 100mg/5ml [HILLCROSS]
29352	IBUPROFEN sugar-free suspension 100mg/5ml [AAH(VANT)]
29524	IBUMETIN tablets 600mg [BENZON]
29587	EBUFAC tablets 400mg [DDSA]
29704	PAXOFEN tablets 200mg [STEINHARD]
29749	IBUPROFEN tablets 200mg [RANBAXY]
30022	FYNNON CALCIUM ASPIRIN soluble tablet 500mg [SSL INT]
30243	ibuprofen effervescent tablet 200mg
30382	IBUPROFEN tablets 200mg [CP PHARM]
30432	ASPIRIN & DOVERS pwdr TAB
30590	MEDISED tablets [SSL INT]
30695	ASPIRIN 120 MG SUP
30724	GALPROFEN IBUPROFEN sugar-free suspension 100mg/5ml [GALPHARM]
30811	PROFLEX sustained release capsules 300mg [NOVARTIS]
30984	PARACETAMOL suspension 250mg/5ml [HILLCROSS]
31196	PARACETAMOL tablets 500mg [IVAX]
31257	PARACETAMOL caplets 500mg [GALPHARM]
31469	APSIFEN -F tablets 600mg [APS]
31482	APSIFEN tablets 200mg [APS]
31499	paracetamol with aspirin tablets
32093	PARACETAMOL suspension 250mg/5ml [ROSEMONT]
32100	IBUPROFEN tablets 600mg [HILLCROSS]
32136	IBULAR tablets 200mg [LAGAP]
32163	PARACETAMOL tablets 500mg [AAH(VANT)]
32242	IBUPROFEN tablets 400mg [STERWIN]
32365	RELCOFEN sugar-coated tablets 400mg [ACTAVIS]
32366	RELCOFEN sugar-coated tablets 200mg [ACTAVIS]
32509	ANADIN IBUPROFEN tablets 200mg [PFIZER]
32554	PLACIDEX syrup 120mg/5ml [DE WITT]
32626	paracetamol with sodium salicylate tablets 150mg + 100mg
32672	DISPROL PARACETAMOL SF
32766	paracetamol solution for infusion 500mg/50ml
32839	PARACETAMOL tablets 500mg [HILLCROSS]
32862	IBUPROFEN sugar-free suspension 100mg/5ml [T & R]
32875	IBUPROFEN tablets 400mg [SANDOZ]
32970	PARACETS capsules 500mg [SUSSEX]
33075	ASPIRIN 600MG/GLYCINE 300MG 600 MG TAB
33104	PARACLEAR soluble tablet 500mg [ROCHE]
33230	promethazine hydrochloride with paracetamol suspension 120mg+1.5mg/5ml
33357	PACIFENE tablets 200mg [SUSSEX]
33386	PARACETAMOL oral suspension 120mg/5ml [HILLCROSS]
33589	IBUPROFEN tablets 400mg [T & R]
33614	OBIMOL tablets 500mg [AYRTONSAUN]
33666	PARACETAMOL tablets 500mg [ACTAVIS]
33687	PARACETAMOL sugar-free suspension 250mg/5ml [HILLCROSS]
33704	IBUPROFEN sugar-free suspension 100mg/5ml [HILLCROSS]
33710	PARACETAMOL caplets 500mg [HILLCROSS]
33785	GALPROFEN tablets 200mg [GALPHARM]
33826	PARACETAMOL tablets 500mg [TEVA]
33838	Herpes zoster with meningitis
34164	PARACETAMOL soluble tablet 500mg [NEOLAB]
34209	PARACETAMOL sugar-free suspension 500mg/5ml [ROSEMONT]
34235	PARACETAMOL suppository 120mg [PENN]
34266	TIXYMOL sugar-free suspension 120mg/5ml [NOVARTIS]
34305	PARACETAMOL tablets 500mg [M&A PHARM]
34350	PARACETAMOL tablets 500mg [CELLTECH]
34354	IBUPROFEN tablets 200mg [AAH(VANT)]
34359	IBUPROFEN tablets 400mg [AAH(VANT)]
34396	PARACETAMOL tablets 500mg [FAMILY H]
34409	PARACETAMOL tablets 500mg [CO-OPERATI]
34425	IBUPROFEN tablets 400mg [FAMILY H]
34447	IBUPROFEN tablets 200mg [T & R]
34500	PARACETAMOL tablets 500mg [KENT]
34527	IBUPROFEN tablets 200mg [STERWIN]
34536	IBUPROFEN tablets 400mg [IVAX]
34550	IBUPROFEN film coated tablets 400mg [ACTAVIS]

PHN treatment- Mild PKs

Product Code	Product Name
34621	IBUPROFEN tablets 200mg [NUCARE]
34663	IBUPROFEN oral suspension 100mg/5ml [NEOLAB]
34669	PARACETAMOL capsules 500mg [WINTHROP]
34700	PARACETAMOL sugar-free suspension 250mg/5ml [PINEWOOD]
34718	PARACETAMOL sugar-free suspension 120mg/5ml [APS]
34729	IBUPROFEN tablets 400mg [OBG]
34757	IBUPROFEN tablets 400mg [UNICHEM]
34850	IBUPROFEN tablets 600mg [APS]
34858	PARACETAMOL capsules [CO-OPERATI]
34861	PARACETAMOL suppository 120mg [AURUMPHARM]
34889	IBUPROFEN tablets 400mg [CELLTECH]
34911	IBUPROFEN tablets 200mg [CELLTECH]
34931	IBUPROFEN tablets 200mg [REGENT]
34954	PARACETAMOL tablets 500mg [ASPAR]
34961	IBUPROFEN tablets 600mg [SANDOZ]
34980	IBUPROFEN sugar-coated tablets 200mg [ACTAVIS]
35292	NUROFEN liquid capsules 200mg [RECKITT B]
35679	PARACETAMOL caplets 500mg [NUCARE]
35890	NUROFEN caplets 200mg [RECKITT B]
36472	paracetamol with pentazocine tablets 500mg + 15mg
36597	HEDEX IBUPROFEN tablets 200mg [GLAXSK CON]
36606	MANORFEN tablets 400mg [MANOR]
36650	NUROFEN tablets 200mg [RECKITT B]
36754	PARACETAMOL soluble tablet 500mg [HILLCROSS]
36945	MANDANOL SIX PLUS sugar-free suspension 250mg/5ml [M&A PHARM]
37002	NUROFEN EXPRESS liquid capsules 200mg [RECKITT B]
37053	MIGRAFEN tablets 200mg [CHATFIELD]
37094	CUPROFEN IBUPROFEN tablets 200mg [SSL INT]
37253	ANADIN ULTRA DOUBLE STRENGTH capsules 400mg [WYETH CONS]
37411	PALDESIC suspension 250mg/5ml [ROSEMONT]
37553	IBUCALM tablets 400mg [ASPAR]
37648	NUROFEN EXPRESS liquid capsules 400mg [RECKITT B]
38032	PARACETAMOL capsules 500mg [TEVA]
38332	IBUCALM tablets 200mg [ASPAR]
38493	ANADIN JOINT PAIN tablets 200mg [PFIZER]
38984	PARACETAMOL capsules 500mg [ACTAVIS]
39019	BRUFEN RETARD tablets 800mg [ABBOTT]
39333	PARACETAMOL caplets 500mg [ASPAR]
39481	PANADOL ADVANCE tablets 500mg [GLAXSK CON]
39502	ibuprofen sodium dihydrate tablets 256mg
39647	MEDINOL OVER 6 oral suspension 250mg/5ml [SSL INT]
39758	NUROFEN EXPRESS caplets 256mg [RECKITT B]
39873	CUPROFEN MAXIMUM STRENGTH tablets 400mg [SSL INT]
39934	PARACETAMOL tablets 500mg [ALMUS]
39940	PANADOL ACTIFAST soluble tablet 500mg [GLAXSK CON]
40083	GALPHARM IBUPROFEN caplets 200mg [GALPHARM]
40107	PARACETAMOL soluble tablet 500mg [KENT]
40158	PARACETAMOL capsules 500mg [AAH(VANT)]
40253	IBUPROFEN tablets 600mg [SOVEREIGN]
40394	ADVIL tablets 400mg [WYETH CONS]
40516	ANADIN LIQUIFAST liquid capsules 200mg [PFIZER]
41409	PARACETAMOL suppository 500mg [AURUMPHARM]
41414	PARACETAMOL oral suspension 120mg/5ml [CO-PHARMA]
41513	IBUPROFEN tablets 200mg [IVAX]
41680	PARACETAMOL sugar-free suspension 120mg/5ml [IVAX]
41701	IBUPROFEN tablets 600mg [ACTAVIS]
42061	ASPIRIN 65 MG SUP
42101	PERFALGAN solution for infusion 1g/100ml [BMS]
42108	IBUPROFEN tablets 200mg [OBG]
42125	PARACETAMOL suppository 120mg [DISTRIPHAR]
42201	PARACETAMOL capsules 500mg [HILLCROSS]
42371	paracetamol tablets 1000mg
42397	NUROFEN EXPRESS tablets 256mg [RECKITT B]
42514	paracetamol oral liquid
42834	PANADOL OA tablets 1000mg [GLAXSK CON]
43028	paracetamol powder for oral solution 650mg
43032	INOVEN caplets 200mg [JANSSEN]
43199	PARACETAMOL suspension 6 plus 250mg/5ml [AAH(VANT)]
43233	PARACETAMOL capsules 500mg [KENT]
43252	PARACETAMOL capsules 500mg [ASPAR]
43456	ANADIN LIQUIFAST liquid capsules 400mg [PFIZER]
43479	PARACETAMOL caplets 500mg [ACTAVIS]
43911	IBUPROFEN tablets 600mg [CP PHARM]
44311	DEXTROPROPOXYPHENE NAPSYLATE/ASPIRIN 100 MG TAB
44483	NUROFEN EXPRESS tablets 512mg [RECKITT B]

PHN treatment- Mild PKs

Product Code	Product Name
44496	sodium salicylate mixture 500mg/5ml
45216	IBUPROFEN tablets 400mg [CP PHARM]
45259	PARACETAMOL tablets 500mg [OBG]
45298	PARACETAMOL tablets 500mg [GALPHARM]
45320	IBUPROFEN tablets 200mg [SANDOZ]
45331	IBUPROFEN tablets 200mg [CO-PHARMA]
45348	PARACETAMOL oral suspension 120mg/5ml [NUCARE]
45349	PARACETAMOL suppository 240mg [AURUMPHARM]
45842	IBUPROFEN tablets 600mg [CELLTECH]
46342	MEDIFEN 3+ MONTHS oral suspension 100mg/5ml [SSL INT]
46544	PARACETAMOL capsules 500mg [WOCKHARDT]
46638	ibuprofen with paracetamol tablets 200mg + 500mg
46763	paracetamol oral suspension 500mg/5ml
46846	paracetamol oral solution 500mg/5ml
46860	ANADIN LIQUIFAST effervescent tablet 200mg [PFIZER]
46904	NUROMOL tablets 200mg + 500mg [RECKITT B]
46921	IBUPROFEN tablets 400mg [RANBAXY]
46942	IBUPROFEN tablets 600mg [IVAX]
47116	PARACETAMOL soluble tablet 500mg [ALMUS]
47211	PARACETAMOL capsules 500mg [FOCUS]

PHN treatment - Strong PKs

Product Code	Product Name
4	co-proxamol (dextropropoxyphene and paracetamol) tablets 32.5mg + 325mg
11	co-dydramol (dihydrocodeine and paracetamol) tablets 10mg+500mg
19	co-codamol (codeine and paracetamol) tablets 8mg+500mg
53	dihydrocodeine tablets 30mg
57	co-codamol (codeine and paracetamol) effervescent tablet 8mg+500mg
96	co-codamol (codeine and paracetamol) tablets 30mg + 500mg
142	CODEINE SOLUBLE TAB
158	codeine phosphate tablets 30mg
191	dihydrocodeine elixir 10mg/5ml
203	CODEINE CO SOLUBLE TAB
213	codeine phosphate syrup 25mg/5ml
241	CODEINE CO TAB
382	ZERIDAME SR tablets 150mg [ACTAVIS]
462	codeine phosphate injection 60mg/1ml
483	co-proxamol (dextropropoxyphene and paracetamol) sugar-free suspension 32.5mg + 325mg/5ml
539	codeine phosphate tablets 60mg
625	co-codamol (codeine and paracetamol) capsules 8mg+500mg
635	codeine phosphate injection 30mg/1ml
656	TYLEX capsules 500mg + 30mg [UCB]
767	SOLPADOL capsules 500mg + 30mg [SANOFI/AVE]
800	co-codamol (codeine and paracetamol) capsules 30mg + 500mg
810	co-codamol (codeine and paracetamol) effervescent tablet 30mg + 500mg
1261	co-codamol (codeine and paracetamol) sugar free effervescent powder 30mg + 500mg
1640	KAPAKE tablets 30mg + 500mg [GALEN]
1708	CODAFEN CONTINUS modified release tablet 300mg + 20mg [NAPPPHARM]
2040	REMEDEINE tablets 20mg + 500mg [NAPPPHARM]
2041	dihydrocodeine modified release tablet 60mg
2047	co-codaprin (codeine and aspirin) tablets 8mg+400mg
2211	SOLPADOL effervescent tablet 500mg + 30mg [SANOFI/AVE]
2250	CODEINE & PARACETAMOL TAB
2555	dihydrocodeine with paracetamol tablets 10mg + 500mg
2698	CODEINE & PARACETAMOL 8 MG TAB
2794	CO-CODAMOL tablets 30mg + 500mg [WOCKHARDT]
2846	paracetamol with codeine phosphate effervescent tablet 500mg + 30mg
2917	paracetamol with codeine phosphate tablets 500mg + 30mg
2986	co-codaprin (codeine and aspirin) dispersible tablet 8mg+400mg
2988	CODEINE PHOSPHATE 15 MG ELI
2998	PARACETAM/DYHYDROCODEINE(500MG/30MG) MG TAB
3029	CO-CODAMOL EFF 30MG/500MG TAB
3156	SOLPADOL caplets 500mg + 30mg [SANOFI/AVE]
3185	paracetamol with codeine phosphate capsules 500mg + 30mg
3272	PARACETAM/DYHYDROCODEINE(500MG/20MG) TAB
3435	TYLEX effervescent tablet 500mg + 30mg [UCB]
3653	dihydrocodeine injection 50mg/1ml
3698	DF118 forte tablets 40mg [MARTINDALE]
3713	MEDOCODENE tablets [???]
4349	PARACETAMOL & CODEINE TAB
4556	PARAMOL tablets 500mg + 7.46mg [SSL INT]
4607	CO-PROXAMOL tablets (DISTA) 32.5/325 [DISTA]
4671	codeine phosphate with paracetamol capsules 30mg + 500mg
4823	dihydrocodeine tablets 40mg
4950	dihydrocodeine with paracetamol tablets 30mg + 500mg
5955	paracetamol with dihydrocodeine tablets 500mg + 30mg
6234	dihydrocodeine modified release tablet 120mg
6886	codeine phosphate with paracetamol tablets 30mg + 500mg
7063	co-dydramol (dihydrocodeine and paracetamol) sugar-free suspension 10mg + 500mg/5ml
7072	co-codamol (codeine and paracetamol) tablets 15mg + 500mg
7104	KAPAKE effervescent tablet 30mg + 500mg [GALEN]
7469	DF118 elixir 10mg/5ml [MARTINDALE]
7518	aspirin with codeine dispersible tablet 400mg + 8mg
7542	codeine phosphate with paracetamol tablets 8mg + 500mg
7696	PARACETAMOL 500MG/CODEINE 10MG MG TAB
7770	ASPIRIN/CODEINE PHOSPHATE/PARACETAMOL 250 MG TAB
7976	PARACETAMOL 450MG/CODEINE 8.1MG TAB
7989	DIHYDROCODEINE TARTRATE/ASPIRIN 300 MG TAB
8246	codeine phosphate with paracetamol effervescent tablet 8mg + 500mg
8335	PARACODOL capsules [BAYER]
8456	DHC CONTINUS tablets 60mg [NAPPPHARM]
9044	CODIS 500 tablets [RECKITT B]
9129	paracetamol with aspirin and codeine tablets 250mg+250mg+6.8mg
9163	REMEDEINE effervescent tablet 20mg + 500mg [NAPPPHARM]
9209	DHC CONTINUS tablets 90mg [NAPPPHARM]
9275	DHC CONTINUS tablets 120mg [NAPPPHARM]

PHN treatment - Strong PKs

Product Code	Product Name
9313	dihydrocodeine modified release tablet 90mg
9432	aspirin with codeine soluble tablet 500mg + 8mg
9457	paracetamol with codeine phosphate tablets 500mg + 8mg
9460	paracetamol with codeine phosphate capsules 500mg + 8mg
9462	paracetamol with codeine phosphate effervescent tablet 500mg + 8mg
9516	KAPAKE capsules 30mg + 500mg [GALEN]
9562	REMEDEINE forte effervescent tablets 30mg + 500mg [NAPPPHARM]
9785	REMEDEINE forte tablets 30mg + 500mg [NAPPPHARM]
9855	paracetamol with dihydrocodeine tablets 500mg + 20mg
9917	KAPAKE INSTS sugar free effervescent powder 30mg + 500mg [GALEN]
10023	dihydrocodeine with paracetamol tablets 20mg + 500mg
10122	dihydrocodeine with paracetamol sugar-free suspension 10mg + 500mg/5ml
10176	CODIPAR caplets 500mg + 15mg [GOLDSHIELD]
10309	DF118 injection 50mg/ml [MARTINDALE]
10519	CODEINE PHOS/IBUPROFEN SR (20MG/300MG) TAB
10582	FORMULIX elixir [CILAG]
10602	PARACODOL effervescent tablet [BAYER]
11129	papaveretum injection 15.4mg/ml
11325	paracetamol with codeine phosphate tablets 500mg + 30mg
11461	ibuprofen and codeine modified release tablet 300mg + 20mg
11554	ibuprofen and codeine tablets 200mg + 12.8mg
11665	ZAPAIN caplets 30mg + 500mg [GOLDSHIELD]
11807	paracetamol with codeine tablets 500mg + 12.8mg
11961	VEGANIN tablets [PFIZER]
12709	ibuprofen and codeine tablets 200mg + 12.5mg
12992	co-codaprin (codeine and aspirin) soluble tablet 8mg+500mg
13598	ASPIRIN & CODEINE 500 MG TAB
13893	NUROFEN PLUS tablets [RECKITT B]
14602	co-codamol (codeine and paracetamol) sugar free effervescent powder 60mg + 1000mg
14688	paracetamol with dihydrocodeine tablets 500mg + 10mg
14785	paracetamol with codeine phosphate tablets 500mg + 15mg
14912	codeine phosphate with paracetamol capsules 8mg+500mg
15198	CO-DYDRAMOL tablets 10mg+500mg [CP PHARM]
15353	papaveretum injection 7.7mg/ml
15779	codeine phosphate with aspirin soluble tablet 8mg + 500mg
15831	codeine phosphate with paracetamol sugar free effervescent powder 30mg + 500mg
15871	KAPAKE INSTS 60/1000 sugar free effervescent powder 60mg + 1000mg [GALEN]
16096	codeine phosphate oral liquid 6.75mg/5ml
16112	PARAMOL soluble tablet [SSL INT]
16467	codeine phosphate with paracetamol effervescent tablet 30mg + 500mg
16818	paracetamol with codeine phosphate sugar free effervescent powder 500mg + 30mg
17158	PANADEINE FORTE tablets [SANOFI S]
17563	SOLPADEINE MAX tablets 500mg + 12.8mg [GLAXSK CON]
17808	CO-CODAMOL 30MG/500MG
17917	dihydrocodeine with paracetamol effervescent tablet 20mg + 500mg
17926	aspirin with codeine tablets 400mg + 8mg
17998	MEDOCODENE capsules 30mg + 500mg [UCB]
18221	codeine phosphate with paracetamol tablets 15mg + 500mg
19206	paracetamol with dihydrocodeine tablets 500mg + 7.46mg
19317	OMNOPON tablets 10mg [ROCHE]
19550	CO-PROXAMOL
19764	papaveretum tablets 10mg
20127	codeine phosphate with aspirin dispersible tablet 8mg+400mg
21104	PARACETAMOL/CODEINE PHOSPHATE 500 MG TAB
21113	dihydrocodeine with paracetamol forte effervescent tablets 30mg + 500mg
21229	paracetamol with dihydrocodeine effervescent tablet 500mg + 7.46mg
21703	paracetamol with codeine phosphate sugar free effervescent powder 1000mg + 60mg
21880	ZAPAIN capsules 30mg + 500mg [GOLDSHIELD]
21927	CO-DYDRAMOL
22450	ASPIRIN & CODEINE 75 MG TAB
22627	CODEINE PHOSPHATE 15/PARACETAMOL 500MG TAB
22764	PANADEINE tablets [GLAXSK PHA]
22817	CO-CODAMOL SF EFF POWDER
23420	codeine phosphate with paracetamol sugar free effervescent powder 60mg + 1000mg
23952	PANADEINE SOLUBLE effervescent tablet [SANOFI S]
24209	CO-CODAMOL EFFERVESCENT
24498	ASPIRIN/CODEINE PHOSPHATE/PARACETAMOL 300 MG TAB
24859	CODEINE 8MG & PARACETAMOL 500MG SUP
25330	SOLPAFLEX tablets 200mg + 12.8mg [GLAXSK CON]
25514	paracetamol with codeine phosphate tablets 500mg + 10mg
26653	DIHYDROCODEINE 10mg/PARACETAMOL 500mg
27784	CO-CODAMOL tablets 8mg+500mg [ACTAVIS]
27785	CO-CODAMOL tablets 30mg + 500mg [WINTHROP]

PHN treatment - Strong PKs

Product Code	Product Name
28253	CO-PROXAMOL sugar-free suspension 32.5/325 [ROSEMONT]
28598	paracetamol with dihydrocodeine sugar-free suspension 500mg +10mg/5ml
28780	CO-DYDRAMOL tablets 10mg+500mg [HILLCROSS]
28784	codeine phosphate with aspirin tablets 8mg+400mg
29342	CO-CODAMOL tablets 8mg+500mg [M&A PHARM]
29488	CO-CODAMOL effervescent tablet 8mg+500mg [WINTHROP]
29828	ACETYLSALICYLIC ACID / CODEINE PHOSPHATE MG TAB
30021	paracetamol with codeine phosphate tablets 500mg + 13.5mg
30123	PANADOL ULTRA tablets 500mg + 12.8mg [GLAXSK CON]
30165	co-dydramol (dihydrocodeine and paracetamol) tablets 7.46mg + 500mg
30295	dihydrocodeine with paracetamol tablets 7.46mg + 500mg
30444	CO-DYDRAMOL tablets 10mg+500mg [GEN (UK)]
30556	CO-CODAMOL effervescent tablet 8mg+500mg [NEOLAB]
30954	CO-PROXAMOL tablets 32.5/325 [ACTAVIS]
30966	CO-PROXAMOL tablets 32.5/325 [DISTA]
31155	PARAKE tablets [GALEN]
31452	CODEINE PHOSPHATE tablets 30mg [CP PHARM]
31577	CO-CODAMOL capsules 30mg + 500mg [HILLCROSS]
31700	CODEINE PHOSPHATE tablets 15mg [ACTAVIS]
31871	paracetamol with codeine phosphate tablets 450mg + 8.1mg
31894	SAFAPRYN -CO tablets [PFIZER]
31943	CODEINE PHOSPHATE tablets 30mg [IVAX]
32692	CO-CODAMOL effervescent tablet 8mg+500mg [HILLCROSS]
32926	CO-DYDRAMOL tablets 10mg+500mg [ACTAVIS]
33340	CO-DYDRAMOL suspension 10mg + 500mg/5ml [ROSEMONT]
33643	CO-CODAMOL tablets 8mg+500mg [FAMILY H]
33647	CO-PROXAMOL tablets 32.5/325 [HILLCROSS]
33653	CO-CODAMOL tablets 8mg+500mg [IVAX]
33654	DIHYDROCODEINE tablets 30mg [WOCKHARDT]
33679	CO-CODAMOL tablets 8mg+500mg [WINTHROP]
33688	CO-CODAMOL effervescent tablet 30mg + 500mg [NEOLAB]
33743	dihydrocodeine with paracetamol effervescent tablet 7.46mg + 500mg
33961	CO-CODAMOL capsules 30mg + 500mg [IVAX]
33995	CO-PROXAMOL tablets 32.5/325 [BERK]
34008	DIHYDROCODEINE tablets 30mg [IVAX]
34022	CO-PROXAMOL tablets 32.5/325 [APS]
34229	CO-CODAMOL dispersible tablet 8mg+500mg [RHONE]
34257	CO-CODAMOL dispersible tablet 8mg+500mg [GEN (UK)]
34264	CO-CODAMOL STRONG tablets 30mg + 500mg [IVAX]
34319	CO-PROXAMOL tablets 32.5/325 [STERWIN]
34348	CODEINE PHOSPHATE tablets 15mg [HILLCROSS]
34349	CO-PROXAMOL tablets 32.5mg + 325mg [IVAX]
34383	CODEINE PHOSPHATE tablets 30mg [HILLCROSS]
34397	CO-PROXAMOL tablets 32.5mg + 325mg [M&A PHARM]
34440	DIHYDROCODEINE tablets 30mg [HILLCROSS]
34444	Herpes zoster with meningitis
34468	CO-PROXAMOL tablets 32.5mg + 325mg [SANDOZ]
34495	CO-CODAMOL tablets 8mg+500mg [GEN (UK)]
34497	CO-CODAMOL tablets 8mg+500mg [BERK]
34518	CO-CODAMOL tablets 8mg+500mg [HILLCROSS]
34546	CO-PROXAMOL tablets 32.5mg + 325mg [NEOLAB]
34552	CODEINE PHOSPHATE tablets 30mg [ACTAVIS]
34554	CO-PROXAMOL tablets 32.5/325 [CP PHARM]
34579	DIHYDROCODEINE tablets 30mg [ACTAVIS]
34597	CO-PROXAMOL tablets 32.5mg + 325mg [KENT]
34662	DIHYDROCODEINE tablets 30mg [GEN (UK)]
34667	CO-CODAMOL tablets 30mg + 500mg [HILLCROSS]
34730	DIHYDROCODEINE tablets 30mg [BERK]
34737	CO-DYDRAMOL tablets 10mg+500mg [TEVA]
34784	CO-CODAMOL effervescent tablet 8mg+500mg [SANDOZ]
34789	CODEINE PHOSPHATE tablets 30mg [KENT]
34815	CO-CODAMOL tablets 8mg+500mg [KENT]
34840	CO-CODAMOL tablets 30mg + 500mg [ALMUS]
34845	CO-CODAMOL effervescent tablet 30mg + 500mg [WINTHROP]
34865	CO-CODAMOL tablets 8mg+500mg [WOCKHARDT]
34920	CO-DYDRAMOL tablets 10mg+500mg [BERK]
34939	CO-DYDRAMOL tablets 10mg+500mg [DF]
34968	CO-CODAMOL tablets 8mg+500mg [TEVA]
35792	CODEINE PHOSPHATE syrup [T & R]
35965	MEDOCODENE effervescent tablet [SCHWARZ]
36019	CO-DYDRAMOL tablets 10mg+500mg [M&A PHARM]
36488	CO-CODAMOL capsules 30mg + 500mg [GEN (UK)]
36608	CO-CODAMOL effervescent tablet [AAH(VANT)]

PHN treatment - Strong PKs

Product Code	Product Name
36993	CO-CODAMOL capsules 30mg + 500mg [TEVA]
37291	CO-DYDRAMOL tablets 10mg+500mg [RANBAXY]
37816	CUPROFEN PLUS tablets [SSL INT]
37904	co-codamol (codeine and paracetamol) tablets 12.8mg + 500mg
38085	paracetamol with codeine phosphate capsules 500mg + 10mg
38088	paracetamol with codeine phosphate tablets 500mg + 30mg
38363	codeine phosphate with paracetamol tablets 12.8mg + 500mg
38430	CO-DYDRAMOL tablets 10mg+500mg [MERCK-GEN]
38521	DIHYDROCODEINE tablets 30mg [TEVA]
38950	REMEDEINE FORTE tablets 30mg + 500mg [NAPPPHARM]
38970	DF118 FORTE tablets 40mg [MARTINDALE]
39340	CO-CODAMOL caplets 8mg+500mg [AAH(VANT)]
39558	DIHYDROCODEINE tablets 30mg [WINTHROP]
40159	DIHYDROCODEINE elixir 10mg/5ml [MARTINDALE]
40385	CO-CODAMOL effervescent tablet 8mg+500mg [ALMUS]
40422	CO-DYDRAMOL tablets 10mg+500mg [WINTHROP]
40662	CO-CODAMOL effervescent tablet 8mg+500mg [ACTAVIS]
40663	CO-CODAMOL effervescent tablet 30mg + 500mg [ACTAVIS]
41259	CO-CODAMOL effervescent tablet 30mg + 500mg [TEVA]
41275	CO-CODAMOL tablets 8mg+500mg [NUCARE]
41276	CO-CODAMOL tablets 8mg+500mg [ALMUS]
41278	CO-DYDRAMOL tablets 10mg+500mg [IVAX]
41407	CO-PROXAMOL tablets 32.5mg + 325mg [RANBAXY]
41416	CODEINE PHOSPHATE tablets 60mg [CP PHARM]
41535	CODEINE PHOSPHATE tablets 30mg [TEVA]
41599	CODEINE PHOSPHATE tablets 15mg [TEVA]
41682	CO-CODAMOL effervescent tablet 30mg + 500mg [ROCHE]
42208	DF118 tablets 30mg [MARTINDALE]
42213	CO-CODAMOL capsules 8mg+500mg [CUSTOM]
42218	CO-CODAPRIN dispersible tablet 8mg+400mg [HILLCROSS]
42791	CO-CODAMOL FORTE tablets 30mg + 500mg [SANDOZ]
43238	CO-CODAMOL effervescent tablet 30mg + 500mg [GEN (UK)]
43244	CO-CODAMOL effervescent tablet 30mg + 500mg [HILLCROSS]
43414	CO-CODAMOL effervescent tablet 8mg+500mg [BAYER]
43441	CO-DYDRAMOL tablets 10mg+500mg [CELLTECH]
43504	CODEINE PHOSPHATE syrup [RANSOM]
43536	CO-PROXAMOL tablets 32.5/325 [NUMARK]
43550	CODEINE PHOSPHATE tablets 15mg [RANBAXY]
43891	co-proxamol oral liquid
44210	KAPAKE tablets 15mg + 500mg [GALEN]
44924	CO-CODAMOL tablets 30mg + 500mg [TEVA]
45231	CO-PROXAMOL tablets 32.5mg + 325mg [REGENT]
45276	CO-PROXAMOL tablets 32.5mg + 325mg [SIGMA]
46511	co-codamol (codeine and paracetamol) effervescent tablet 15mg + 500mg
46633	CO-CODAMOL capsules 8mg+500mg [HILLCROSS]
46729	co-codamol (codeine and paracetamol) capsules 15mg + 500mg
46898	CODIPAR capsules 15mg + 500mg [GOLDSHIELD]
46906	CO-CODAMOL effervescent tablet 8mg+500mg [NUMARK]
46925	CO-CODAPRIN dispersible tablet 8mg+400mg [ACTAVIS]
46987	CO-CODAMOL tablets 15mg + 500mg [HILLCROSS]
47003	CODEINE PHOSPHATE tablets 60mg [RANBAXY]
47071	co-dydramol (dihydrocodeine and paracetamol) oral suspension 10mg + 500mg/5ml
47072	OMNOPON injection 15.4mg/ml [ROCHE]
47508	CODIPAR effervescent tablet 15mg + 500mg [GOLDSHIELD]

PHN treatment - Tramadol

Product Code	Product Name
86	tramadol capsules 50mg
187	ZYDOL capsules 50mg [GRUNENTHAL]
687	TRAMACET film coated tablets 37.5mg + 325mg [GRUNENTHAL]
701	tramadol modified release capsules 50mg
3378	tramadol soluble tablet 50mg
3644	ZYDOL SR tablets 100mg [GRUNENTHAL]
4114	tramadol modified release capsules 100mg
4115	tramadol 12 hour modified release tablets 100mg
4834	tramadol modified release capsules 150mg
4999	tramadol 24 hour modified release tablets 150mg
5028	tramadol 24 hour modified release tablets 200mg
5169	ZYDOL SR tablets 200mg [GRUNENTHAL]
5257	tramadol 12 hour modified release tablets 150mg
6153	ZYDOL SR tablets 150mg [GRUNENTHAL]
6215	tramadol modified release capsules 200mg
6558	tramadol with paracetamol tablets 37.5mg + 325mg
8416	tramadol 12 hour modified release tablets 200mg
9389	ZAMADOL SR modified release capsules 50mg [MEDA]
9396	ZAMADOL SR modified release capsules 100mg [MEDA]
9739	tramadol sachets 100mg
11101	ZYDOL soluble tablet 50mg [GRUNENTHAL]
11275	ZYDOL injection 100mg/2ml [GRUNENTHAL]
11471	tramadol injection 100mg/2ml
11549	tramadol 12 hour modified release tablets 75mg
11559	tramadol sachets 50mg
11734	tramadol orodispersible tablet 50mg
11746	tramadol 24 hour modified release tablets 300mg
11748	tramadol 24 hour modified release tablets 400mg
13813	ZAMADOL capsules 50mg [MEDA]
14490	TRAMAKE capsules 50mg [GALEN]
16076	paracetamol with tramadol tablets 325mg + 37.5mg
16271	ZYDOL XL tablets 300mg [GRUNENTHAL]
16395	ZYDOL XL tablets 200mg [GRUNENTHAL]
19993	DROMADOL SR tablets 100mg [IVAX]
20310	ZAMADOL MELT orodispersible tablet 50mg [MEDA]
21256	TRAMAKE INSTS sachets 50mg [GALEN]
21397	ZYDOL XL tablets 400mg [GRUNENTHAL]
21777	DROMADOL SR tablets 200mg [IVAX]
21797	ZAMADOL SR modified release capsules 200mg [MEDA]
21947	ZYDOL XL tablets 150mg [GRUNENTHAL]
23625	DROMADOL SR tablets 150mg [IVAX]
23981	ZAMADOL SR modified release capsules 150mg [MEDA]
24383	TRAMAKE INSTS sachets 100mg [GALEN]
26336	DROMADOL XL tablets 300mg [IVAX]
26986	ZAMADOL 24 hour modified release tablets 200mg [MEDA]
27591	ZAMADOL 24 hour modified release tablets 150mg [MEDA]
28728	ZAMADOL 24 hour modified release tablets 300mg [MEDA]
29324	DROMADOL SR tablets 75mg [IVAX]
29860	TRAMADOL capsules 50mg [IVAX]
31105	DROMADOL XL tablets 200mg [IVAX]
31107	DROMADOL XL tablets 150mg [IVAX]
31734	DROMADOL XL tablets 400mg [IVAX]
32165	TRAMADOL capsules 50mg [GEN (UK)]
32450	ZAMADOL 24 hour modified release tablets 400mg [MEDA]
34065	TRAMADOL SR modified release tablet 150mg [WINTHROP]
34260	TRAMADOL SR modified release tablet 100mg [WINTHROP]
34281	TRAMADOL SR modified release tablet 200mg [WINTHROP]
34422	TRAMADOL capsules 50mg [ACTAVIS]
34521	TRAMADOL capsules 50mg [HILLCROSS]
34570	TRAMADOL capsules 50mg [TEVA]
34639	TRAMADOL capsules 50mg [GENUS]
34808	TRAMADOL capsules 50mg [PLIVA]

PHN treatment - Tramadol

Product Code	Product Name
35347	tramadol 24 hour modified release tablets 100mg
35438	TRAMQUEL SR capsules 100mg [MEDA]
35651	TRADOREC XL tablets 200mg [LABOPHARM]
35656	TRADOREC XL tablets 100mg [LABOPHARM]
35806	LARAPAM SR tablets 100mg [SANDOZ]
36035	TRADOREC XL tablets 300mg [LABOPHARM]
36697	MABRON prolonged release tablet 200mg [MORNINGSID]
36732	tramadol 12 hour modified release tablets 50mg
36873	ZYDOL SR tablets 50mg [GRUNENTHAL]
36949	TRAMQUEL SR capsules 50mg [MEDA]
37020	tramadol modified release tablet 150mg
37021	tramadol modified release tablet 200mg
37831	MABRON prolonged release tablet 100mg [MORNINGSID]
37867	tramadol (roi) tablets 100mg
38196	LARAPAM SR tablets 200mg [SANDOZ]
38528	TRAMADOL capsules 50mg [TILLOMED]
38874	ZAMADOL injection 100mg/2ml [MEDA]
38956	TRAMQUEL SR capsules 200mg [MEDA]
39505	MAROL prolonged release tablet 100mg [MORNINGSID]
39709	MAROL prolonged release tablet 200mg [MORNINGSID]
39750	MAROL prolonged release tablet 150mg [MORNINGSID]
39798	NOBLIGAN RETARD tablets 100mg [GRUNENTHAL]
39811	Herpes zoster with meningitis
40058	TRAMULIEF SR tablets 100mg [SOVEREIGN]
40060	TRAMULIEF SR tablets 200mg [SOVEREIGN]
40061	TRAMULIEF SR tablets 150mg [SOVEREIGN]
40166	TRAMADOL capsules 50mg [NICHE]
40249	MAXITRAM SR modified release capsules 100mg [CHIESI]
40254	MAXITRAM SR modified release capsules 50mg [CHIESI]
40718	TRAMADOL capsules 50mg [ALMUS]
40805	TRAMQUEL SR capsules 150mg [MEDA]
40883	MAXITRAM SR modified release capsules 150mg [CHIESI]
40926	LARAPAM SR tablets 150mg [SANDOZ]
41976	TRAMADOL SR tablets 100mg [HILLCROSS]
42280	tramadol with paracetamol effervescent tablet 37.5mg + 325mg
42332	TRAMACET effervescent tablet 37.5mg + 325mg [GRUNENTHAL]
42798	TRAMADOL SR tablets 150mg [HILLCROSS]
43198	TRAMADOL SR capsules 50mg [HILLCROSS]
43513	TRAMADOL capsules 50mg [WINTHROP]
44371	MABRON prolonged release tablet 150mg [MORNINGSID]
46279	TRAMADOL SR capsules 200mg [HILLCROSS]
46587	tramadol oral drops 100mg/ml
46643	ZERIDAME SR tablets 150mg [ACTAVIS]

PHN treatment - TCA

Product Code	Product Name
49	amitriptyline hydrochloride tablets 25mg
83	amitriptyline hydrochloride tablets 10mg
182	TRYPTIZOL injection 10mg/ml [M S D]
487	amitriptyline hydrochloride modified release capsules 25mg
873	AMITRIPTYLINE 100 MG TAB
1310	imipramine tablets 10mg
1809	imipramine tablets 25mg
1888	amitriptyline hydrochloride tablets 50mg
2039	trimipramine maleate tablets 25mg
2486	LENTIZOL capsules 25mg [PFIZER]
2525	amitriptyline hydrochloride modified release capsules 75mg
2531	SURMONTIL capsules 50mg [AVENTIS]
2532	SURMONTIL tablets 25mg [AVENTIS]
2533	TRIMIPRAMINE 50 MG TAB
2579	TOFRANIL tablets 10mg [NOVARTIS]
2936	Herpes zoster with meningitis
2985	LENTIZOL capsules 50mg [PFIZER]
3183	nortriptyline tablets 10mg
3196	trimipramine maleate capsules 50mg
3668	IMIPRAMINE 100 MG TAB
3771	AMITRIPTYLINE 75 MG TAB
3777	amitriptyline hydrochloride sugar free oral solution 10mg/5ml
3903	nortriptyline tablets 25mg
4118	nortriptyline capsules 10mg
4310	trimipramine maleate tablets 10mg
4404	TOFRANIL syrup 25mg/5ml [NOVARTIS]
4682	amitriptyline hydrochloride modified release capsules 50mg
4690	amitriptyline hydrochloride sugar free oral solution 50mg/5ml
6312	amitriptyline hydrochloride sugar free oral solution 25mg/5ml
6895	duloxetine gastro-resistant capsules 60mg
7122	ZERIDAME SR tablets 150mg [ACTAVIS]
7147	duloxetine gastro-resistant capsules 40mg
7153	duloxetine gastro-resistant capsules 20mg
7573	IMIPRAMINE 25 MG CAP
7677	ALLEGRON tablets 10mg [KING]
7678	nortriptyline capsules 25mg
7751	TRYPTIZOL tablets 25mg [M S D]
7780	nortriptyline with fluphenazine tablets 10mg + 500micrograms
7784	IMIPRAMINE 50 MG TAB
7910	TOFRANIL tablets 25mg [NOVARTIS]
7979	PERTOFRAN tablets 25mg [NOV/GEIGY]
7981	desipramine tablets 25mg
8055	imipramine syrup 25mg/5ml
8250	AMITRIPTYLINE S/F 25 MG/5ML SYR
8332	TRYPTIZOL tablets 50mg [M S D]
8493	MOTIPRESS tablets 30mg + 1.5mg [SANOFI S]
8640	ALLEGRON tablets 25mg [KING]
8726	TRYPTIZOL tablets 10mg [M S D]
8831	TRYPTIZOL MR capsules 75mg [M S D]
8878	TRYPTIZOL sugar free mixture 10mg/5ml [M S D]
8928	SURMONTIL tablets 10mg [AVENTIS]
10649	IMIPRAMINE 75 MG TAB
11963	LIMBITROL 10 capsules [ROCHE]
12194	NORTRIPTYLINE 10 MG ELI
12353	AVENTYL capsules 25mg [LILLY]
12549	AVENTYL liquid 10mg/5ml [LILLY]
13151	CYMBALTA gastro-resistant capsules 30mg [LILLY]
13496	AMITRIPTYLINE 200 MG TAB
14534	LIMBITROL 5 capsules [ROCHE]
14578	nortriptyline with fluphenazine tablets 30mg + 1.5mg
14803	YENTREVE gastro-resistant capsules 40mg [LILLY]
14849	CYMBALTA gastro-resistant capsules 60mg [LILLY]
16969	YENTREVE gastro-resistant capsules 20mg [LILLY]
17183	AVENTYL capsules 10mg [LILLY]
18342	amitriptyline hydrochloride with chlordiazepoxide capsules 25mg + 10mg
19779	amitriptyline hydrochloride injection 10mg/ml

PHN treatment - TCA

Product Code	Product Name
20026	DOMICAL tablets 25mg [BERK]
20571	fluphenazine with nortriptyline tablets 500mcg + 10mg
20712	AMITRIPTYLINE S/R
21081	amitriptyline hydrochloride with chlordiazepoxide capsules 12.5mg + 5mg
22070	AMITRIPTYLINE sugar free oral solution 10mg/5ml [ROSEMONT]
23497	AMITRIPTYLINE 300 MG TAB
24134	AMITRIPTYLINE tablets 25mg [KENT]
24141	AMITRIPTYLINE tablets 10mg [ACTAVIS]
24145	AMITRIPTYLINE tablets 25mg [ACTAVIS]
24147	AMITRIPTYLINE tablets 25mg [TEVA]
24152	AMITRIPTYLINE tablets 10mg [TEVA]
24680	ELAVIL tablets 10mg [DDSA]
25045	TRIMIPRAMINE
25085	TRIMIPRAMINE
26213	DOMICAL tablets 10mg [BERK]
27008	DOMICAL tablets 50mg [BERK]
27876	AMITRIPTYLINE
30738	AMITRIPTYLINE S/F
32439	AMITRIPTYLINE tablets 25mg [SUSSEX]
32863	IMIPRAMINE tablets 10mg [TEVA]
33074	PRAMINIL tablets 10mg [DDSA]
33090	AMITRIPTYLINE tablets 10mg [HILLCROSS]
33624	AMITRIPTYLINE tablets 50mg [TEVA]
34107	AMITRIPTYLINE tablets 50mg [WOCKHARDT]
34129	AMITRIPTYLINE tablets 25mg [WOCKHARDT]
34182	AMITRIPTYLINE tablets 50mg [KENT]
34197	AMITRIPTYLINE tablets 25mg [BERK]
34222	IMIPRAMINE tablets 10mg [ACTAVIS]
34224	AMITRIPTYLINE sugar free oral solution 25mg/5ml [ROSEMONT]
34251	AMITRIPTYLINE sugar free oral solution 50mg/5ml [ROSEMONT]
34274	AMITRIPTYLINE tablets 50mg [HILLCROSS]
34355	IMIPRAMINE tablets 25mg [ACTAVIS]
34401	AMITRIPTYLINE tablets 10mg [WOCKHARDT]
34474	AMITRIPTYLINE tablets 25mg [REGENT]
34503	AMITRIPTYLINE tablets 25mg [IVAX]
34634	AMITRIPTYLINE tablets 50mg [ACTAVIS]
34731	AMITRIPTYLINE tablets 10mg [KENT]
34782	AMITRIPTYLINE tablets 25mg [HILLCROSS]
34813	IMIPRAMINE tablets 25mg [HILLCROSS]
34872	IMIPRAMINE tablets 25mg [CP PHARM]
34916	AMITRIPTYLINE tablets 10mg [BERK]
39145	nortriptyline liquid 10mg/5ml
40396	AMITRIPTYLINE tablets 50mg [BERK]
41408	IMIPRAMINE tablets 25mg [TEVA]
41681	IMIPRAMINE tablets 10mg [HILLCROSS]
41729	AMITRIPTYLINE tablets 25mg [CELLTECH]
42078	AMITRIPTYLINE tablets 25mg [ALMUS]
42228	TRIMIPRAMINE tablets 10mg [HILLCROSS]
42247	imipramine oral solution 25mg/5ml
42394	AMITRIPTYLINE tablets 25mg [CROSS-PHAR]
45226	TRIMIPRAMINE tablets 25mg [HILLCROSS]
45233	AMITRIPTYLINE tablets 10mg [IVAX]
45242	AMITRIPTYLINE tablets 10mg [SUSSEX]
46801	amitriptyline hydrochloride oral solution 10mg/5ml
46818	amitriptyline hydrochloride oral suspension 10mg/5ml
46970	AMITRIPTYLINE tablets 50mg [IVAX]

Rheumatoid arthritis

Medical code	Read term
844	Rheumatoid arthritis
4186	Juvenile rheumatoid arthritis - Still's disease
5723	Rheumatoid nodule
6916	Seronegative rheumatoid arthritis
8350	ZERIDAME SR tablets 150mg [ACTAVIS]
9707	Seropositive errosive rheumatoid arthritis
9954	Rheumatoid lung
12019	Seropositive rheumatoid arthritis, unspecified
18155	Rheumatoid bursitis
21358	Rheumatoid arthritis of shoulder
21533	Pauciarticular juvenile rheumatoid arthritis
23552	Felty's syndrome
23834	Adult Still's Disease
27557	Juvenile rheumatoid arthritis NOS
27603	Rheumatoid arthritis and other inflammatory polyarthropathy
28853	Fibrosing alveolitis associated with rheumatoid arthritis
30548	Rheumatoid vasculitis
31054	Herpes zoster with meningitis
31209	Myopathy due to rheumatoid arthritis
31360	Juvenile rheumatoid arthritis
31724	Rheumatoid lung
32001	Adult-onset Still's disease
33264	O/E-hands-rheumatoid spindling
36276	Monarticular juvenile rheumatoid arthritis
37431	Rheumatoid arthropathy + visceral/systemic involvement NOS
41941	Rheumatoid arthritis of PIP joint of finger
42299	Rheumatoid arthritis of MCP joint
43816	Rheumatoid carditis
44203	Other rheumatoid arthritis of spine
44743	Rheumatoid arthritis of cervical spine
46436	Rheumatoid lung disease
47831	Acute polyarticular juvenile rheumatoid arthritis
48832	Rheumatoid arthritis of wrist
49067	Rheumatoid arthritis of hip
49227	Other rheumatoid arthropathy + visceral/systemic involvement
49787	Rheumatoid myocarditis
50644	Juvenile rheumatoid arthropathy unspecified
50863	Rheumatoid arthritis of knee
51238	Rheumatoid arthritis of 1st MTP joint
51239	Rheumatoid arthritis of ankle
53621	Rheumatoid nodule
56202	[X]Seropositive rheumatoid arthritis, unspecified
56838	Caplan's syndrome
59738	Rheumatoid arthritis of elbow
62401	Polyneuropathy in rheumatoid arthritis
63198	Rheumatoid arthritis of DIP joint of finger
63365	Rheumatoid arthritis of distal radio-ulnar joint
70221	[X]Other specified rheumatoid arthritis
70658	Rheumatoid arthritis of talonavicular joint
71784	Rheumatoid arthritis of other tarsal joint
73619	Rheumatoid arthritis of subtalar joint
93715	[X]Other seropositive rheumatoid arthritis
99414	Rheumatoid arthritis of lesser MTP joint
100776	Rheumatoid arthritis of sacro-iliac joint
100914	Rheumatoid arthritis of acromioclavicular joint
102088	Delivery of rehabilitation for rheumatoid arthritis

Smoking

Medical code	Read term	Smoking status
33	Never smoked tobacco	non-smoker
54	Tobacco consumption	current smoker
60	Current non-smoker	non-smoker
90	Ex smoker	ex-smoker
93	ZERIDAME SR tablets 150mg [ACTAVIS]	current smoker
776	Stopped smoking	ex-smoker
1822	Very heavy smoker - 40+cigs/d	current smoker
1823	Smoker	current smoker
1878	Moderate smoker - 10-19 cigs/d	current smoker
2111	Health ed. - smoking	current smoker
3568	Heavy smoker - 20-39 cigs/day	current smoker
6359	Nicotine withdrawal	current or ex-smoker
7130	Stop smoking monitoring admin.	current or ex-smoker
7622	Smoking cessation advice	current or ex-smoker
9045	Advice on smoking	current smoker
9833	Nicotine replacement therapy	current or ex-smoker
10184	Pregnancy smoking advice	current smoker
10211	Herpes zoster with meningitis	ex-smoker
10558	Current smoker	current smoker
10742	Referral to stop-smoking clinic	current or ex-smoker
10898	Smoking free weeks	ex-smoker
11356	Seen by smoking cessation advisor	current or ex-smoker
11527	DNA - Did not attend smoking cessation clinic	current smoker
11713	Pack years	current or ex-smoker
11788	Non-smoker	non-smoker
12240	Trying to give up smoking	current or ex-smoker
12878	Date ceased smoking	ex-smoker
12941	Occasional smoker	current smoker
12942	Smoker - amount smoked	current smoker
12943	Cigar smoker	current smoker
12944	Light smoker - 1-9 cigs/day	current smoker
12945	Rolls own cigarettes	current smoker
12946	Ex-smoker - amount unknown	ex-smoker
12947	Pipe smoker	current smoker
12951	Smoking restarted	current smoker
12952	Smoking started	current smoker
12953	Attends stop smoking monitor.	current or ex-smoker
12954	[V]Tobacco use	current smoker
12955	Ex-moderate smoker (10-19/day)	ex-smoker
12956	Ex-heavy smoker (20-39/day)	ex-smoker
12957	Ex-light smoker (1-9/day)	ex-smoker
12958	Trivial smoker - < 1 cig/day	current smoker
12959	Ex-very heavy smoker (40+/day)	ex-smoker
12960	Tobacco consumption NOS	current smoker
12961	Ex-trivial smoker (<1/day)	ex-smoker
12962	Tobacco consumption unknown	current smoker
12963	Cigar consumption	current smoker
12964	Keeps trying to stop smoking	current smoker
12965	Cigarette consumption	current smoker
12966	Smoking reduced	current smoker
12967	Pipe tobacco consumption	current smoker
13351	Passive smoker	non-smoker
16717	Smokers' cough	current smoker
18573	Referral to smoking cessation advisor	current or ex-smoker
18926	Lifestyle advice regarding smoking	current smoker
19485	Stop smoking monitor.chck done	current or ex-smoker
19488	Ex cigar smoker	ex-smoker
21637	Stop smoking monitor admin.NOS	current or ex-smoker
24529	Nicotine replacement therapy refused	current smoker
25106	Nicotine replacement therapy provided free	current or ex-smoker
26096	Smokes drugs	current or ex-smoker
26470	Ex pipe smoker	ex-smoker
28834	Anti-smoking monitoring admin.	current or ex-smoker
30423	Thinking about stopping smoking	current smoker

Smoking

Medical code	Read term	Smoking status
30762	Not interested in stopping smoking	current smoker
31114	Ready to stop smoking	current smoker
32083	Stop smoking clinic admin.	current or ex-smoker
32572	Over the counter nicotine replacement therapy	current or ex-smoker
32687	Tobacco dependence	current smoker
34126	Negotiated date for cessation of smoking	current smoker
35055	[V]Tobacco abuse counselling	current smoker
38112	Smoking cessation programme start date	current smoker
40417	Stop smoking monitor default	current or ex-smoker
40418	Refuses stop smoking monitor	current smoker
41042	Smoking cessation advice provided by community pharmacist	current or ex-smoker
41979	Smoking restarted	current smoker
42288	Pack years	current or ex-smoker
42722	Stop smoking monitor 1st lettr	current or ex-smoker
43433	Toxic effect of tobacco and nicotine	current smoker
46300	Cigarette pack-years	current or ex-smoker
46321	Reason for restarting smoking	current smoker
47273	Motives for smoking scale	current smoker
49418	RFS - Reasons for smoking scale	current smoker
52503	No smokers in the household	non-smoker
53101	Stop smoking monitor verb.inv.	current or ex-smoker
56144	[X]Mental and behav dis due to use of tobacco: harmful use	current smoker
57639	Bupropion refused	current smoker
58597	Stop smoking monitor phone inv	current or ex-smoker
59866	Reasons for smoking scale	current smoker
60720	Stop smoking monitor 2nd lettr	current or ex-smoker
61905	[X]Mental and behavioural disorder due to use of tobacco	current smoker
62686	Minutes from waking to first tobacco consumption	current smoker
63016	[X]Bupropion causing adverse effects in therapeutic use	current or ex-smoker
63299	FTND - Fagerstrom test for nicotine dependence	current smoker
63666	Fagerstrom test for nicotine dependence	current smoker
63717	Bupropion contraindicated	current or ex-smoker
63901	Stop smoking monitoring delete	current or ex-smoker
66387	Stop smoking monitor 3rd lettr	current or ex-smoker
66409	Nicotine replacement therapy contraindicated	current or ex-smoker
67178	Nicotine replacement therapy provided by community pharmacis	current or ex-smoker
68658	Tobacco dependence NOS	current smoker
70746	Tobacco dependence, continuous	current smoker
72700	[V]Personal history of tobacco abuse	current or ex-smoker
72706	Tobacco dependence in remission	ex-smoker
74907	Smoking cessation therapy	current or ex-smoker
81440	Nicotine replacement therapy using nicotine patches	current or ex-smoker
85247	Nicotine replacement therapy using nicotine inhalator	current or ex-smoker
85975	Nicotine replacement therapy using nicotine gum	current or ex-smoker
89464	Nicotine replacement therapy using nicotine lozenges	current or ex-smoker
90522	Smoking cessation therapy NOS	current or ex-smoker
91513	Occasions for smoking scale	current smoker
91708	Other specified smoking cessation therapy	current or ex-smoker
94958	Smoking cessation drug therapy	current or ex-smoker
95610	Tobacco dependence, unspecified	current smoker
96992	Smoking cessation - enhanced services administration	current or ex-smoker
97210	Ex-cigarette smoker	ex-smoker
97643	Fagerstrom test for nicotine dependence	current smoker
97973	Maternal tobacco abuse	current smoker
98137	Brief intervention for smoking cessation	current or ex-smoker
98154	Referral to NHS stop smoking service	current or ex-smoker
98177	Non-smoker annual review - enhanced services administration	non-smoker
98245	Stop smoking face to face follow-up	current or ex-smoker
98283	COPD structured smoking assessment declined - enh serv admin	current or ex-smoker
98284	Refer COPD structured smoking assessment - enhanc serv admin	current or ex-smoker
98347	Current smoker annual review - enhanced services admin	current smoker
98447	Ex-smoker annual review - enhanced services administration	ex-smoker
98493	Smoking cessatn monitor template complet - enhanc serv admin	current or ex-smoker
99838	Recently stopped smoking	ex-smoker

Smoking

Medical code	Read term	Smoking status
100099	Smoking cessation advice declined	current smoker
100495	Ex roll-up cigarette smoker	ex-smoker
100963	Ex-smoker annual review	ex-smoker
101210	Consent given for smoking cessation data sharing	current or ex-smoker
101325	Declin cons follow-up evaluation after smoking cess interven	current or ex-smoker
101338	Failed attempt to stop smoking	current smoker
101385	Consent given for follow-up by smoking cessation team	current or ex-smoker
101519	[X]Mental and behav dis due to use tobacco: withdrawal state	ex-smoker
101634	Consent given follow-up after smoking cessation intervention	current or ex-smoker
101764	Practice based smoking cessation programme start date	current or ex-smoker
101851	Declined consent for follow-up by smoking cessation team	current or ex-smoker
101854	Declined consent for smoking cessation data sharing	current or ex-smoker
101878	Non-smoker annual review	non-smoker
102361	Referral for smoking cessation service offered	current smoker
102951	Lost to smoking cessation follow-up	current or ex-smoker
103760	COPD structured smoking assessment declined	current or ex-smoker
103955	Asthma trigger - tobacco smoke	current smoker
104310	Current smoker annual review	current smoker

Systemic Lupus Erythematosis

Medical code	Read term
4125	Lupus erythematosus
7522	Lupus erythematosus NOS
7871	Systemic lupus erythematosus
11920	Systemic lupus erythematosus with pericarditis
20007	ZERIDAME SR tablets 150mg [ACTAVIS]
22205	Lupus nephritis
25390	Subacute cutaneous lupus erythematosus
29519	Systemic lupus erythematosus with organ or sys involv
31564	Lung disease with systemic lupus erythematosus
33449	Lupus erythematosus chronicus
36942	Drug-induced systemic lupus erythematosus
40797	Lupus erythematosus migrans
42719	Systemic lupus erythematosus NOS
44095	Polyneuropathy in disseminated lupus erythematosus
44984	Lupus erythematosus tumidus
45726	Systemic lupus erythematosus disease activity index
46148	Lupus erythematosus profundus
47672	Herpes zoster with meningitis
51798	Systemic lupus activity measure
58706	[X]Other forms of systemic lupus erythematosus
63955	Lupus erythematosus unguium mutilans
65391	Lupus erythematosus nodularis
99435	Neonatal lupus erythematosus
101433	Cerebral lupus