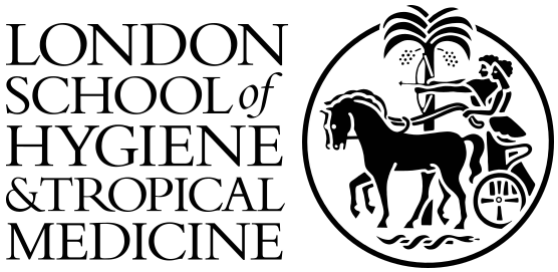

# Long-term antibiotics for acne and antimicrobial resistance

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

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**Department of Non-Communicable Disease Epidemiology**

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**LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE**

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# Declaration of authorship and statement of own work

I, Ketaki Bhate, 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.

Signature: Ketaki Bhate

Date: 7th of April 2023

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# Abstract

**Long-term oral antibiotics of acne vulgaris and antimicrobial resistance**

**Background:** The inappropriate use of oral antibiotics contributes to antimicrobial resistance. Oral antibiotics are regularly used to treat moderate to severe acne vulgaris. Acne guidelines recommend oral antibiotics for a minimum duration of three months of daily exposure and to repeat treatment if acne recurs. It is unclear how long-term oral antibiotics for acne are prescribed in the United Kingdom, and how they contribute to antibiotic treatment failure and antimicrobial resistance.

**Objectives:** The objectives of my thesis were to 1) systematically review evidence published in the literature on the association between oral antibiotics for acne and antibiotic treatment failure or infection caused by a resistant organism 2) to describe how people with acne are managed with oral antibiotics in UK primary care using the Clinical Practice Research Datalink (CPRD) over five years; and 3) to investigate the association between long-term oral antibiotics for acne and antibiotic treatment failure for common infections using the CPRD.

**Results:** Objective 1) Weak evidence was found in the literature for an association between antibiotic use for acne and subsequent increased rates of upper respiratory tract infections and pharyngitis. Objective 2) In the CPRD, a total of 217,410 people between the ages of 8 and 50 had a new acne diagnosis of which 96,703 (44.5%) people received 248,560 prescriptions for long-term oral antibiotics during a median follow up of 5.3 years (IQR 2.8-8.5). People received a median of four (IQR 2-6) continuous course of antibiotic therapy (≥28days). The median duration of the first course of oral antibiotic prescribed after acne diagnosis was 56 days (IQR 50-93 days) and 18,127 (18.7%) were for <6 weeks. Of those who received one course of oral antibiotic, 56,261 (58.2%) received a second course of antibiotic. The cumulative duration of exposure during follow up was 255 days (8.5 months). Objective 3) Of 847,760 people with acne, 114,770 had an LRTI, 73,648 had an SSTI, and 94,017 had a UTI. For LRTI, after adjusting for sex, deprivation, alcohol use, asthma and diabetes, oral antibiotics for acne were associated with an 8% increase in antibiotic treatment failure

(Adjusted HR =1.08, (1.04,1.13)). For SSTI, there was an 11% increase (HR=1.11, (1.07,1.16)) and for UTI, there was a 6% increase in treatment failure (HR= 1.06 (1.02, 1.10)). For LRTI, associations were greater for trimethoprim use (HR=1.77 (1.63,1.93)) than macrolides (HR=1.13 (1.07,1.20)) and tetracyclines (HR=0.99 (0.95,1.04)) and shorter courses of oral antibiotics for acne were less strongly associated with antibiotic treatment failure than longer durations (duration 28-41 days (HR=1.07 (0.92,1.24)), 42-90 days (HR=1.07 (1.03,1.11)), 91-180 days (HR=1.06 (0.97,1.15)), 181-365 days (HR=1.23 (1.06,1.42)) and >366 days (HR=1.84 (1.48,2.28)).

**Conclusions:** Further work is needed to understand the consequences of using antibiotics for shorter periods than recommended in acne treatment guidelines. Findings suggest an association between oral antibiotics for acne and antibiotic treatment failure within five years. There is some evidence that trimethoprim is more strongly associated with antibiotic treatment failure and shorter durations of antibiotics for acne are associated with less antibiotic treatment failure.

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# Abbreviations

| | |
|---|---|
| AMR | Antimicrobial Resistance |
| BNF | British National Formulary |
| CI | Confidence Interval |
| CPRD | Clinical Practice Research Datalink |
| DNA | Deoxyribonucleic Acid |
| HER | Electronic Health Records |
| GDP | Gross Domestic Product |
| GP | General Practice |
| GPs | General Practitioners |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HES | Hospital Episode Statistics |
| HR | Hazard Ratio |
| IMD | Index of Multiple Deprivation |
| LRTI | Lower Respiratory Tract Infection |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| ONS | Office for National Statistics |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO | International Prospective Register of Systematic Reviews |
| QOF | Quality and Outcomes Framework |
| RNA | Ribonucleic Acid |
| SSTI | Skin and Soft Tissue Infection |
| UK | United Kingdom |
| US | United States |
| UTI | Urinary Tract Infection |
| UTS | Up to Standard |

| | |
|---|---|
| WHO | World Health Organisation |

# Chapter 1: Introduction

In this opening chapter, I describe the rationale for my thesis. I firstly give an overview of antimicrobial resistance (AMR). I then provide an overview of the skin disease acne vulgaris including a description of it's epidemiology and treatment. I then focus on one particular treatment for acne, oral antibiotics and how this treatment may impact upon AMR. I describe how the link between oral antibiotics for acne and AMR is important to public health and people with acne and give an overview of initiatives to reduce oral antibiotic use. This chapter provides the setting from which I describe the overall aim of my PhD and specific objectives in chapter two.

## 1.1 AMR

When bacteria, viruses, fungi and parasites that cause infections change over time they cease to respond to the medicines given to target them. Infections become harder to treat and there is a higher risk of disease spreading, severe illness and death.(1) The drugs used to treated bacteria, viruses, fungi and parasites are collectively called antimicrobials. Antimicrobials are used to prevent and treat infections in humans, animals and plants.(1)Antibiotics are the antimicrobial drugs used to treat bacterial infections and my thesis focuses on bacterial AMR in humans. Throughout this thesis I use term AMR to refer to bacterial AMR.

The discovery of penicillin, a broad spectrum antibiotic still in use today, by Alexander Fleming in the late 1920s has significantly changed medical practice.(2) Bacterial resistance was first described two years after the mass production of penicillin began in 1945.(3-5) In December 1945, Alexander Fleming in his Nobel lecture warned "There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."(6) Since then, antibiotic resistance has been reported with nearly all antibiotic classes that have been developed (**Table 1.1**).(7) Bacteria can be either be intrinsically resistant to antibiotics or they can acquire resistance by the mutation of chromosomal genes or via horizontal gene transfer.(8) Bacteria become resistant to antibiotics in several different pathophysiological ways: 1) they can develop

protective mechanisms to prevent entry of the drug, or to export it; 2) they can develop mechanisms to produce enzymes to breakdown the antibiotic; 3) they can destroy or alter the antibiotic rendering it inefficient in targeting bacteria; or 4) bacteria can make changes to the antibiotic target (e.g. the bacterial cell wall).(9) The treatment with oral antibiotics can also lead to AMR in ordinarily commensal flora at other sites of the body, not intended for treatment.(10) Furthermore, exposure to antibiotics can encourage the proliferation of opportunistic bacteria elsewhere in the body and cause damage to the steady state microbiome.(11)

| Class of antibiotic | Year of discovery/introduction | Year resistance observed | Activity or target species |
|---|---|---|---|
| Inhibitors of cell wall synthesis | | | |
| Penicillins | 1928/1938 | 1945 | Broad-spectrum |
| Vancomycin | 1953/1958 | 1960 | Gram-positive bacteria |
| RNA polymerase inhibitors | | | |
| Rifampicin | 1957/1958 | 1962 | Gram-positive bacteria |
| DNA synthesis inhibitors | | | |
| Ciprofloxacin | 1961/1968 | 1968 | Broad-spectrum |
| Protein synthesis inhibitors | | | |
| 30s subunit—aminoglycosides | | | |
| Streptomycin | 1943/1946 | 1946 | Broad-spectrum |
| Tetracyclines | 1944/1952 | 1950 | Broad-spectrum |
| 50s subunit—macrolides | | | |
| Chloramphenicol | 1946/1948 | 1950 | Broad-spectrum |
| Streptogramin B | 1963/1998 | 1964 | Gram-positive bacteria |

**Table 1.1:** Description of the date of antibiotic class discovery, date resistance first observed and spectrum of antibiotic activity. Adapted from Nelson et al. Antimicrobial resistance (AMR): significance to food quality and safety, Food Quality and Safety, 2019. 

AMR is one of the leading threats to global public health and the World Health Organisation (WHO) has declared the threat of AMR a most urgent crisis.(12) The future effectiveness of antibiotics are in jeopardy – a report commissioned by the United Kingdom (UK) government in 2016 has predicted that future deaths from infections as a result of AMR without any intervention are estimated at 10 million per year, that is, one death every three seconds.(13) By 2050, the cumulative cost to global economic output of AMR could reach 100 trillion United States (US) dollars, with a loss of 2-3.5% of world GDP (Gross Domestic Product). There is some controversy surrounding these figures due to uncertainties about the incidence of infection and resistance, and the assumptions required when modelling future scenarios which may not be realistic (14) however, they have provided impetus for action to tackle AMR on a global level. AMR is expensive with high costs to health systems; loss of productivity of patients with AMR and their carers; and severe complications of AMR which often require prolonged hospital stays and costly intensive care.(1, 15) In the United States, AMR contributes 20 billion US dollars to the direct costs of healthcare and 35 billion US dollars additionally to loss of productivity per annum.(16)

The over and inappropriate use of antibiotics in the human, animal and environmental sectors has increased the emergence of AMR.(15, 17, 18) Additionally, the increased GDP in low and middle income countries (LMICs) has been positively correlated with higher levels of antibiotic use.(19, 20) While AMR was first a problem of secondary care (in hospitals), it is now seen in the community too.(21) Without interventions for the prevention of drug resistance and the adequate treatment of drug resistant infections, and without the availability of and access to new antibiotics, the number of people who die from infections will rise.(1) Resistant bacteria lead to AMR and threatens the ability to treat common infections such as pneumonia, tuberculosis and malaria.(1) Additionally, antibiotics are prescribed prophylactically for other medical indications including post or intra surgical infections (for example in caesarean sections), for the treatment of immunocompromised patients and for organ transplant or prosthetic implant recipients.(22-25) Without antibiotics, relatively routine surgical procedures could be life threatening.(13)
AMR allows bacterial strains that can withstand the effects of antibiotics to grow and flourish as they lack competition from strains that are sensitive to antibiotics, thereby leading to the emergence of highly resistant bacteria such as Methicillin-resistant

*Staphylococcus aureus* (MRSA) and highly drug resistant tuberculosis.(13) The highly rapid, global spread of bacteria which are multi drug or pan resistant to antibiotics, the so called 'superbugs' are particularly threatening as there are no known antibiotics that can treat these pathogens.(1)

**New antimicrobials**

The WHO has identified 32 antibiotics which are in various stages of clinical development that target the WHO list of priority pathogens.(26) Of the new antibiotics in development, only six were novel antibiotics, i.e. potential new, innovative classes of antibiotic with new mechanisms of action. The rest were derived from existing classes of antibiotics already in use. There have been no new classes of antibiotic that have been fully developed since 1987 (27), however Teixobactin, an antibiotic which works by inhibiting cell wall synthesis and may be able to treat MRSA, drug resistant TB and anthrax is, at the time of writing, currently in the late stages of development.(28, 29) At present therefore, we do not have new classes of antibiotic drugs for use in medical care that can treat highly resistant bacteria. New antibiotics which target bacteria with novel mechanisms of action, are urgently needed, particularly for the pathogens identified on the WHO priority pathogen list.

The issues surrounding antibiotic drug development are compounded by the drive to reduce the use of antibiotics, and to reserve some antibiotics as last resort treatments. If the use of novel antibiotics are relatively infrequent, there is less revenue and sales for pharmaceutical companies and therefore less incentive for them to invest in antibiotic drug development. To tackle this, upfront payments in a subscription model where flat-rate payments are made for the use of an antibiotic within the health system have been introduced in the UK since June 2020.(30) A subscription model works to decrease to use of antibiotics and to ensure pharmaceutical companies have a market even if novel antibiotics are reserved for last resort use in resistant infections but they may not adequately attract small or medium pharmaceutical companies into the expensive drug development space.(31) A similar incentivisation approach is being trialled in Sweden (32) however, in Europe, an alternative scheme is being proposed with the introduction of a 'Transferable Exclusivity Voucher' where the company which has developed a new antibiotic is awarded a voucher that can be applied to any medicine (which can be unrelated to the antibiotic) to extend a drug patent

period for up to one year.(33) There may be issues surrounding equitable access to the antibiotic with this scheme.(34) While new antibiotics may reduce the burden of AMR, if the way in which antibiotics are prescribed is not changed, any newly developed antibiotics could also become ineffective.

## 1.2 Acne vulgaris

Acne vulgaris (herein referred to as acne) is a disease of the pilosebaceous unit. The pilosebaceous unit comprises hair follicles with an associated oil gland in the skin. Excess sebum production, disturbed keratinisation within the hair follicle, colonisation with the bacterium *Cutibacterium acnes* and inflammation are the pathophysiological features.(35, 36) The cardinal clinical features of acne are seborrhoea (greasy skin), non-inflammatory acne (open and closed comedones also referred to as blackhead and whiteheads) inflammatory acne (papules (red spots), pustules (pus filled spots), nodules or cysts (larger, often sore red spots), post-inflammatory hyperpigmentation (flat red or brown discoloration of the skin left residually when an acne lesion recovers) which can take many months to resolve and scarring (permanent disfigurement of the skin despite no active inflammation) (**Figure 1.1**).

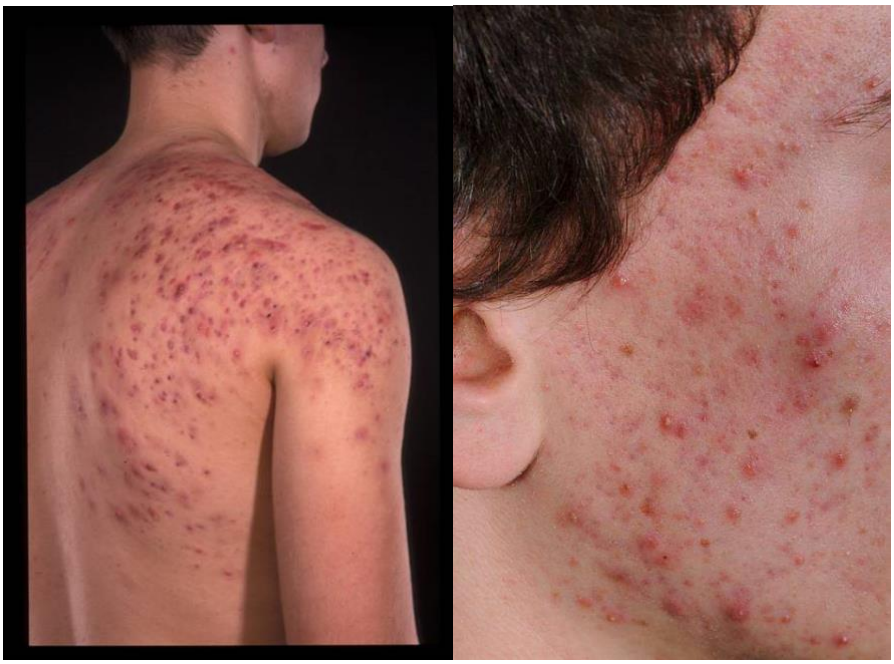

**Figure 1.1 A:** Severe acne vulgaris on the back (left) and moderate acne vulgaris on the cheek (right) with nodules, papules, pustules, comedones and scarring seen (permission for use of images from patient obtained).

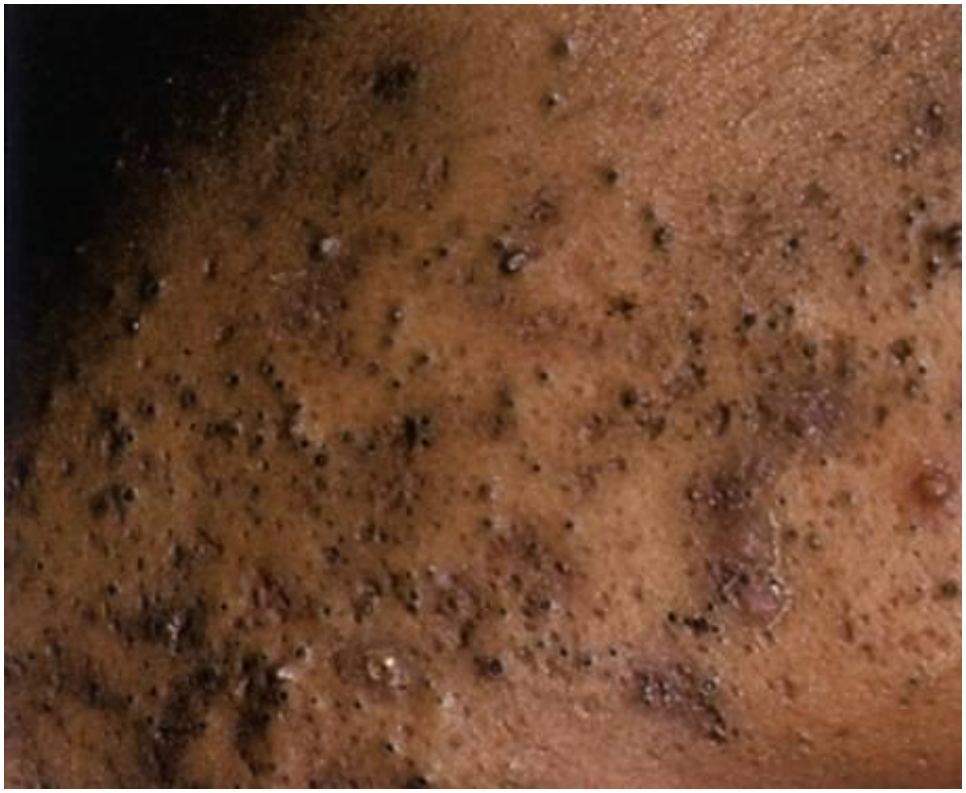

**Figure 1.1 (B):** Scarring acne seen on the temple with open comedones and inflammatory acne

Acne is a chronic, inflammatory skin condition with onset in predominantly adolescence. Many NHS appointments are needed in both primary care and secondary care, particularly if therapies such as isotretinoin, a vitamin A derivative with teratogenic (causes foetal abnormality when exposed to drug during pregnancy) side effects, are indicated. In the UK, Over 90% of acne is managed in primary care by general practitioners.(37), and 3.5 million GP visits annually are for acne.(38)

**Epidemiology of acne**

In Western countries, nearly everyone between the ages of 15 and 17 are affected by acne to a degree, and in 15-35% of adolescents, acne is moderate to severe.(39-45) Overall, 9.4% of the global population are affected by acne according to the Global Burden of Disease study making it the eighth most prevalent disease worldwide.(46, 47) Prevalence varies by

geographical location with developed nations having higher rates of acne than non-industrialised countries.(48) Acne begins with the onset of puberty and predominantly affects people between the ages of 12 – 24 with 85% of people with acne being in this age group. Acne affects 8% of people between 25 and 34 years, and 3% between the ages of 35 and 44 (49-51), and consistently represents the top three most prevalent skin conditions in the general population and worldwide.(52-55)

Acne is associated with a large psychosocial burden. Acne is associated with self-consciousness, anxiety in social interactions, unhappiness with appearance and an impaired quality of life.(39, 56, 57) Acne reduces the perception of overall health and teasing and bullying is a significant cause of morbidity.(58, 59) A European multicentre study in a dermatology outpatient clinic setting in secondary care used validated scoring tools to identify anxiety, depression and quality of life in acne patients versus a control group without any skin disease and found that 15% of people with acne suffered with anxiety compared to 9% of people without acne, and 6% of people with acne suffered with clinical depression compared to 2% of people without acne.(60)
The presence of acne has also been reported to have a negative effect upon work and school performance.(61) In the US, it is estimated that over 3 billion dollars per year is spent on the direct and indirect costs of treatment and loss of productivity related to acne in those of working age.(53) A later study in 2017 found that in 2013, 5.1 million people in the U.S.A. sought medical care for acne, and these individuals were predominantly adolescents and young adults. The study also reported that the total cost associated with acne including the direct cost of acne treatments and the indirect costs of loss of productivity for people who sought medical care was approximately 1.2 billion US dollars, of which 400 million US dollars was due to loss of productivity amongst patients and their carers.(62)
These estimates do not take into consideration the potential cost of AMR occurring as a consequence of the long-term antibiotics used to treat acne. There are no UK data on the burden or cost of acne treatment, or loss of productivity.(63)

Worldwide, **Figures 1.2** and **1.3** display the greatest burden of skin diseases by age. The highest burden of acne is between the first and third decade of life, and acne has the highest burden of all skin diseases in these age groups.

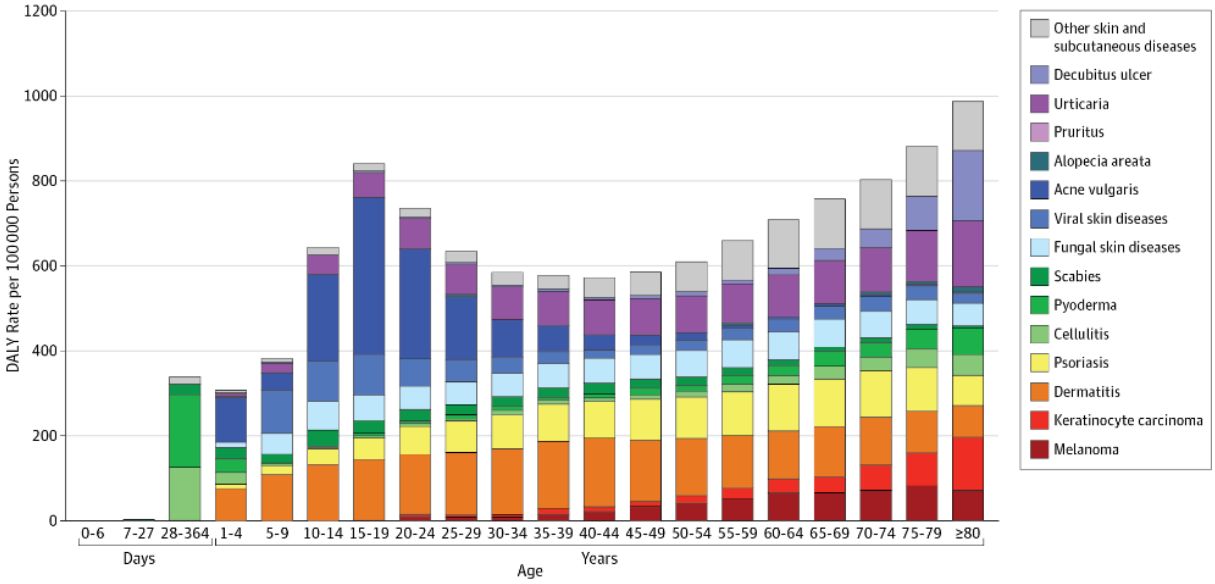


**Figure 1.2**: Figure shows disability-adjusted life year (DALY) rate per 100 000 persons from 15 skin disease categories throughout the human life span.(55) Reproduced with permission under the CC-BY license from Karimkhani et al. Global Skin Disease Morbidity and Mortality: An update from the Global Burden of Disease Study 2013.

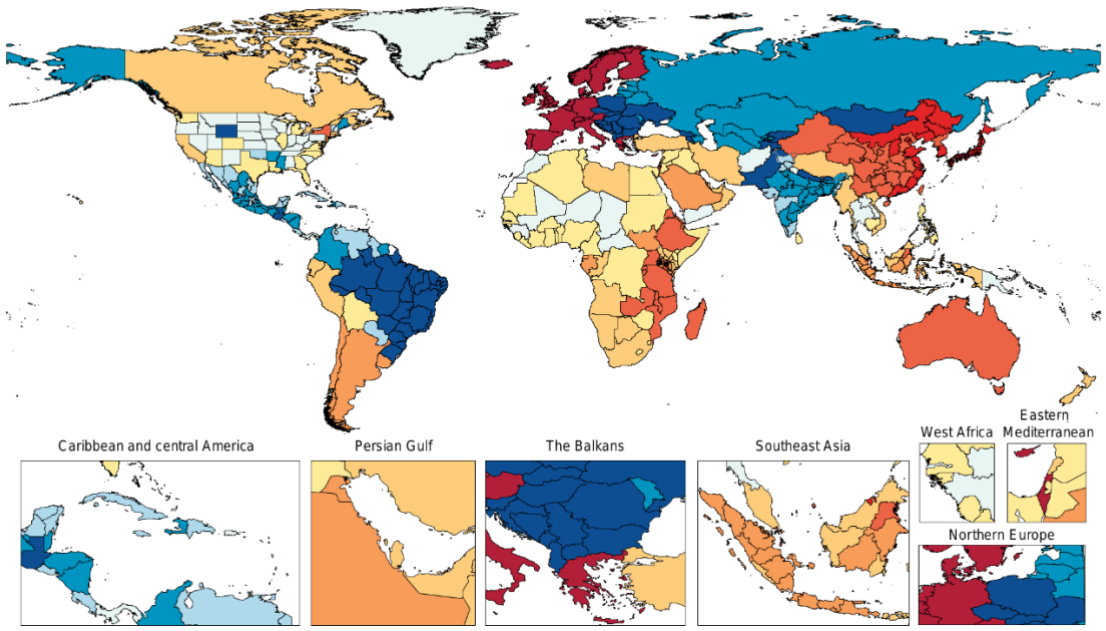


**Figure 1.3**: Age standardised Disability Associated Life year (DALY) rates per 100,000 people by location for both sexes diagnosed with acne combined in 2019. Taken from the Institute of Health Metrics and Evaluation Global Burden of Disease Summaries.(64) Reproduced with permission under the Creative Commons Attribution Non Commercial No Derivatives 4.0 International License.

**Epidemiology of acne**

Acne typically occurs with the onset of puberty and affects males and females equally, with the onset of puberty being earlier in females than males. Studies regarding the onset and severity of acne by ethnicity vary. There are suggestions of morphological variations by ethnic group, with darker skin developing more post inflammatory hyperpigmentation which can be prolonged.(63) The current acne management guidelines do not consider variations between ethnic groups.(65) There is some evidence that a high Glycaemic Index and a high dairy containing diet can worsen the severity of pre-existing acne, however existing studies on the relationship between diet and acne are either small or suffer from recall bias.(65-67)

**Acne diagnosis and treatment**

The diagnosis of acne is made clinically when characteristic lesions, on the face, chest and/or back are present in people between the ages of 8 and 50. There are other rare subtypes of acne, such as acne conglobata (a severe form of acne predominantly affecting young males) and acne fulminans (severe acne, predominantly affecting young males, with additional features of fever, malaise, joint pain and hepatosplenomegaly). Acneiform lesions can be present in babies and toddlers, often referred to as infantile acne.(36) The aetiology of variants of acne vulgaris is presumed to be different, therefore I will discuss only acne vulgaris, the predominant and most common form of acne. (68)

There are several major acne treatment guidelines including guidance produced by National Institute for Health and Care Excellence (NICE) and the American Association of Dermatologists (AAD).(45, 69-71) (**Figure 1.4**) In the UK, individual regions providing health care (or Primary Care Trusts (PCTs), replaced by Clinical Commissioning Groups (CCGs) in April 2013, and now replaced by Integrated Care Systems (ICSs) as of July 2022) often form their own guidance documents for the treatment of acne for use by clinicians treating patients residing within their region.(72, 73) Often major guidelines are used as reference to compile local acne guidelines, and local guidelines vary depending upon local prescribing policies. Generally, for mild to moderate acne without scarring, a stepwise approach to acne treatment is recommended, with the use of topical therapy first. Topical therapies include

benzoyl peroxide, topical vitamin A derivatives such as adapalene, topical antibiotics, or combination drugs of two of the above. It is usually recommended that after failure of topical therapy, treatment is escalated to oral tablet therapy (an oral antibiotic or combined oral contraceptive in females) or by referral to dermatology for secondary care treatment particularly if there is scarring. In secondary care, treatment with the oral vitamin A derivative, Isotretinoin (brand name Roaccutane) is often considered. In primary care, NICE recommends the pharmaceutical treatment for moderate to severe acne consists of a twelve week course of combination topical adapalene and benzoyl peroxide, tretinoin with topical clindamycin, or benzoyl peroxide with adapalene and oral lymecycline or doxycycline.(69) NICE further recommends that for people who cannot tolerate or have contraindications to oral lymecycline or doxycycline that these are replaced with trimethoprim or with an oral macrolide such as erythromycin.

| | Mild | Moderate | Severe |
|---|---|---|---|
| **1st Line Treatment** | Benzoyl Peroxide (BP)<br>or Topical Retinoid<br>-or-<br>Topical Combination Therapy**<br>BP + Antibiotic<br>or Retinoid + BP<br>or Retinoid + BP + Antibiotic | Topical Combination Therapy**<br>BP + Antibiotic<br>or Retinoid + BP<br>or Retinoid + BP + Antibiotic<br>-or-<br>Oral Antibiotic + Topical Retinoid + BP<br>-or-<br>Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic | Oral Antibiotic<br>+<br>Topical Combination Therapy**<br>BP + Antibiotic<br>or Retinoid + BP<br>or Retinoid + BP + Antibiotic<br>-or-<br>Oral Isotretinoin |
| **Alternative Treatment** | Add Topical Retinoid or BP (if not on already)<br>-or-<br>Consider Alternate Retinoid<br>-or-<br>Consider Topical Dapsone | Consider Alternate Combination Therapy<br>-or-<br>Consider Change in Oral Antibiotic<br>-or-<br>Add Combined Oral Contraceptive or Oral Spironolactone (Females)<br>-or-<br>Consider Oral Isotretinoin | Consider Change in Oral Antibiotic<br>-or-<br>Add Combined Oral Contraceptive or Oral Spironolactone (Females)<br>-or-<br>Consider Oral Isotretinoin |

**Figure 1.4:** Acne treatment algorithm. Reprinted from The Journal of the American Academy of Dermatology. Zaenglein et al, Guidelines for the management of acne vulgaris, Copyright (2016), with permission from Elsevier.(70)

### Oral antibiotics for acne

Oral antibiotics are a mainstay of oral treatments for acne in primary care. Tetracyclines and macrolides are the two most commonly prescribed oral antibiotic classes for acne. Trimethoprim is often prescribed as a second-line antibiotic for acne.(74, 75) Average use durations vary depending on treatment setting. The high prevalence of acne means that antibiotics are often prescribed in the adolescent population, for variable durations ranging from six weeks to many months and, in some cases, years.(74, 76) Although acne guidelines vary, most recommend antibiotics are continued for 3–4 months with some mentioning treatment effectiveness begins, or can be assessed at, six weeks.(45, 69, 70, 77-79) Guidelines also state that each 3 to 4-month course can be repeated if acne recurs.
A study using routinely collected health records from General Practice (primary care) in the UK published in 2017 described how acne medications are prescribed in the UK; however, patients included in the study population were followed up for only one year. While the study did not aim to analyse durations of courses of oral antibiotics for acne, this would not have been possible due to the study design, as some courses of antibiotic could extend for durations longer than one year. It was also therefore not possible to fully ascertain if people received a second course of oral antibiotic, and the duration of the second course.(80) The study found that 45% of people who were prescribed a medication for acne were prescribed an oral antibiotic.

Given acne is a chronic condition, which can span decades, it is important to understand how courses of antibiotics are repeated and are prescribed long-term throughout the course of the disease. Another study using UK primary care data found median duration of tetracycline therapy in people with acne between 12 and 22 years of age was 112 days, but we do not know if antibiotic courses were repeat prescribed for individuals during follow-up.(74) A study of health insurance claims data in the US found the number of courses of oral antibiotics per 100 individuals with acne was approximately 20 and the median duration of therapy was 129 days (no interquartile range provided by the authors) when

antibiotics were prescribed by a non-dermatologist.(75) To my knowledge, there have been no studies in the UK that have assessed the use of oral antibiotics for acne long-term for time periods longer than one year.

Studies using UK primary care data have previously looked at the concomitant prescription of topical non antibiotic acne therapy with oral antibiotics. Using a topical non antibiotic treatment alongside an oral antibiotic for acne is an approach recommended in most acne guidelines, because the co-prescription of both treatments is thought to act synergistically and reduce the duration required of oral antibiotic.(74, 80)

A systematic review which sought to establish the efficacy of oral antibiotics for acne reported that they were safe and effective, however the review did not find evidence to support the use of one class of antibiotic over another.(81) Furthermore, a randomised controlled trial of various oral antibiotic therapies for acne found little comparative advantage in efficacy of either minocycline (a tetracycline class antibiotic) or erythromycin (a macrolide class antibiotic) for acne.(77) There are no studies to my knowledge assessing the long-term efficacy or clinical effectiveness of oral antibiotics for acne, however it is generally understood that oral antibiotics for acne are not disease modifying, in that they do not alter the chronicity of disease compared to if acne were left untreated. Oral Isotretinoin is the only proven disease modifying anti acne drug.

In addition to antimicrobial effects, oral antibiotics are proposed to have anti-inflammatory properties which are important for the treatment of acne.(82) Using antibiotics for their anti-inflammatory effects, in addition to their antimicrobial activity is not uncommon, and is an approach used for cystic fibrosis and Chronic Obstructive Pulmonary Disease (COPD).(83-85) . It is thought that oral antibiotics for acne predominantly act via their anti-inflammatory effect, given that acne is not an infectious disease, and the pathophysiology of acne is multifactorial with *Cutibacterium acnes* implicated in only part of the pathophysiological disease process.(86) However, the extent of the relative contributions of oral antibiotics for acne as an anti-inflammatory or as an antibiotic treating *Cutibacterium acnes* remains to be fully elucidated.(87) Despite the mainstream use of oral antibiotics for acne, the risk to

benefit ratio of using oral antibiotics for acne may not have considered AMR in sufficient detail for robust conclusions to be drawn.(10)

Oral doxycycline, is a tetracycline class antibiotic commonly used to treat acne. Doxycycline is also a treatment for MRSA.(88) The development of resistance to doxycycline could limit its future efficacy. Methicillin-resistant Staphylococcus aureus (MRSA) are strains of the common bacterium Staphyloccocus aureus which have become resistant to a number of antibacterial agents including the beta-lactam antibiotic flucloxacillin. MRSA can live as a colonising bacterium on the skin without causing an active infection or alternatively, can cause skin or bone infections. If left untreated, MRSA can become invasive for example through the skin or mucous membranes to cause severe, potentially life-threatening systemic infections, for example, urinary tract infections, pneumonia and sepsis.(89) Antibiotic exposure increases the risk of MRSA.(90) Doxycycline, a tetracycline class of antibiotic, is recommended for the treatment of MRSA, and it is unclear how its use long-term for the treatment of acne might affect its ability to treat MRSA.(91)

## 1.3 Challenges of studying AMR

To confirm antimicrobial resistance, bacteria are cultured in laboratories and tested by exposing them to various antibiotics to look for bacteriostatic or bactericidal activity.(92) Worldwide, especially in LMICs, lab based data systems are not sufficiently linked to diagnoses and outcomes, therefore rendering any conclusions about AMR difficult. There are also difficulties with selection bias surrounding which data are entered on to surveillance software systems, and the scarcity of laboratory testing for AMR.(93) In LMICs hospital microbiological data is skewed towards urban populations where secondary care facilities are more easily accessed. Additionally, there are issues with sharing data for inclusion into studies.(92) Furthermore, selection bias might be present when using microbiological data to investigate AMR if bacterial cultures (laboratory test to establish type of bacteria and sensitivity of bacteria to antibiotics) are not routinely taken. Often, samples for bacterial culture are only taken if a patient does not respond to antibiotic therapy. Similar practices occur in UK primary care, therefore there is limited routine microbiological data in order to investigate AMR. While secondary and tertiary care may

have more data from cultures, these data will not represent the true burden of resistance as they exclude culture data for infections diagnosed and treated in the community, and secondary care harbours a unique environment for the development of AMR and so called 'superbugs' such as MRSA and *Clostridium difficile*. Studying AMR prospectively, with sufficient power, using microbiological data, is expensive and given the urgent need to investigate AMR sequalae, it is important to use alternative research and analytic methods to quantify AMR.(15)

## 1.4 Antibiotics for acne and AMR

Oral and topical antibiotics are used to treat acne vulgaris. Several studies have provided evidence of resistance to topically applied antibiotics for acne and resistance of *Cutibacterium acnes*, the bacteria pathophysiologically associated with the formation of an acne lesion,(94-96) however there is little evidence in support of the potential AMR effects of oral antibiotics for acne. We do not know how long-term oral antibiotics for acne attenuate flora elsewhere in the body, and affect the ability of other bacteria at other body sites to withstand the effect of antibiotics. Prolonged or repeated exposure to antibiotics may alter commensal bacteria (non-harmful bacteria usually present in the body) so that they develop and acquire mechanisms to resist antibiotics, potentially giving rise to invasive infections.(10, 11, 88, 97)

In a study published in 2007 of 40 primary care doctors, or General Practitioners (GPs) in the UK, it was reported that more than half of the GPs did not perceive antimicrobial resistance as a problem within their practice as the infections they were treating were susceptible to first line antibiotics, and they rarely encountered treatment failure. Some GPs felt that AMR was an issue found in hospitals only with some stating they needed proof of AMR in primary care before they changed their practice. (98) Another study also found that GPs and the public perceive AMR to be an issue pertaining to secondary care, (99) and do not consider AMR to be of concern when prescribing antibiotics for acne.(100)

Overall, over 80% of antibiotics in the UK are prescribed in primary care,(101) and acne is a common condition for which oral antibiotics are prescribed for longer durations of at least three months. Given that over 90% of acne management is primary care based, and acne affects younger people who have fewer comorbidities than people who are older,

individuals with acne provide an ideal population in which the effects of long-term oral antibiotics for acne can be studied in relation to AMR. In order to offset the aforementioned inherent challenges of quantifying AMR using microbiological data at the population level, routinely collected electronic health records with proxy measures of AMR can be used to undertake observational studies. (102) Antibiotic treatment failure may be a proxy measure of AMR, (103) and one of the causes of antibiotic treatment failure is AMR. A study by Currie et al in 2014 established several proxy measures of antibiotic treatment failure using UK based routinely collected health data in primary care(102), and this methodology has been similarly used to identify antibiotic treatment failure in other studies.(104-106) Despite the use of proxies in routinely collected health data, antibiotic treatment failure is only a proxy measure for AMR, and characterising antibiotic treatment failure carries difficulties, given the vast numbers of antibiotics available, infection types and diverse pathogen characteristics, which may change over time and therefore alter outcome signals causing challenges in interpretation.(107)

## 1.5 Antimicrobial stewardship

Antimicrobial stewardship is 'a framework, strategy, or a coherent set of actions which promote the use of antimicrobials responsibly, where the specific action depends on the role of the individuals within the healthcare system'.(108) Examples of antimicrobial stewardship activities with regard to antibiotics include adequate monitoring of antibiotic use and routine surveillance of AMR, the development of new antibiotics or treatments of AMR, diagnostics of antibiotic resistance and appropriate prescribing decisions with AMR in mind.(109, 110)

## 1.6 Importance to patients and the public

The importance of understanding the use of oral antibiotics for acne and AMR and has been highlighted in the acne Priority Setting Partnership (PSP) (acnepsp.org) in collaboration with the James Lind Alliance (www.jla.nihr.ac.uk).(111) The aim of the PSP was to identify and prioritise unmet research needs to drive improvement in clinical care. Acne was determined to be a key area for undertaking a PSP, given the high prevalence of acne in adolescents. Over 6,000 responses were collated about acne treatment uncertainties from a

collaboration of various stakeholders including people with acne, healthcare professionals and members of the public. Prior to beginning this PhD, I was involved in the process by being part of the team which helped inform the design of publicity materials and the harvesting survey (where all the initial responses were collected), and which helped rephrase, sort and collate the submissions from the survey. The final stage of the PSP was where the 18 highest scoring uncertainties were voted upon and discussed by a panel of 30 patients and healthcare professionals in order to reach a consensus and identify the top ten priorities for research.

Two of these top ten treatment uncertainties will be addressed by my proposed programme of work:

1. What is the correct way to use antibiotics in acne to achieve the best outcomes with least risk?

2. What management strategy should be adopted for the treatment of acne in order to optimise short and long-term outcomes?

These two outcomes highlight the importance surrounding the effects of acne treatments to people with acne and members of the public.

## 1.7 Summary

The inappropriate use of antibiotics is a known cause of AMR. Repeated and sustained exposure may allow bacteria to develop mechanisms to avoid the effects of the drugs designed to treat them and allows selection in favour of bystander or commensal bacteria with resistance which can subsequently cause infection. While acne is not an infectious disease and aetiologically is multifactorial, we already know that some strains of *Cutibacterium acnes,* the bacteria pathophysiologically associated with acne, are now resistant to commonly used topical antibiotics, making their initial use as anti-microbial agents futile.(94-96)

We do not know however, how long-term oral antibiotics for acne may attenuate microbiota elsewhere at other body sites or how they affect the ability of other bacteria at other infective sites to withstand the effect of antibiotics. Considering the relationship between long term exposure to antibiotics and AMR, using oral antibiotics to treat acne may not be optimal practice.

Given the global health emergency of AMR and the frequent use of oral antibiotics to treat acne in primary care, understanding how they are used, if they contribute to AMR or subsequent treatment failure, and how this will impact upon the future health of patients, the wider society and the NHS financially, is imperative for future resource allocation and planning.

Antibiotic stewardship programmes have been shown to be effective for other infective conditions, particularly in secondary care,(109, 112) however to ensure their successful implementation and execution, robust evidence must be generated to establish how oral antibiotics for acne are prescribed in the UK and show that antibiotic usage has important implications for future infective episodes and resistance sequelae. The use of long-term antibiotics to treat acne in a large, relatively healthy and young population provides an ideal and unique model in which to study AMR.

# Chapter 2: Aims and objectives

## 2.1 Overall aim

My overall aim was to investigate the association between long-term oral antibiotics prescribed for acne vulgaris and antimicrobial resistance (AMR) in the United Kingdom.

## 2.2 Objectives

1) To determine the existing evidence for long-term oral antibiotics used to treat acne being associated with a subsequent risk of antibiotic treatment failure, infection caused by a resistant organism or other evidence of AMR.

2) To establish the existing prescribing patterns of oral antibiotics prescribed for acne over time in UK primary care.

3) To investigate the association between long-term oral antibiotics for acne and subsequent antibiotic treatment failure when oral antibiotics are used to treat lower respiratory tract infections, skin and soft tissue infections or urinary tract infections.

## 2.3 Outline of thesis

My thesis will be presented in a research paper style format with my published manuscripts and manuscripts in draft presented in chapters. Four manuscripts have been written, three of which are published and one is in the final stages of preparation for submission to a journal. My thesis is organised into the following chapters:

Chapter 3 – a published systematic review protocol and published systematic review of the evidence of long-term oral antibiotics being positively associated with antibiotic treatment failure, infection with a resistant organism or other evidence of AMR.

Chapter 4 – an overview of the data sources I used for the original studies in my thesis.

Chapter 5 - a published drug utilisation study describing the prescriptions of long-term oral antibiotics in a population of people with acne in UK primary care over time.

Chapter 6 – a draft manuscript of my cohort study which investigated the association between long-term oral antibiotics for acne and antibiotic treatment failure.

Chapter 7 – A summary of my main results, an assessment of the biological plausibility of my results within the framework of the Bradford-Hill criteria, a description of my findings in the context of what is already known, a summary of the strengths and limitations of my study and the implications for future work, prescribing and public health policy and clinical practice.

## 2.4 Summary

- The future deaths from infections without intervention as a result of antimicrobial resistance (AMR) is estimated at ten million people per year worldwide.
- Acne is a common chronic inflammatory skin condition affecting 80-100% of adolescents and can persist into adulthood.
- Oral antibiotics are commonly prescribed for acne in general practice for a minimum duration of three months.
- Acne is not an infectious disease and its pathophysiology is multifactorial; antibiotics may work to reduce acne by exerting an anti-inflammatory effect.
- In the UK, primary care accounts for over 81% of antibiotic prescribing, and over 90% of acne is treated in primary care by GPs.
- The association between oral antibiotics for acne and AMR is unknown and there have been no rigorous systematic reviews which investigate an association in the literature.
- Without biological data, it is difficult to confirm AMR.
- The correct way to use antibiotics for acne and the management of acne to reduce short and long-term outcomes are two treatment uncertainties highlighted by people with acne, their carers and healthcare professionals as priorities for research.
- Lower respiratory tract infections, skin and soft tissue infections and urinary tract infections are three common infections treated by GPs in primary care.
- In order for antibiotic stewardship initiatives to be implemented, the burden of oral antibiotic prescribing for acne needs to be quantified in the UK and the association between oral antibiotics for acne and AMR needs to be further investigated.

# Chapter 3: Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review

## 3.1 Introduction

This chapter addresses objective one: to determine the existing evidence for long-term oral antibiotics used to treat acne being associated with a subsequent risk of antibiotic treatment failure, infection caused by a resistant organism or other evidence of AMR. When I was preparing for my fellowship application for funding for this PhD, I conducted a brief review of the literature to find the existing evidence of oral antibiotics for acne being associated with AMR. I found that there had been no literature search undertaken with a clearly outlined systematic search strategy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria that investigated the effects of oral antibiotics prescribed for acne and how these impact upon infection sequelae or AMR.(113) The results of this systematic review informed me of the further objectives in this thesis.

The chapter includes my two published papers (the systematic review protocol and the completed systematic review), an update to my search conducted in April 2023 and a summary of my findings.

I registered my systematic review protocol on the International Prospective Register of Systematic Reviews (PROSPERO) to document the methodology of study *a priori* and furthermore to ensure that there was no duplication of work with a similar protocol already registered.

## 3.2 Systematic review protocol – published paper

My systematic review protocol presented in the following section was published in a peer reviewed journal in 2020, The BMJ Open. My protocol details my search strategy, inclusion

criteria and planned method of data synthesis. The full search strategy is presented in the appendix for chapter three.

## 3.3 Research paper one

Ketaki Bhate, Liang-Yu Lin, John S Barbieri, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Liam Smeeth, Nick Francis, Rohini Mathur, Sinéad M Langan, Sarah-Jo Sinnott.

Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review protocol. *BMJ Open* 2020;10:e033662. doi: 10.1136/bmjopen-2019-033662

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1512948 | **Title** | Dr |
| **First Name(s)** | Ketaki | | |
| **Surname/Family Name** | Bhate | | |
| **Thesis Title** | Long-term antibiotics for acne and antimicrobial resistance | | |
| **Primary Supervisor** | Prof Sinéad Langan | | |

**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 Open | | |
| When was the work published? | July 2020 | | |
| 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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| Stage of publication | Choose an item. |

**SECTION D – Multi-authored work**

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|---|---|
| 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 of this paper. I wrote the protocol of this study and the manuscript. The manuscript was reviewed by all co-authors. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Ketaki Bhate |
| **Date** | 12.04.2023 |

| | |
|---|---|
| **Supervisor Signature** | Sinéad Langan |
| **Date** | 12.04.2023 |

BMJ Open

# Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review protocol

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## ABSTRACT

**Introduction** Antimicrobial resistance (AMR) is a global health emergency. Acne vulgaris is a highly prevalent condition and the dominant role antibiotics play in its treatment is a major concern. Antibiotics are widely used in the treatment of acne predominantly for their anti-inflammatory effect, hence their use in acne may not be optimal. Tetracyclines and macrolides are the two most common oral antibiotic classes prescribed, and their average use can extend from a few months to several years of intermittent or continuous use. The overall aim of this systematic review is to elucidate what is known about oral antibiotics for acne contributing to antibiotic treatment failure and AMR.

**Methods and analysis** A systematic review will be conducted to address the question: What is the existing evidence that long-term oral antibiotics used to treat acne in those over 8 years of age contribute towards antibiotic treatment failure or other outcomes suggestive of the impact of AMR? We will search the following databases: Embase, MEDLINE, the Cochrane Library and Web of Science. Search terms will be developed in collaboration with a librarian by identifying keywords from relevant articles and by undertaking pilot searches. Randomised controlled trials, cohort and case-controlled studies conducted in any healthcare setting and published in any language will be included. The searches will be re-run prior to final analyses to capture the recent literature. The Cochrane tool for bias assessment in randomised trials and ROBINS-I for the assessment of bias in non-randomised studies will be used to assess the risk of bias of included studies. GRADE will be used to make an overall assessment of the quality of evidence. A meta-analysis will be undertaken of the outcome measures if the individual studies are sufficiently homogeneous. If a meta-analysis is not possible, a qualitative assessment will be presented as a narrative review.

**Ethics and dissemination** Ethical approval is not required for this systematic-review. The results will be published in a peer-reviewed journal and any deviations from the protocol will be clearly documented in the published manuscript of the full systematic-review.

**PROSPERO registration number** CRD42019121738.

## Strengths and limitations of this study

- To our knowledge, this is the first comprehensive systematic review that will address the use of oral antibiotics for acne and their contribution to antimicrobial resistance.
- Screening, data extraction and quality assessment will be undertaken independently by three medically qualified researchers with training in systematic review methodology, thereby ensuring scientific rigour, transparency and repeatability.
- There are no date or language restrictions; however, this systematic review will not examine the grey literature.

## INTRODUCTION

The future effectiveness of antibiotics is in jeopardy with the WHO declaring the threat of antimicrobial resistance (AMR) as a most urgent crisis.[1] Future deaths from infections as a result of AMR without any intervention is estimated at 10 million per year and by 2050 the cost of AMR could reach 100 trillion US Dollars.[2]

Topical and oral antibiotics are commonly prescribed for the treatment of acne vulgaris, a chronic skin disorder with onset predominantly in adolescence. Given the psychosocial consequences and the potential for permanent disfigurement with scarring, it is imperative that people with acne receive effective treatment.[3 4] Prevalence studies show that 80% to 100% of teenagers have acne and that 20% are moderately-to-severely affected. The high prevalence means that both topical and oral antibiotics are used in a large proportion of the adolescent population and for variable durations ranging from 6 weeks to many months, and in some cases, several years.[5 6] Differences between international guidelines regarding duration of treatment is one of the

reasons that antibiotics for acne are used for significantly longer than recommended as there is uncertainty about the optimal duration of treatment.[6–11] Tetracyclines and macrolides are the two of the most common oral antibiotic classes prescribed for acne with varying durations of average use depending on treatment setting and between different countries.[6 12]

The overuse of antibiotics is a known cause of AMR as repeated and sustained exposure allows microbes to develop mechanisms to avoid the effects of the drugs designed to treat them and allows selection in favour of bystander or commensal bacteria with resistance subsequently causing invasive infection. Acne is aetiologically multifactorial and we already know that some strains of *Cutibacterium acnes* (formally *Propionibacterium acnes*), the bacteria pathophysiologically associated with acne, are now resistant to commonly used antibiotics in acne, making their initial use as anti-microbial agents futile.[13 14] However, we do not know how these long-term antibiotics for acne may attenuate microbiota elsewhere at other body sites and the ability of other bacteria at other infective sites to withstand the effect of antibiotics. Despite this, the anti-inflammatory effect and proven efficacy of antibiotics in treating acne ensures their continued use,[15] although their effects may not be sustained. Considering the relationship between long-term exposure to antibiotics and AMR, this practice may not be optimal.

The effects long-term antibiotics for acne have on future infections caused by resistant organisms, subsequent antibiotic treatment failure or the rate of infections (or any other measures which may indicate antimicrobial resistance) and how long any effect may last, is not yet known and has not been systematically reviewed in the literature before. While antibiotic stewardship programmes have been shown to be effective[16] in other settings, to ensure their successful execution, robust evidence must be generated to show that using antibiotics in the treatment of acne has important implications for future infective episodes and resistance sequelae. Until there is evidence of how the use of oral antibiotics for acne may cause AMR, changing current practice will be challenging.[17]

Given the global health emergency of AMR and the dominant role antibiotics play in the treatment of acne—a highly prevalent and ubiquitous skin condition worldwide, there is a clearly defined evidence gap which needs to be urgently addressed.[18] This systematic review aims to establish what is already known about resistance sequelae for those with acne who are treated with long-term topical or oral antibiotics.[19]

## METHODS AND ANALYSIS

### Literature search strategy

We will search the following databases; Embase, MEDLINE, the Cochrane Library and Web of Science. We will develop the search terms by identifying keywords from relevant articles and by undertaking pilot searches to identify index or MedicalSubject Heading (MeSH) terms. We will modify the search terms according to each database, for example, the MeSH terms in MEDLINE and Emtree terms in Embase. Searches will be undertaken by the lead author who has medical and search training in collaboration with a librarian. Search strategies will be reviewed by all authors. The searches will be kept as broad as possible, for example, by using the 'explode' function on the Ovid platform to maximise the number of relevant articles. The search strategy is available to view in the accompanying supplement (online supplementary file 1). Searches were undertaken on the 19th of July 2019 and date back to inception of the databases.

### Eligibility criteria

#### Inclusion criteria

To address the question, the following inclusion criteria will apply:

- A study population including participants aged over the age of 8 in any healthcare setting with acne vulgaris.
- Original studies will be eligible for assessment for inclusion if they address the specific research question.
- Randomised controlled trials (of any trial design).
- Observational studies limited to cohort and case-control studies.
- We will include conference abstracts if the full paper is unpublished and can be obtained from the authors.

#### Exclusion criteria

- Ecological studies and studies that do not assess temporality such as case-series and case reports.
- We will exclude unpublished studies, ongoing studies and the grey literature.
- In addition, studies which only look at antimicrobial resistance in *Propionibacterium acnes* or *Cutibacterium acnes*.
- Studies including people who are under the age of 8 exclusively will be excluded. The age of 8 was chosen as acne vulgaris is unlikely to present in younger children and in addition, tetracyclines are not recommended in younger children—the British National Formulary recommends tetracyclines are given to children aged 12 years and above.
- Studies including people who are treated with antibiotics for other acne subtypes, for example, hidradenitis suppurativa or drug-induced acne.

### Exposure

At least 28 days of continuous (daily doses) oral antibiotics for acne vulgaris, the duration helping to ensure treatment is not targeted at an acute infective episode and, in addition, 28 days is the minimum duration a prescription will be issued for an antibiotic treatment of acne. The exposure is likely to include commonly used antibiotic classes—tetracyclines, macrolides and dihydrofolate reductase inhibitors, however there will be no limits placed on the antibiotic class used to treat acne. We have excluded the use of topical antibiotics are these are

less likely to have an effect at sites other than the skin to where they are applied.

### Comparator

No exposure to long-term oral antibiotics within an acne population or within a general population.

### Outcome

The primary outcome is antibiotic treatment failure or any infection caused by a resistant organism. The secondary outcome is the detection of resistant organisms without a clinical infection, rate of infection or changes to the microbiota profile, for example, with the colonisation of resistant microbiota without a clinical infection or different microbiota in a sampled site compared with baseline prior to having received a long-term antibiotic for acne. Any measure (including proxy measures) will be included, for example, laboratory measures (such as an elevated C-reactive protein or positive culture in the case of an infection at any body site), patient observations (such as an elevated temperature and/or pulse rate which may indicate an infective process) or proxy measures that may have been used in epidemiological studies, for example, difficult to treat infections which may indicate a resistant infection. Each outcome will be assessed separately. The outcome can occur at any time point after at least 28 days of continuous oral antibiotic exposure for acne; we will stratify according to the length of follow-up, for example, up to 6 months, 6 months to 1 year, 1 year to 2 years, and so on.

### Potential confounding variables/effect modifiers

Confounding factors that may be considered by studies investigating treatment failure or AMR as a result of long-term antibiotics for acne are: age, sex, socioeconomic status, treatment adherence, medical conditions such as primary immunodeficiency, diabetes, asthma, cancer requiring immunosuppressive medication, recent hospitalisation within the last 6 months, repeated admissions to hospital, any recurrent infections, other prescribed medication in particular immunosuppressive therapy including oral corticosteroids, smoking, alcohol use and ethnicity. We will also explore effect modification. The inclusion of these confounding factors will be acknowledged in the bias assessment of each study along with a statement of the direction and magnitude of bias their omission may be associated with.

### Eligibility assessment and data extraction

#### Phase 1

Covidence, an online literature review data management programme, will be used to facilitate the systematic review process inclusive of title and abstract screening, full paper retrieval and storage and decisions on which papers to include at full text review. In the first phase, all titles and abstracts will be uploaded to Covidence. Duplicates will then be removed by the lead reviewer (KB). Three reviewers (KB, L-YL and JB) will then independently screen the search results based on title and abstract. Each title/abstract will require two votes. Consensus will be achieved on the number of titles and abstracts to include in the full study review. Any disputes will be resolved by the involvement of a fourth reviewer (SML).

#### Phase 2

Full text papers will be assessed independently by the reviewer pairs using a standardised data extraction form. The extraction tool will be piloted using the first three included records, after which modifications may be made following discussion with other members of the review team. The quality of the studies will be scored using assessment tools and free text explanations for the score given will be included on the score sheet. Any disagreements will be discussed by the three reviewers (KB, L-YL and JB) and in instances of disagreement, a fourth reviewer (SML) will make a final decision. If ambiguity still remains after the full text is obtained, the study authors will be contacted for further clarification.

#### Data items

Three data domains will be extracted:

#### Data relating to study design

Author, country, specific study design, the year the study was conducted or the years over which the data were collected. Healthcare setting, the number of study participants, the ages of the participants and the gender balance will be collected for the whole population under study, including the comparator group. If the study is a trial, then specifics of the study design such as randomisation, allocation concealment and blinding will be noted.

#### Data relating to exposure

The dose, frequency and antibiotic used, the median/mean length of treatment of acne with the antibiotic, the definition of long-term treatment with antibiotics used in the study, the number of participants exposed to antibiotics and if multiple courses are prescribed, the length of time between antibiotic courses and the intervention applied to comparators.

#### Data relating to outcomes

The measure of antibiotic treatment failure or AMR and the degree of antibiotic treatment failure or AMR, for example, repeat course required, hospitalisation or death. The length of follow-up will be stratified.

### Study quality assessment

Each study will be critically appraised by reviewers. The Cochrane tool for bias assessment in randomised studies and the ROBINS-I tool for the assessment of bias in non-randomised studies will be used to assess the risk of bias in included studies.[20–22] GRADE (Grading of Recommendations Assessment, Development and Evaluation) will be used to make an overall assessment of the quality of evidence.[22] Pairs of reviewers will make independent assessments of the risk of bias. Markers of bias depending on study design included in the aforementioned scoring

tools will include factors such as the method of participant selection, follow-up, randomisation, adjustment for confounding and measurement error of exposures or outcomes. If a proportion of studies have a high risk of bias found using the scoring tool we will do a sensitivity analysis excluding them.

### Data synthesis/statistical analysis

We will analyse interventional and observational studies separately. If there is homogeneity across studies and a meta-analysis is possible, we will generate a pooled effect estimate for those exposed to long-term antibiotics and those unexposed within each category of study design. If there are a sufficient number of studies, subgroup analyses will be undertaken, for example, by class of antibiotic and antibiotic treatment duration. The $I^2$ statistic will be used to assess heterogeneity.[23] Sources of heterogeneity may include methodology, age of participants, study duration, the confounding factors considered, the exposure (ie, length/duration, the class of antibiotic), the comparators and the outcomes measured. If heterogeneity is above 50% we will not undertake a meta-analysis. If studies are sufficiently homogeneous with regard to exposures, comparators and outcomes, a random effects model will be used to generate a pooled relative risk and its 95% CI. Study characteristics and the effect estimate for the association between antibiotics for acne and the specific measure of AMR will be clearly presented. We will also do a sensitivity analysis using a fixed effects model. Publication bias will be assessed using Funnel plots and Egger tests.[24] Forest plots will be presented. All statistical analyses will be performed using Stata. If quantitative synthesis is not possible due to heterogeneity, we will conduct a narrative synthesis. We will also study each category of outcome measure separately: for example, laboratory-based measures of resistance or outcome measures thought to be proxies for AMR using routinely collected health records. Given the breadth of outlined outcomes, it is likely that the evidence obtained will be diverse. An overall description of the strength of the body of evidence generated using GRADE will be described.[21]

The study will be reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.[19]

### Patient and public involvement

This systematic review has been informed by the results of the Acne Priority Setting Partnership (PSP) (acnepsp.org) in collaboration with the James Lind Alliance (www.jla.nihr.ac.uk). Over 6000 responses were collated and voted on to give a top 10 list of treatment uncertainties. Two of these top 10 uncertainties will be addressed with this systematic review:

1. What is the correct way to use antibiotics in acne to achieve the best outcomes with the least risk?
2. What management strategy should be adopted for the treatment of acne in order to optimise short-term and long-term outcomes?

In addition, five people comprising members of the public and patients with acne or their carers will attend a focus group to help write the summary which will be used to disseminate the results of this systematic review to the public.

### Ethics and dissemination

As this is a systematic review, ethical approval was not required. This systematic review protocol was registered on the 8th of April 2019 on the International Prospective Register of Systematic Reviews (PROSPERO). Any amendments to the protocol will be updated and published on the PROSPERO website with clear notes of where specific changes were made with detailed explanations of why. The results of this systematic review will be submitted for peer-review publication.

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**Contributors** KB wrote the protocol and led the study. S-JS, SML and RM supervised the writing process and contributed equally. L-YL and JB contributed to the screening and review process. CL, RS, LS, SH, NAF and LS form an advisory group and reviewed the protocol.

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## 3.4 Systematic review – published paper

The systematic review was published in a peer-reviewed journal in 2021 - The British Journal of General Practice. The supplementary tables are presented in the appendix for chapter three (**Appendix 1**).

## 3.5 Research paper two

Ketaki Bhate, Liang-Yu Lin, John S Barbieri, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Liam Smeeth, Nick Francis, Rohini Mathur, Sinéad M Langan, Sarah-Jo Sinnott.

Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review. BJGP Open 9 March 2021; BJGPO.2020,0181 DOI: 10.3399/BJGPO.2020.0181

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| **Student ID Number** | 1512948 | **Title** | Dr |
| **First Name(s)** | Ketaki | | |
| **Surname/Family Name** | Bhate | | |
| **Thesis Title** | Long-term antibiotics for acne and antimicrobial resistance | | |
| **Primary Supervisor** | Prof Sinéad Langan | | |

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

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| **Date** | 12.04.2023 |

| | |
|---|---|
| **Supervisor Signature** | Sinéad Langan |
| **Date** | 12.04.2023 |

BJGP Open

RESEARCH

# Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review

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## Abstract

**Background:** Antimicrobial resistance (AMR) is a global health priority. Acne vulgaris is a common skin condition for which antibiotic use ranges from a few months to years of daily exposure.

**Aim:** To systemically search for and synthesise evidence on the risk of treatment-resistant infections, and other evidence of AMR, following long-term oral antibiotic use for acne.

**Design & setting:** In this systematic review, a literature search was carried out using the databases Embase, MEDLINE, Cochrane, and Web of Science. They were searched using MeSH, Emtree, or other relevant terms, and followed a pre-registered protocol.

**Method:** Search strategies were developed with a librarian and undertaken in July 2019. All searches date from database inception. The primary outcome was antibiotic treatment failure or infection caused by a resistant organism. Secondary outcomes included detection of resistant organisms without an infection, rate of infection, or changes to flora.

**Results:** A total of 6996 records were identified. Seventy-three full-text articles were shortlisted for full review, of which five were included. Two investigated rates of infection, and three resistance or changes to microbial flora. Three studies had 35 or fewer participants (range 20–118 496). Three studies had a serious or high risk of bias, one moderate, and one a low risk of bias. Weak evidence was found for an association between antibiotic use for acne and subsequent increased rates of upper respiratory tract infections and pharyngitis.

**Conclusion:** There is a lack of high quality evidence on the relationship between oral antibiotics for acne treatment and subsequent AMR sequelae. This needs to be urgently addressed with rigorously conducted studies.

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**Competing interest:** See page 8

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**Author Keywords:** acne vulgaris, antibiotic, antimicrobial resistance, tetracycline, macrolides, dihydrofolate reductase inhibitor


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## How this fits in

AMR is a global threat and the prolonged use of antibiotics in the treatment of skin conditions may contribute to this burden. Long-term oral antibiotics are frequently used to treat acne in relatively well, young adult populations. This review has highlighted the dearth of high quality studies on the implications of long-term oral antibiotic use on infectious or AMR sequelae. It is not understood how the long-term use of oral antibiotics for acne affects the subsequent rate of infections, changes to microbiota, or AMR. This systematic review has highlighted an urgent need for rigorous, well-conducted studies investigating the relationship between long-term antibiotics for acne and AMR.

## Introduction

The World Health Organization has declared the threat of AMR a most urgent crisis.[1] Currently, approximately 700 000 people die per year as a result of AMR and a report predicted that there will be 50 million deaths per year as a result of AMR by 2050, with a total cumulative cost to lost global production of 100 trillion USD.[2] Acne vulgaris is a chronic, inflammatory skin disorder, predominantly of adolescence. It affects 80–100% of adolescents, and 20% have moderate to severe acne.[3] Topical and oral antibiotics are commonly prescribed in the treatment of acne. Although there is conflicting information in international acne guidelines, they generally recommend treatment with an oral or topical antibiotic for 3–6 months.[4–9] Tetracyclines and macrolides are the two most common oral antibiotic classes prescribed for people with acne in UK primary care.[4]

The overuse of antibiotics is a cause of AMR. Exposures to antibiotics selects for bacteria with spontaneous or acquired mechanisms of resistance. In turn, commensal bacteria also develop and acquire mechanisms to resist the effects of antibiotics, which may give rise to invasive infection. While it is understood that acne is not an infectious disease and the pathophysiology of acne is multifactorial, with *Cutibacterium acnes* implied in one step in the development of an acne lesion, several studies have shown topical antibiotics for acne leads to resistant *C. acnes*.[10–14] Less is known about whether antibiotic treatment for acne impacts on bacterial flora at other sites. Despite this, oral antibiotics are considered to have anti-inflammatory effects, and their short-term efficacy ensures continued use, alongside other treatments used for acne such as isotretinoin.[15,16] Given the potential relationship between exposure to antibiotics and AMR, this practice may not be sustainable.[17]

Antimicrobial stewardship, a framework employed to ensure the judicious use of antibiotics, is effective for other infections in other settings;[18] however, to ensure its implementation in acne treatment, evidence is needed to show that using antibiotics for acne increases future infective episodes and resistance sequelae. Until this evidence is obtained, there will be little impetus to change clinical practice.[19]

The question of whether antibiotics for acne contribute towards AMR is an evidence gap that needs to be urgently addressed.[20] This study aims to address this gap by systematically reviewing published evidence on the association between long-term use of oral antibiotics for acne and subsequent risk of antibiotic treatment failure, infection caused by a resistant organism, or other evidence of AMR.

## Method

The review protocol was registered on PROSPERO on 8 of April 2019 before the literature search ( www.crd.york.ac.uk/PROSPERO) and is published in *BMJ Open*.[21] PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and RECORD (Reporting of studies Conducted Using Observational Routinely collected Data) guidance was followed.[22]

### Literature search strategy

The databases Embase, MEDLINE, Cochrane, and Web of Science were searched. Search terms were developed by finding keywords from relevant articles and by running pilot searches. Searches were developed alongside a librarian to ensure completeness. To keep the searches as broad as possible the 'explode' function on Ovid was used. The search strategy was reviewed by all authors. The final searches were undertaken by the lead author who has medical and search training. Searches were undertaken in July 2019 from inception of the databases.

## Inclusion and exclusion criteria

The review included randomised controlled trials, and both cohort and case–control observational studies. Conference abstracts were included if the full article was unpublished but the full manuscript could be obtained from the authors. Studies were included if they met the above criteria in addition to the following criteria:

- The study population included participants aged ≥8 years with acne, in any healthcare setting.
- The study investigated oral antibiotics prescribed for acne, for a minimum of 28 days of daily dosing.
- The comparison group included people who have not been treated with oral antibiotics for acne (or the general population).
- Studies where outcomes met the primary outcome of antibiotic treatment failure or infection caused by a resistant organism, or the secondary outcome of the detection of resistant organisms without an infection, rate of infection, or changes to bacterial flora. Any measure including proxy measures were used.

Ecological studies and studies that did not assess temporality or looked at specific subtypes of acne (for example, acne fulminans) were excluded. Unpublished, ongoing, and studies in grey literature were excluded. Studies that only looked at AMR of *C. acnes* or those including people aged <8 years were excluded, as acne vulgaris is unlikely to present in children aged <8 years and tetracyclines are not recommended in younger children.

## Exposure and comparator

The exposure was at least 28 days of continuous daily doses of antibiotics for acne. This duration was chosen as 28 days is the usual minimum duration of therapy for acne and it was more likely to distinguish between people receiving antibiotics for acne and those receiving short-course antibiotics for an acute infection. Topical antibiotics were excluded as these are less likely to have an effect at sites other than the skin where they are applied. The comparator group included people with acne who were not treated with oral antibiotics or the general population.

## Outcome

The primary outcome was antibiotic treatment failure (insufficient clinical improvement following treatment of an infection with an antibiotic), or any infection caused by a resistant organism. The secondary outcome was the detection of resistant organisms without a clinical infection, rate of infection, or changes to flora. This included: any measure of AMR, for example, laboratory measures (such as a raised C-reactive protein [an inflammatory marker, which if raised may support the diagnosis of a persistent infection despite prior treatment with an antibiotic or it can be used to monitor antibiotic treatment response to infection] or positive culture in the case of a subsequent resistant infection at any body site); patient observations (such as an elevated temperature and/or pulse rate [which may indicate an infection and could represent antibiotic treatment failure if persistent after treatment with an antibiotic]); or proxy measures that may have been used in epidemiological studies, for example, difficult-to-treat infections. Antibiotic treatment failure is a proxy for AMR. The outcome could occur at any time point after at least 28 days of continuous oral antibiotic exposure for acne. Outcome measures were developed a priori.

## Eligibility assessment and data extraction

Covidence, an online literature review data management programme, was used to facilitate the systematic review process.[23] All titles and abstracts were uploaded to Covidence. Duplicates were removed and three reviewers — KB, LYL, and JB — independently screened the search results based on title and abstract. Each title and/or abstract needed two votes to undergo full-text review. Conflicts were resolved by the involvement of a fourth reviewer not involved in the screening process, SML.

Full-text articles were assessed independently by the same reviewers. The extraction of the first included record was piloted by all reviewers and discrepancies were discussed. The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the risk of bias in randomised studies and Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias in non-randomised studies.[24,25] Grading of Recommendations, Assessment, Development and Evaluations

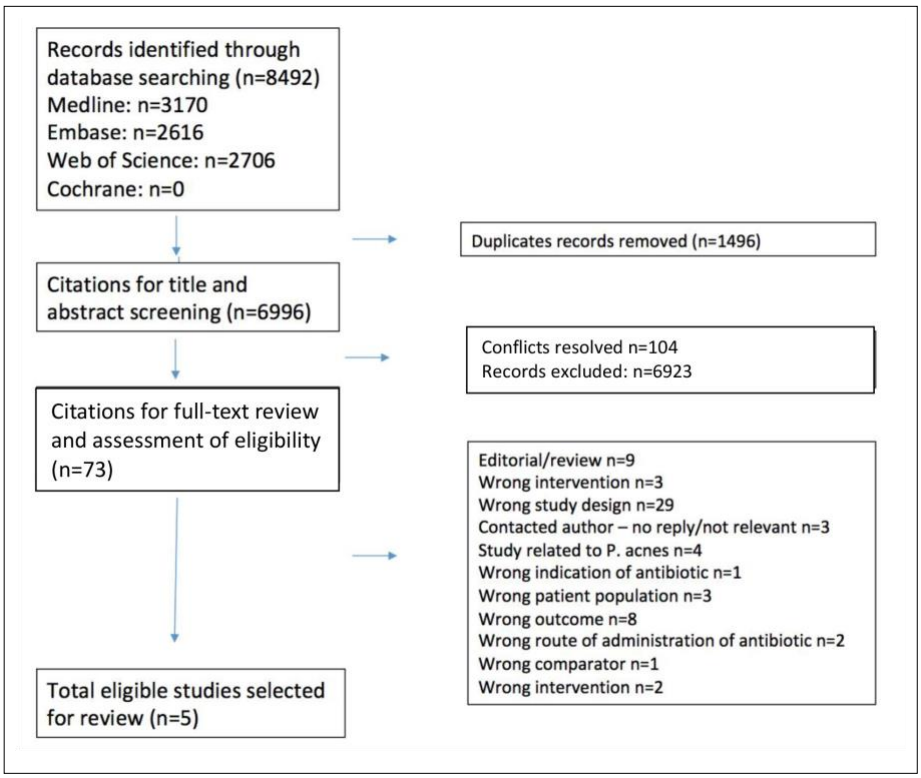


Figure 1 Flow diagram of study selection

(GRADE) was used to make an overall assessment of the quality of evidence. [26] Pairs of reviewers made independent assessments of the risk of bias.

## Results

A total of 6996 records were identified for title and abstract screening after de-duplication (*Figure 1*). Of these, 73 full-text articles were shortlisted for full-text review. The full-text of one study could not be obtained despite contacting library repositories in both the UK and US as well as contacting authors; this study was therefore excluded. Overall, five studies were included in the systematic review.[27–31] The reasons the full-text articles were excluded are in Supplemetary Appendix A. The characteristics of the included studies are summarised in supplementary Table 1, and study results, risk of bias, and overall GRADE assessment are summarised in supplementary Table 2 and *Tables 1–3*.

### Study characteristics

None of the five included studies measured the primary outcomes; three studies investigated the carriage or AMR bacteria using bacterial culture methods, and two studies investigated the rate of infection following antibiotics for acne. Only one study was a randomised controlled trial;[30] the remaining four were all cohort studies, two of which were undertaken involving patients solely in the UK, and one of those used routinely collected medical records from UK general practice. All studies were from high or upper-middle income countries (three studies from the UK, one from Sweden, and

**Table 1** Risk of bias summary showing judgments about each risk of bias domain in ROBINS-I and overall bias assessment across all domains

| | Domain 1: Bias owing to confounding | | | Domain 2: Bias in selection of participants into the study | | | Domain 3: Bias in classification of interventions | | | Domain 4 ITT: Bias owing to deviations from intended interventions: effects of assignment to intervention | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First author, publication year** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** |
| Margolis 2005[27] | | Low | Low | | Low | Low | | Low | Low | | NI | NI |
| Margolis 2012[28] | | Low | Low | | Moderate | Moderate | | Low | Low | | NI | NI |
| Basak 2013[29] | Critical | Critical | | Moderate | Moderate | | Low | Low | | NI | NI | |
| Adams 1985[31] | Critical | Critical | | NI | NI | | Low | Low | | NI | NI | |

| **Domain 4: Bias owing to deviations from intended interventions: effect of starting and adhering to intervention** | | | **Domain 5: Bias owing to missing data** | | | **Domain 6: Bias in measurement of outcomes** | | | **Domain 7: Bias in selection of the reported result** | | | **Overall bias assessment across all domains** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** | **LYL** | **JB** | **KB** |
| | NI | NI | | Low | Low | | Low | Low | | Low | Low | | Low | Low |
| | NI | NI | | Moderate | Moderate | | Serious | Serious | | Low | Low | | Moderate | Moderate |
| NI | NI | | Low | Low | | Low | Low | | Serious | Serious | | Serious | Serious | |
| NI | NI | | NI | NI | | Moderate | Moderate | | Moderate | Moderate | | Serious | Serious | |

Authors: LYL, JB, KB. ITT = intention-to-treat. NI = no information. ROBINS-I = Risk of Bias in Non-randomised Studies - of Interventions.

**Table 2** The Risk of Bias 2 (RoB 2) assessment for randomised controlled trial[30]

| Borglund *et al*[30] RoB 2 | LYL | KB |
|---|---|---|
| Domain 1 Randomisation process | High | High |
| Domain 2 Deviations from intended interventions | High | High |
| Domain 3 Missing outcome data | Low | Low |
| Domain 4 Measurement of the outcome | Some concerns | Some concerns |
| Domain 5 Selection of the reported results | Some concerns | Some concerns |
| Overall risk of bias | High | High |

Authors: LYL, KB.

one from Turkey). Study sizes ranged from 20–118 496 participants, and three studies had 35 or fewer included individuals. The mean age of study participants ranged from 17.6–21.7 years (age range 15–38 years).

Given the heterogeneity of included studies, particularly with regard to outcomes, it was not possible to perform a meta-analysis. Therefore, the results of this systematic review are reported narratively.

Borglund *et al*[30] investigated changes in the quantity and resistance patterns of skin and intestinal flora in a randomised controlled trial comparing topical clindamycin 1% along with a tablet placebo, and tetracycline 250 mg twice a day orally along with a topical placebo.[30] The authors reported pronounced reductions in the numbers of streptococci, enterococci, fusobacteria, and enterobacteria in the colon during the treatment period with oral tetracycline and, in particular, new colonisation with tetracycline-resistant strains was noted. The flora normalised to pre-treatment levels 8 weeks

**Table 3** Summary of findings (GRADE assessment of quality of evidence)

| Summary of findings | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Number of patients** | **Quality** |
| **Rate of infection** | | | | | | | | |
| 2 | Cohort | Not serious | Not serious | Not Serious | Serious | No: publication bias, large effect, plausible confounding, dose response gradient | Intervention total: 79 807, Control total: 33 792 | ⊕⊕ LOW a,b |
| **Detection of resistant organisms without an infection or changes to flora or microbiota** | | | | | | | | |
| 3 | 1 RCT and 2 cohort studies | Serious | Not serious | Not serious | Serious | No: publication bias, large effect, plausible confounding, dose response gradient | Intervention total: 36, Control total: 45 | ⊕ VERY LOW c,d,e,f,d,g |
| **Explanations** | | | | | | | | |
| a. Selection bias: students selected from one university campus. | | | | | | | | |
| b. Imprecise estimates: wide 95% confidence intervals. | | | | | | | | |
| c. Selection bias: patients not randomised to treatment. | | | | | | | | |
| d. Confounding factors not reported or incorporated in analysis. | | | | | | | | |
| e. Follow-up inconsistent between treatment groups. | | | | | | | | |
| f. Confidence intervals not reported and small sample size. | | | | | | | | |
| g. No 95% confidence intervals reported: predominantly numbers and percentages reported. | | | | | | | | |

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomised controlled trial.

after treatment was stopped. Resistance to tetracycline during treatment was seen in 40% of the staphylococcal and enterococcal isolates from the skin.

Two of the studies Margolis *et al* 2005[27] and Margolis *et al* 2012[28] investigated the rate of infections following the use of antibiotics for acne. The first used routinely collected electronic health records from the UK (Clinical Practice Research Datalink, formerly General Practice Research Datalink) (*n* = 118 496) to evaluate the association between oral antibiotics prescribed for acne and subsequent upper respiratory tract infections (URTI) and urinary tract infections (UTI).[27] The authors identified statistically significant associations between being prescribed a long-term oral antibiotic for acne (*n* = 197) and having a subsequent consultation coded for a URTI (odds ratio [OR] = 2.75 (95% confidence interval [CI] = 2.37 to 3.18) or UTI (in women; OR = 1.87 [95% CI = 1.38 to 2.53]; information received via communication with authors [numbers of UTI in men too small for analysis]). The number of individuals with a UTI diagnosis who had received an oral antibiotic for their acne was not reported.

The second study by Margolis *et al* was a cohort study in 2012 (*n* = 579), which investigated the risk of developing pharyngitis in students with acne receiving antibiotic treatment who were based on one university campus in North America.[28] Thirty-six (6.2%) individuals took an oral antibiotic for their acne. Four out of 36 (11.3%) of those taking an antibiotic for acne reported an episode of pharyngitis compared with 18 out of 543 (3.3%) of those not taking an antibiotic for their acne. The OR associating oral antibiotic use with pharyngitis was 4.34 (95% CI = 1.51 to 12.47) using mixed model multivariable regression.

The final two studies investigated changing resistance patterns among flora following exposure to oral antibiotics for acne. Adams *et al* studied the changing pattern of bowel flora resistance in 26 individuals comprising patients with acne receiving oral erythromycin (*n* = 6) and tetracycline (*n* = 5) and family members living in the same household as the patient with acne.[31] Patients who had received tetracycline for acne and their relatives developed greater numbers of tetracycline *Escherichia coli* resistant isolates. Conversely, the numbers of erythromycin-resistant *E. coli* isolates decreased in acne patients receiving an antibiotic for acne but increased in their relatives.

The other study aimed to investigate changes in the microbial flora of the nose, oropharynx, and faeces following use of systemic isotretinoin (*n* = 20) and oral antibiotic therapy (*n* = 15).[29] The authors described it as a randomised controlled trial, however, patients were placed into treatment groups based on acne severity with no description of any random element to treatment allocation. The methods stated that logistic regression was used in analyses, however, no odds ratios were presented. The study reported that antibiotics caused less differentiation (which authors defined as the isolation of *Salmonella* spp., *Shigella* spp., *Pseudomonas aeruingosa* and extended-spectrum beta-lactamase [ESBL] gram negative bacilli) of microbial flora compared with isotretinoin at all the cultured sites.

## Discussion

### Summary

This systematic review found five studies that met the inclusion criteria. All studies investigated secondary outcomes: the detection of resistant organisms without an infection or the rate of infection. No studies in the review addressed the primary outcome of antibiotic treatment failure or infection caused by a resistant organism. Overall, across all outcomes, low or very low quality of evidence was found supporting long-term oral antibiotics for acne being associated with infectious outcomes or AMR (***Table 3***).

The mechanisms for how *C. acnes* (the bacterium pathophysiologically implicated in the formation of an acne lesion) becomes resistant to topical antibiotics used to treat acne are well described, but oral antibiotic treatments for acne are distributed throughout the body, and the impact of their use on the spread of AMR and risk of treatment-resistant infections is not fully understood.[32,33] There are reviews aiming to summarise the evidence of AMR secondary to antibiotics for acne; however, this is the first systematic review to the authors' knowledge that aims to address infectious outcomes and resistance of flora other than *C. acnes* as a result of oral antibiotics for acne.

### Strengths and limitations

Strengths of the systematic review included: following a pre-specified protocol published on PROSPERO and *BMJ Open;* designing and reporting the review following PRISMA guidance;

undertaking a comprehensive search developed in collaboration with a librarian; having no language or time limits; and completing a full bias risk assessment and reporting the overall quality of evidence using GRADE. In addition, the screening process was undertaken by medical healthcare professionals with epidemiological training.[22] Limitations included not searching the grey literature, and the lack of studies from developing countries where antibiotics may be used for acne and may be bought over the counter.

## Implications for research and practice

This review has highlighted the dearth of high quality scientific research on the implications of long-term oral antibiotic use for acne on infectious or AMR sequelae. The impact that use of oral antibiotics for acne has on microbial resistance in commensal organisms and difficult-to-treat infections caused by organisms resistant to common antibiotics remains unclear. The degree to which cross-resistance to antibiotic classes other than the one prescribed for acne is also unclear.[34,35] Given the predicted impact of AMR on death rates — in the order of one death every 3 seconds by 2050 — and the widespread use of long-term oral antibiotics for acne in a relatively healthy, young population,[2] it is imperative to understand how these antibiotics may contribute to the burden of AMR with high quality prospective studies, so that practice can be modified if needed.

### Funding

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### Ethical approval

No ethical approval was required for this systematic review.

### Registration number

The review protocol was registered on PROSPERO on 8 April 2019 prior to literature search, (CRD42019121738 – www.crd.york.ac.uk/PROSPERO)

### Provenance

Freely submitted; externally peer reviewed.

### Competing interests

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## 3.6 Update to systematic review – April 2023

The searches of my systematic review included studies published up until July 2019. I therefore updated my search to find more recent studies. I repeated searches on the 6th of April 2023. A total of 1,054 articles were highlighted for title and abstract screening and of those, seven were shortlisted for full text review. Of the seven shortlisted studies, five were review articles (114-118), one was a letter to the editor commenting on another laboratory based study about the use of the antibiotic azithromycin for acne (119), and one was a study investigating *Cutibacterium acnes*.(120) None of the studies met my inclusion criteria for the systematic review.

## 3.7 Summary

- My systematic review aimed to review published evidence on the association between the long-term use of oral antibiotics for acne and the subsequent risk of antibiotic treatment failure, infection caused by a resistant organism or other evidence of AMR.
- I searched Embase, Medline, Cochrane and Web of science using a search strategy developed alongside a librarian.
- I identified a total of 6996 articles for title and abstract screening and 73 were shortlisted for full text review. Five studies met inclusion and exclusion criteria.
- None of the five included studies addressed the primary outcome of antibiotic treatment failure or infection caused by a resistant organism. All studies investigated secondary outcomes: the detection of resistant organisms without an infection or the rate of infection.
- Three studies investigated the carriage of resistant bacteria or resistant bacteria using bacterial culture methods; two studies investigated the rate of infection following antibiotics for acne.
- One study was a randomised controlled trial and four were cohort studies.
- Due to heterogeneity of the included studies, it was not possible to undertake a meta-analysis; the results were therefore reported narratively.
- Overall using Grading of Recommendations Assessment Development and Evaluation (GRADE)(121), the studies investigating the carriage of resistant bacteria or resistant bacteria using bacterial cultures methods were evaluated as very low and the quality of evidence for studies investigating the rate of infection following oral antibiotics for acne were evaluated as low.
- The systematic review highlighted the dearth of studies investigating the relationship between long-term oral antibiotics for acne and antimicrobial resistance.

## 3.8 Motivation for thesis

The results of my systematic review have shown that it is clear that there is little published evidence of consequences of using oral antibiotics for acne on AMR. Given the widespread use of oral antibiotics for acne and the threat of AMR on the effectiveness on antibiotics, it is important to quantify the risk imposed. In the following chapters, I aim to investigate the use of oral antibiotics for acne and quantify how they may contribute to AMR.

# Chapter 4: Data sources

## 4.1 Introduction

In this chapter, I outline the data sources I used for research questions two and three and summarise my contribution in acquiring the data, cleaning, and preparing the dataset for analyses.

For research questions two and three, I used datasets from the Clinical Practice Research Datalink GOLD (CPRD GOLD) hereafter referred to as the CPRD and additional linked datasets for Index of Multiple Deprivation (IMD). The CPRD is a large source of routinely collected primary health care data from General Practices in England, Scotland, Wales and Northern Ireland and IMD provides information on relative deprivation.

## 4.2 Clinical Practice Research Datalink

The CPRD is a primary care database containing de-identified data from over 914 General Practices in the UK. The CPRD is a UK government research programme and is supported by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute of Health Research (NIHR).(122) The CPRD has been collecting, processing and releasing de-identified health data from primary care patient encounters since 1987.(123) Until 1993, the CPRD was called the small Value Added Medical Products dataset, and thereafter until 2012, the General Practice Research Database.(124) The CPRD has contributed to over 3,000 peer reviewed publications as of March 2023 and has therefore strengthened the epidemiological evidence base and clinical practice across most medical specialties.(125)

The National Health Service (NHS) is the only healthcare system in the UK which is free at the point of access. The NHS is a closed system, where all health encounters are provided through one service provider. Outside of emergencies, General Practitioners (GPs) act as gatekeepers where they are the first point of contact for patient care and can make referrals, if necessary, to secondary specialist care or community services. Over 98% of people are registered with a GP, and this therefore ensures that nearly all primary care encounters of individuals living in the UK who are registered with a general practice which

contributes to the CPRD are captured. (126) The missing two percent may comprise people who opt to seek healthcare though private providers or healthy people who stay in UK for shorter periods and don't register with a GP, e.g. students who study in the UK whose usual residence is elsewhere. Data from people not registered with a GP and who seek healthcare elsewhere are not captured by the CPRD.

The CPRD GOLD comprises data collected from the software system InPS Vision (Vision). There are four predominant software systems used by GPs in the UK (TPP SystmOne, EMIS Web and Microtest Evolution are the other three). The number of practices using Vision as their recording software has decreased in the previous few years with several GP practices moving to EMIS Web or TPP SystmOne. As of 2016, approximately 9% of GP practices in England used Vision.(127) **Figure 4.1** below shows the distribution of general practices using Vision in 2016. More recently, Vision is the least well geographically distributed software in England with GPs using Vision largely concentrated in the South of England (London, Manchester and Birmingham). However overall, prior studies have shown that the CPRD is representative of the UK population in terms of age, sex and ethnicity.(122, 127, 128) CPRD Aurum, uses data collected by EMIS Web, and was not available at the time of initiating my studies.

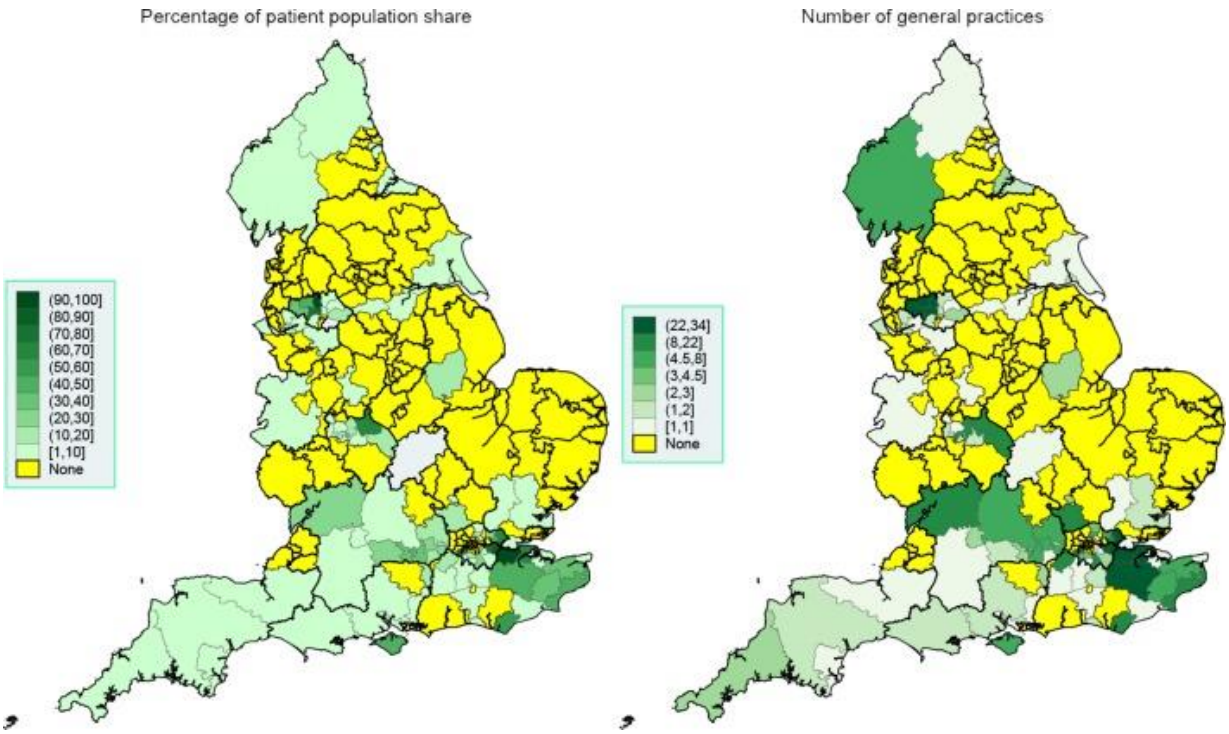


**Figure 4.1**: Distribution of 7526 General Practices in the UK that using InPS Vision at the Clinical Commissioning Group (CCG) level. Kontopantelis et al, 2018 Reproduced with permission under the CC BY licensing.

Data are entered on Vision during a patient's encounter with their GP. Information on demographics, lifestyle, diagnoses, prescriptions, the results of investigations ordered by the GP and the details of referrals made to secondary care are recorded for each individual. While GPs are able to record data into freetext spaces, the CPRD does not provide these freetext data, nor does it consistently include data (letters) from hospital communication to GPs. Diagnoses made in secondary care included on discharge summaries are sometimes entered onto Vision by the staff in general practices, but not always.

No consent from individual patients are required for data collection as data are primarily recorded and stored for the purpose of clinical care. General practices opt into sharing anonymised data with the CPRD for research use.

As of April 2020, the CPRD contains information on over 18 million patients (including patients who have transferred out of practices contributing to the CPRD to other practices not contributing to the CPRD and deceased patients) from 914 participating practices across the UK. From these 18 million people, 3,146,003 from 398 practices were registered and contributing to the CPRD at the time I obtained my data, covering 4.4% of the UK population

(86 practice from England (21.61%); 31 practices from Northern Ireland (7.79%); 180 practices from Scotland (45.23%) and 101 practices from Wales (25.38%)).(129)

## 4.3 Data Structure

Each patient in the CPRD has a unique identifier (Patient ID). This patient ID can be used to link various data files to provide one complete record for each patient. The unique patient ID is present in all files. **Table 4.1** summarises the data files.

| File | Description |
|---|---|
| Patient | Patient demographics and patient registration information |
| Practice | Practice information including when data were of acceptable quality to be included in the CPRD |
| Consultation | Types of consultation (e.g. emergency, surgery Consultation, phone encounter) |
| Clinical | Patient's medical history information (e.g. signs, symptoms and diagnoses (coded using Read codes) |
| Therapy | Prescription data on the GP system. All prescriptions issued by the GP |
| Referral | Referrals to secondary care settings (e.g. hospitals) and other external care centres |
| Test | Details of tests and examinations performed in the GP practice |
| Immunisation | GP Vaccination records |
| Additional Clinical Details | Structured data areas that contain information that is not stored as coded data e.g. smoking and alcohol intake |
| Staff | Details of the GP practice staff members |

**Table 4.1:** Datafiles contained within the CPRD.

## 4.4 CPRD data quality

Data quality is dependent upon how the GPs and associated practice staff enter data on to Vision. GP practices who have opted into contributing to the CPRD are provided with

guidance to improve the quality and completeness of patient data, however, data quality overall varies between practices.

The CPRD employs a flag system to indicate if data for a particular patient has met quality standards sufficient for use in research. Patients who have low quality data records or non-continuous recording of data with parts of the record missing are labelled as unacceptable and are not recommend for use in research. Further indications of records of poor quality is a recording of the date the data in a patient records is Up To Standard (UTS) and meets quality assurance criteria. The CPRD do not recommend using data prior to the UTS date for research.(122)

QOF (Quality and Outcomes Framework), was introduced in 2004. QOF is a series of standards designed to renumerate general practices for providing good quality of care to their patients and to help fund work to further improve the quality of health care. It was introduced as part of the General Medical Services (GMS) Contract in 2004.(130) One of the QOF outcomes includes a set standard for the accurate recording of patient data. This led to better quality and completeness of CPRD data from the introduction of QOF. There are no QOF criteria for antibiotic prescribing or for acne diagnoses or treatments. Some PCTs or CCGs employ Pharmaceutical prescribers who look at prescribing trends of the individual practices compared to the local, regional and national averages and advise GPs accordingly.

## 4.5 Linked data

The CPRD is linked to various other datasets; these include Index of Multiple Deprivation (IMD) and Hospital Episode Statistics (HES). (131, 132) Consent for data linkage is obtained from GP practices and can be withdrawn at any time. For the studies in my thesis, I used IMD linked datasets if they were available for individuals in my study population.
Linkage is undertaken by NHS Digital, the national information and technology partner to the NHS.(133) Patient identifiable data are submitted from GPs to NHS Digital who merge the data in with linked datasets. Secondary care and other external data sources also submit their data to NHS Digital.

**Index of Multiple Deprivation**

The English indices of deprivation measure relative deprivation in small geographical areas in England known as lower-layer Super Output Areas. Of these indices, the Index of Multiple Deprivation is the most commonly used. At the time of conducting my studies in this thesis, the IMD 2015 version was available to use and linked with CPRD data. The IMD 2015 is based on 37 indicators, across seven key domains including deprivation, employment deprivation, health deprivation and disability, education, skills and deprivation, crime, barriers to housing and services and living environment deprivation.(134) The CPRD data can be linked to IMD data either at the patient or general practice level. Ideally patient level data are used as it is more specific to the individual, however, if unavailable, practice level IMD can be used as an alternative. IMD can be used as a proxy measure of socioeconomic status and is divided into groups ranking from least to most deprived.(134) The CPRD GOLD is broadly representative of the general population in England for patient-level SES, however general practices contributing to the CPRD are from slightly more deprived areas of the UK.(135)

## 4.6 CPRD strengths and limitations

The CPRD is a large data source comprising longitudinal, routinely collected health data from 914 general practices with a median follow up of 5.58 years (Inter quartile range 1.97 – 13.33 years) for all patients including those who have transferred out of a practice that contributes to the CPRD and those who have deceased.(129)

A key strength of the CPRD is its large size which generally provides more opportunity for greater study power, however this does depend upon the specific research question and if the exposure or outcomes are common or rare. Higher magnitudes of study power give more precise estimates of associations between exposures and outcomes and also allow for greater precision of estimates for subgroup analyses. The large size of the CPRD is also an important strength when studying more rare outcomes as these are more likely to occur when there are more individuals contained within study populations.

CPRD data contains information on socio-demographics and lifestyle factors such as smoking and alcohol use meaning that confounding variables can be adjusted for in analyses. Furthermore, a major strength of the CPRD is that it has a long period of follow up

meaning that outcomes which occur after long time gaps after exposures can be more adequately studied. Linkage of CPRD to other datasets, particularly secondary care data, mean diagnoses frequently made in secondary care settings and associations in different health care settings can be investigated. Lastly, the CPRD collects data from general practices and 98% of people are registered with a GP, and the CPRD is representative of the UK in terms of age, sex and ethnicity meaning findings from studies using the CPRD are generalisable to the UK population.(122, 128)

Given GPs record information about patients for the use of clinical care and not research, data completeness and consistency are important limitations of the CPRD. Misclassification of variables is also an issue - the absence of a diagnostic Read code does not necessarily mean an absence of the condition. People suffering with more mild conditions may not seek a consultation from their GP, therefore these diagnoses will not be recorded. This limitation will particularly affect conditions such as acne vulgaris, where milder disease may be treated with over the counter treatments. The CPRD however, has been validated for several diagnoses.(136-139) There is also a possibility of misclassification of diagnoses as conditions that present similarly may be misdiagnosed by GPs – for example, there could be diagnostic uncertainty with acute eczema and a fungal infection. There is variability of prescribing practices likely from practice to practice: as mentioned previously, some Primary Care Networks/Trusts employ pharmaceutical advisors who work with GPs to assess prescriptions against the standard of average prescribing practices in the region and provide guidance to alter prescribing practices to be consistent with what is expected locally. Guidance received may vary between Trusts and regions. Lastly, the recording of lifestyle factors, such as alcohol use, smoking and Body Mass Index (BMI) are not well captured, leading to missing data. The recording of these lifestyle factors varies across other patient factors such as age and frequency of encounters with the GP. The CPRD holds little information on other lifestyle factors such as diet, physical activity, education and income, which limits the ability to adjust for these in analyses.

## 4.7 Contribution

I obtained the fellowship to undertake this programme of work. I led on the study design, protocol development and was supported by my PhD supervisors and wider advisory group.

I obtained ISAC (Independent Scientific Advisory Committee) approval for both studies using the CPRD as well as ethical approval at LSHTM. Once I received approvals, I obtained data from the CPRD and led the cleaning and analyses of the data.

## 4.8 Summary

- My thesis uses datasets comprised of CPRD data linked to IMD for the studies outlined in chapters six and seven.

- The CPRD is a de-identified, large data source of routinely collected health data of over 18,000,000 individuals from UK primary care.

- An important strength of the CPRD is its size and representativeness of the UK population in terms of age, sex and ethnicity.

- Drawbacks of using CPRD data include misclassification of exposures, outcomes and covariates, missing data, and possible biased recording of lifestyle factors such as smoking, alcohol and socioeconomic status. Vision, the recording software GPs use is also becoming less representative of the UK population over time.

# Chapter 5: Long-term oral antibiotic use in people with acne vulgaris in UK primary care: a drug utilisation study

## 5.1 Introduction

This chapter addresses objective number two – the use of long-term oral antibiotics for people with acne vulgaris in UK primary care. The systematic review outlined in chapter 3 investigating the published literature on the relationship between oral antibiotics for acne and AMR (objective one) found overall weak evidence for a relationship between oral antibiotics for acne and subsequent AMR, infection with a resistant organism or other evidence of AMR. In order to further investigate oral antibiotics for acne and their relationship with AMR, it is first necessary to establish how oral antibiotics are used to treat acne in the UK at the population level. In this chapter, I used CPRD to investigate how oral antibiotics for acne are prescribed long-term over a period of up to five years.

## 5.2 Study protocol and Ethical approval

The study protocol was developed *a priori* (Appendix 4) and was approved by the CPRD's Independent Scientific Advisory Committee (ISAC) (ISAC protocol number: 19_168) and the London School of Hygiene and Tropical Medicine's Ethics Committee (Reference number: 17864) (**Appendix 2**).

## 5.3 Research paper three

The following pages contain the research article. The supplementary tables are provided in Appendix 3.

Ketaki Bhate, Kathryn E Mansfield, Sarah-Jo Sinnott, David J Margolis, Elizabeth Adesanya, Nick Francis, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Sinéad M Langan, Rohini Mathur.

Long-term oral antibiotic use in people with acne vulgaris in UK primary care: a drug utilization study. Br J Dermatol. 2022 Dec 13:ljac084. doi: 10.1093/bjd/ljac084. Epub ahead of print. PMID: 36670540.

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1512948 | **Title** | Dr |
| **First Name(s)** | Ketaki | | |
| **Surname/Family Name** | Bhate | | |
| **Thesis Title** | Long-term antibiotics for acne and antimicrobial resistance | | |
| **Primary Supervisor** | Prof Sinéad Langan | | |

**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 Dermatology | | |
| When was the work published? | December 2022 | | |
| 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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**SECTION C – Prepared for publication, but not yet published**

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|---|---|
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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 of this paper. I wrote the protocol for this study, completed all the analyses and wrote the manuscript. The co-authors contributed to the design of the study and provided comments on the manuscript. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Ketaki Bhate |
| **Date** | 12.04.2023 |

| | |
|---|---|
| **Supervisor Signature** | Sinéad Langan |
| **Date** | 12.04.2023 |

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# Long-term oral antibiotic use in people with acne vulgaris in UK primary care: a drug utilization study

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## Abstract

**Background** The inappropriate use of antibiotics is understood to contribute to antimicrobial resistance. Oral antibiotics are regularly used to treat moderate-to-severe acne vulgaris. In practice, we do not know the typical length of oral antibiotic treatment courses for acne in routine primary care and what proportion of people receive more than one course of treatment following a new acne diagnosis.

**Objectives** To describe how oral antibiotics are prescribed for acne over time in UK primary care.

**Methods** We conducted a descriptive longitudinal drug utilization study using routinely collected primary care data from the Clinical Practice Research Datalink GOLD (2004–2019). We included individuals (8–50 years) with a new acne diagnosis recorded between 1 January 2004 and 31 July 2019.

**Results** We identified 217 410 people with a new acne diagnosis. The median age was 17 years [interquartile range (IQR) 15–25] and median follow-up was 4.3 years (IQR 1.9–7.6). Among people with a new acne diagnosis, 96 703 (44.5%) received 248 560 prescriptions for long-term oral antibiotics during a median follow-up of 5.3 years (IQR 2.8–8.5). The median number of continuous courses of antibiotic therapy ($\geq$ 28 days) per person was four (IQR 2–6). The majority ($n$ = 59 010, 61.0%) of first oral antibiotic prescriptions in those with a recorded acne diagnosis were between the ages of 12 and 18. Most ($n$ = 71 544, 74.0%) first courses for oral antibiotics were for between 28 and 90 days. The median duration of the first course of treatment was 56 days (IQR 50–93 days) and 18 127 (18.7%) of prescriptions of $\geq$ 28 days were for < 6 weeks. Among people who received a first course of oral antibiotic for $\geq$ 28 days, 56 261 (58.2%) received a second course after a treatment gap of $\geq$ 28 days. The median time between first and second courses was 135 days (IQR 67–302). The cumulative duration of exposure to oral antibiotics during follow-up was 255 days (8.5 months).

**Conclusions** Further work is needed to understand the consequences of using antibiotics for shorter periods than recommended. Suboptimal treatment duration may result in reduced clinical effectiveness or repeated exposures, potentially contributing to antimicrobial resistance.

**What is already known about this topic?**

- Long-term oral antibiotics are frequently used to treat acne.
- Antimicrobial resistance is one of the leading causes of death worldwide and the prolonged use of antibiotics in the treatment of skin conditions may contribute to this burden.

**What does this study add?**

- In total, 66% of people who receive an oral antibiotic course for acne subsequently receive a further course.
- Although acne guidelines recommend antibiotic therapy for $\geq$ 3 months, most receive a median of 56 days per course with a median gap between first and second courses of 135 days.
- People with acne receive a median of four oral antibiotic courses over a follow-up of 5.3 years (with a median cumulative duration of 255 days).

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Topical and oral antibiotics are commonly prescribed for the treatment of acne vulgaris, a chronic skin disorder with onset predominantly in adolescence. Prevalence studies show that the majority (80–100%) of adolescents experience acne and that 20% are moderately to severely affected.[1] The high prevalence of acne means that antibiotics are often prescribed in the adolescent population, for variable durations ranging from 6 weeks to many months and, in some cases, years.[2,3] Although acne guidelines vary, most recommend antibiotics are continued for ≥ 3–4 months with some mentioning treatment effectiveness begins, or can be assessed at, 6 weeks.[4–9] Guidelines also state that each 3- to 4-month course can be repeated if acne recurs. Tetracyclines and macrolides are the two most commonly prescribed oral antibiotic classes for acne with varying average use durations depending on treatment setting. Trimethoprim is often prescribed as a second-line antibiotic for acne.[3,10]

Overuse of oral antibiotics is known to cause antimicrobial resistance (AMR) as repeated and sustained antibiotic exposure allows microbes to develop mechanisms to avoid them.[11] The use of oral antibiotics for acne may also lead to antibiotic resistance of flora at other body sites.[11] AMR is one of the leading causes of death worldwide with almost five million deaths associated with bacterial AMR.[12] Without interventions, future infection-related deaths because of AMR are estimated at 10 million per year, and by 2050, the cost of AMR could reach 100 trillion US dollars.[13] We do not know how long-term oral antibiotics for acne have an impact on bacterial flora elsewhere in the body, and affect AMR.

The effectiveness of antimicrobial stewardship – a framework to ensure judicious use of antibiotics – has been demonstrated for infections such as urinary tract or respiratory tract infections in care homes, but not for acne and the younger population predominantly affected.[14] To ensure the successful implementation of an antimicrobial stewardship framework in acne treatment, we first need to understand how antibiotics are used for acne. We currently do not know how antibiotics for acne are prescribed in the UK beyond 1 year, the duration of treatment courses, and if individuals are prescribed multiple courses of antibiotic therapy over time. In the context of AMR, it is important to understand how those with moderate-to-severe acne are prescribed antibiotics over time as acne guidelines recommend further oral antibiotics if acne relapses. Without evidence regarding current antibiotic prescribing in acne, there will be little impetus to change practice.[15,16] The overall aim of this study is therefore to describe how people with acne are managed with oral antibiotics in UK primary care over the course of their disease, specifically duration of oral antibiotic courses and how often multiple courses of oral antibiotics are required.

## Patients and methods

### Study design and setting

We undertook a descriptive study using routinely collected UK primary care health record data from between 1 January 2004 and 31 July 2019. We described the use of tetracyclines, macrolides and trimethoprim for acne, including the total number of courses (of ≥ 28 days) prescribed during follow-up, the duration of the first two courses of antibiotic therapy and the specific classes of antibiotics prescribed (see Appendix S1 in the Supporting Information for a definition of terms).

### Data source

The UK Clinical Practice Research Datalink (CPRD) GOLD is a database of primary care electronic health record data from over 600 GP practices and is broadly representative of the UK population in terms of age, sex and ethnicity.[17] The CPRD holds information on diagnoses, prescriptions and demographics for approximately 7% of the UK population.[18]

### Study population

We included people aged 8–50 years, who were registered with primary care practices contributing to the CPRD that met CPRD quality control standards. Individuals were eligible for inclusion if they had ≥ 1 year of GP registration prior to their first record of an acne morbidity code (to ensure that we included people with newly diagnosed acne and robustly captured their baseline health status). We identified people with ≥ 1 record of an acne diagnostic code between 1 January 2004 and 31 July 2019 and no acne morbidity code or prescription for acne medication (contained in the acne British National Formulary chapter and excluding oral antibiotics) for acne in the 365 days before their first acne record to capture newly diagnosed acne more reliably. Follow-up started at the first recorded acne diagnosis on or after 1 January 2004 and ended at the earliest of the following: death; end of registration with the practice; the last date that data were collected from the practice; or the study end date (31 July 2019).

### Study measures

Acne was defined based on a record of one acne diagnostic morbidity code in primary care. We excluded morbidity codes for rare forms of acne such as chloracne or tropical acne from our list of morbidity codes used to identify acne to exclude acne caused by a clear trigger and therefore unlikely to recur.

Acne-related antibiotic exposure was identified using primary care prescribing records recorded on, or after, the date of the first acne diagnostic record. Antibiotic exposure was defined using prescriptions for oral antibiotic classes commonly prescribed in primary care for acne: tetracyclines, macrolides and trimethoprim. All code lists are available on datacompass.lshtm.ac.uk. Antibiotic courses with a duration of ≥ 28 days were considered as long term and antibiotics prescribed for acne (Appendix S1). We defined long-term courses of antibiotic therapy as (i) a single prescription of ≥ 28 days; or (ii) ≥ 2 consecutive antibiotic prescriptions of any duration with a gap of ≤ 28 days between the end of one prescription and the start of the next totalling 28 days or longer. Antibiotics for a duration of < 28 days we considered short term. We considered individuals to be on a continuous course of antibiotic therapy during any gaps in prescribing of ≤ 28 days (Figure 1a–c). Upon creating continuous courses from individual prescriptions, we assumed antibiotics with durations of < 28 days were unlikely to be for acne.[19]

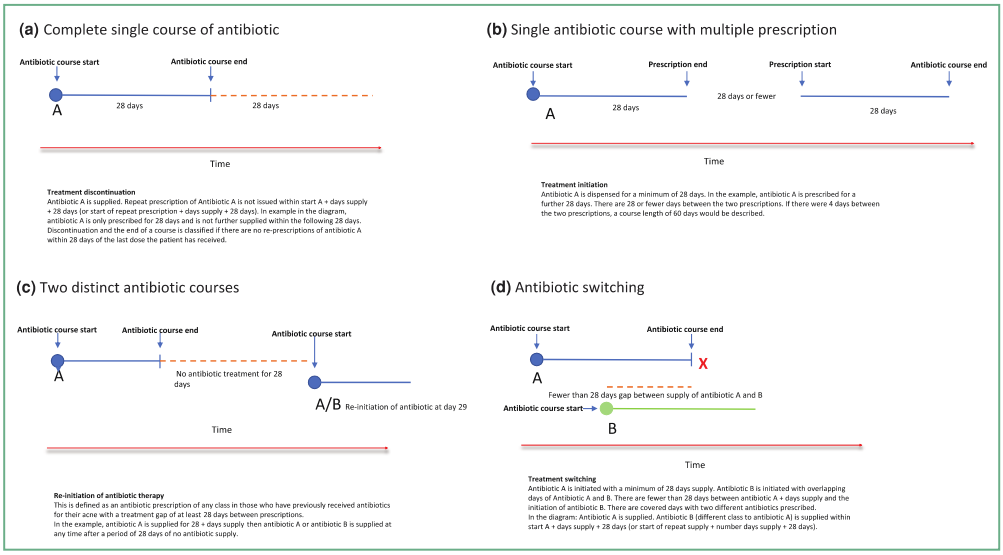


**Figure 1** (a) Complete single course of antibiotic. Treatment discontinuation: Antibiotic A is supplied. Repeat prescription of Antibiotic A is not issued within start A + days supply + 28 days (or start of repeat prescription + days supply + 28 days). In (a), antibiotic A is only prescribed for 28 days and is not further supplied within the following 28 days. Discontinuation and the end of a course is classified if there are no re-prescriptions of antibiotic A within 28 days of the last dose the patient has received. (b) Single antibiotic course with multiple prescription. Treatment initiation: Antibiotic A is dispensed for a minimum of 28 days. In (b), antibiotic A is prescribed for a further 28 days. There are ≤ 28 days between the two prescriptions. If there were 4 days between the two prescriptions, a course length of 60 days would be described. (c) Two distinct antibiotic courses. Re-initiation of antibiotic therapy: this is defined as an antibiotic prescription of any class in those who have previously received antibiotics for their acne with a treatment gap of ≥ 28 days between prescriptions. In (c), Antibiotic A is supplied for 28 + days supply then antibiotic A or antibiotic B is supplied at any time after a period of 28 days of no antibiotic supply. (d) Antibiotic switching. Treatment switching: Antibiotic A is initiated with a minimum of 28 days supply. Antibiotic B is initiated with overlapping days of Antibiotic A and B. There are < 28 days between antibiotic A + days supply and the initiation of antibiotic B. There are covered days with two different antibiotics prescribed. In (d), Antibiotic A is supplied. Antibiotic B (different class to antibiotic A) is supplied within start A + days supply + 28 days (or start of repeat supply + number of days supply + 28 days).

We assumed a course of antibiotic therapy started on the day it was prescribed. We chose 28 days between prescriptions to allow sufficient time for people to request a repeat prescription and collect their antibiotics from pharmacies.[20] If there was a new class of antibiotic prescribed < 28 days from the end date of a previously prescribed antibiotic, we ended the prescription of the first antibiotic class as intended on the prescription. Antibiotic class switches were classified if prescriptions for two different classes of antibiotic had overlapping covered days (days where there were two antibiotics prescribed), or a new antibiotic class was prescribed within 28 days of the last covered day of the first antibiotic prescription (Figure 1d). We described time in person-years on any of the three classes of antibiotic overall.

To reflect early adolescent, adolescent, early adult and adult acne, we categorized age as: 8–11, 12–18, 19–25, 26–35 and 36–50 years. To reflect changes in recording practices and acne prescribing guidelines, we divided calendar time into the following periods: 2004–2008, 2009–2013 and 2014–2019.[4,5,8] We divided prescription duration into the following categories: 28–41 days (category chosen to reflect that effectiveness of antibiotics may be assessed at week six[4,7,9,21]), 42–90 days, 91–180 days, 181–365 days and > 365 days. Based on a UK census, we categorized ethnicity in five categories: White, South Asian, Black, mixed/other, and missing or unknown.[17] We defined deprivation using individual-level quintiles of the Index of Multiple Deprivation and, where individual-level data were not available, at practice level.[22]

## Statistical analysis

### *Study population characteristics*

We described characteristics (median follow-up, age, sex, calendar period at first acne diagnosis, deprivation and ethnicity) of the overall study population including everyone with their first acne diagnosis recorded between 1 January 2004 to 31 July 2019. We then described the same characteristics for subgroups of people with acne based on whether or not they received antibiotics: (i) those who received no oral antibiotics; (ii) those who received a short course of oral antibiotics (of durations < 28 days); and (iii) those who received ≥ 28 days of an oral antibiotic in a single course.

### *Overall prescription patterns*

We described median follow-up and median duration of all antibiotic courses (short and long term) during follow-up. We described the median number of courses (Appendix S1)

of oral antibiotic with durations of ≥28 days per individual during follow-up.

#### *First prescription of long-term antibiotic after acne diagnosis and time spent on antibiotic*

Of those with acne who had ≥1 long-term antibiotic prescription (i.e. who received ≥28 days of an oral antibiotic), we described the characteristics (sex, age, calendar period of prescription, deprivation and ethnicity) of individuals when they had their first antibiotic prescription of ≥28 days (Appendix S1). We described characteristics overall for those with first prescriptions for any of the three antibiotic classes, and subsequently stratified by specific antibiotic class (tetracycline, macrolide, trimethoprim). We also described first prescriptions for each of the three classes by sex and age category. In addition, we described the median time between acne diagnosis and first acne prescription. We calculated person-time spent on antibiotics as percentages of total person-time in specific strata of sex, age category during the time recipients were prescribed the antibiotic, calendar period when they were prescribed the antibiotic, deprivation and ethnicity.

#### *Prescription duration*

Long-term prescriptions (of ≥28 days) and missing data

We described the median duration of all long-term antibiotic courses and the missing data associated with prescription duration. The median duration of all oral antibiotic prescriptions in people who received ≥28 days of oral antibiotic was entered for any prescriptions with a missing duration. We described antibiotic class switches (Figure 1d) and the median gap between all courses by looking at the time between the last covered day of a course and the start date of a new course. We also calculated median cumulative duration spent on any of the three antibiotic classes of interest per person during follow-up.

#### *First prescription (of ≥ 28 days)*

We described the first antibiotic course length after an acne morbidity code, divided into categories of duration by antibiotic class as well as the median duration of the first course of antibiotic of ≥28 days.

#### *Second antibiotic prescription for ≥ 28 days*

We calculated the proportions of those receiving a first antibiotic of ≥28 days who subsequently received a second antibiotic with a treatment gap of ≥28 days between prescriptions. We also described the class of the second antibiotic received relative to the first by cross-tabulating class of the first antibiotic against class of the second antibiotic. In addition, we also looked at the duration of the second course and the median gap between the first and second course.

### Sensitivity analysis

In our main analysis, we defined continuous courses of antibiotic therapy allowing a gap of ≤28 days between consecutive prescriptions and in our sensitivity analysis we reduced this to 14 days to allow for the possibility that less time would be needed for individuals to request a repeat prescription and have their medication dispensed.

### Patient involvement

A focus group of eight patient or carer representatives helped guide the interpretation of our findings. The focus group were recruited through an open advertisement on www.peopleinresearch.org.

### Ethics

The study protocol was approved by CPRD's Independent Scientific Advisory Committee (Protocol number: 19_168) and the London School of Hygiene and Tropical Medicine's Ethics Committee (Reference number: 17 864).

## Results

### Study population characteristics

We identified 217 410 people with a first diagnosis of acne between 1 January 2004 and 31 July 2019 who were eligible for inclusion (Figure 2). Median follow-up for all participants was 4.3 years [interquartile range (IQR) 1.9–7.6 years] and the median age was 17 years (IQR 15–25).

The overall study population included more females ($n$=142 789, 65.7%) than males ($n$=74 621, 34.3%) (Table 1). Of the total study population, 96 703 (44.5%) had a prescription for one of the oral antibiotics included in the study (tetracycline, macrolide or trimethoprim) for a minimum duration of 28 days on or after the date of their first acne diagnostic code. For those receiving an oral tetracycline, macrolide or trimethoprim antibiotic for ≥28 days, median duration of follow-up was 5.3 years (IQR 2.8–8.5) compared with 5.8 years (IQR 3.3–9.0) for those treated with an antibiotic for <28 days and 2.6 years (IQR 1.1–5.3) for those individuals who received no antibiotic prescriptions during follow-up. More females ($n$=57 229, 59.2%) with an acne code were prescribed an antibiotic associated with acne for ≥28 days than males (39 474 40.8%). Ethnicity data were missing or unknown for 60.7% ($n$=58 712) of those in the long-term use group.

### Overall prescription patterns

During the median follow of up 5.3 years (IQR 2.8–8.5), participants had a median of four individual courses of long-term antibiotic (IQR 2–6); 13 452 of 96 703 people (13.9%) were prescribed ≥5 courses, and 1715 (1.8%) people were prescribed ≥10 or more courses (Figure 3). The median duration of long-term antibiotic courses was 56 days (IQR 47–88) (Table 2). The median follow-up of people with ≥10 long-term courses was 10 years (IQR 7.6–12.3) and the median follow-up for people with ≤9 long-term courses was 5.2 years (IQR 2.7–8.4).

### First prescription of long-term oral antibiotic after acne diagnosis and time spent on antibiotics

Of 96 703 individuals prescribed a long-term oral antibiotic (regardless of antibiotic class), $n$=59 010 (61.0%) were initiated between the ages of 12 and 18 years (Table 3). More females than males were prescribed oral antibiotics than

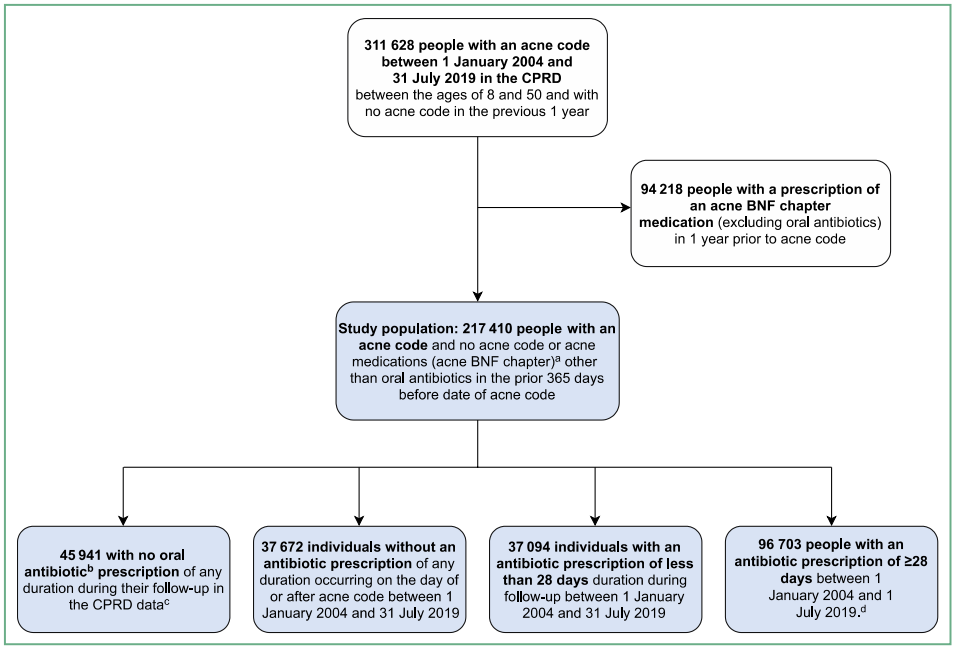


**Figure 2** Identification of study participants. Only data from practices that met quality control standards were included and only individuals who had been registered at the practice for 1 year prior to study entry were included. BNF, British National Formulary; CPRD, Clinical Practice Research Datalink. [a]Acne medication found in the acne BNF chapter. [b]Antibiotic typically prescribed for acne (tetracycline, macrolide or trimethoprim). [c]Not restricted to follow-up period of study 1 January 2004 to 31 July 2019. [d]Continuous courses have been constructed if duration between subsequent prescriptions of the same antibiotic class is < 28 days.

males throughout all age categories; however, proportions were similar between the ages of 12 and 18 [for example $n = 2021$ (83.6%) of females between 8 and 11 years and $n = 23\,192$ (46.2%) of females between 12 and 18 years were prescribed a tetracycline, Table S1; see Supporting Information].

A smaller proportion ($n = 21\,075/96\,703$, 21.8%) of first prescriptions of long-term antibiotic were issued between 2014 and 2019 compared with 2004 and 2008 ($n = 37\,719$, 39.0%) and 2009–2013 ($n = 37\,909$, 39.2%).

The median gap between acne diagnosis and first antibiotic prescription was 170 days (IQR 28–566). Most people ($n = 83\,393$, 84.6%) who were treated with a long-term antibiotic received a tetracycline as their first-line antibiotic.

Of the total population with an acne code (217 410 individuals with 1 102 202 person-years of follow-up), 19.4% (213 721 person-years) of time was spent on long-term oral antibiotic treatment during follow-up (prescriptions lasting ≥ 28 days) (Table 4). The greatest proportion of total follow-up spent on long-term oral antibiotics was in those aged 8–11 years (2509/5708 person-years, 44.0%) followed by 12–18 years (101 332/356 339 person-years, 28.4%).

The proportion of time spent on an oral antibiotic for acne varied with calendar period: (i) 2004–2008, 31.1% of study population follow-up (54 525 person-years on antibiotic/175 526 person-years); (ii) 2009–2013, 22.5% of study population follow-up (102 544 person-years on antibiotic/456 566 person-years); and (iii) 2014–2019 12.1% of study population follow-up (56 651 person-years on antibiotic/470 110 person-years).

## Prescription duration

### *Long-term prescriptions (of ≥ 28 days) and missing data*

The median duration of all oral antibiotic prescriptions in people who received a long-term antibiotic ($n = 248\,560$ total number of prescriptions for 96 703 people) was 56 days (IQR 47–88); for 1.9% of prescriptions (4816 prescriptions for 4428 people) the antibiotic duration was missing, and median duration of 56 days was entered. Overall, 4494 (4.6%) people switched antibiotic class during a course of treatment, that is, they had received two prescriptions for different classes of antibiotic (with antibiotic covered days overlapping or, < 28 days between them) (Figure 1d). The median gap between all courses was 119 days (IQR 64–260 days). The median cumulative duration spent on antibiotics per person during follow-up was 255 days (IQR 130–455).

**Table 1** Characteristics of the study population

| Characteristic | Overall study population: people with an acne diagnosis ($n=217\,410$)[a] | No antibiotics prescribed during follow-up[b] ($n=83\,613$) | Any acne antibiotic with a duration of <28 days during follow-up (short duration) ($n=37\,094$)[b,c] | Antibiotic given for a minimum duration of 28 days at any time on the day of or after first acne (long duration) ($n=96\,703$)[b,d] |
|---|---|---|---|---|
| Follow-up in years, median (IQR) | 4.3 (1.9–7.6) | 2.6 (1.1–5.3) | 5.8 (3.3–9.0) | 5.3 (2.8–8 .5) |
| Sex | | | | |
| Female | 142 789 (65.7) | 55 167 (66.0) | 30 393 (81.9) | 57 229 (59.2) |
| Male | 74 621 (34.3) | 28 446 (34.0) | 6701 (18.1) | 39 474 (40.8) |
| Age at acne diagnosis, years | | | | |
| 8–11 | 7082 (3.3) | 2861 (3.4) | 843 (2.3) | 3378 (3.5) |
| 12–18 | 120 094 (55.2) | 44 464 (53.2) | 16 620 (44.8) | 59 010 (61.0) |
| 19–25 | 39 269 (18.1) | 15 966 (19.1) | 7797 (21.0) | 15 506 (16.0) |
| 26–35 | 34 383 (15.8) | 14 121 (16.9) | 7744 (20.9) | 12 518 (12.9) |
| 36–50 | 16 582 (7.6) | 6201 (7.4) | 4090 (11.0) | 6291 (6.5) |
| Calendar period at acne diagnosis | | | | |
| 2004–2008 | 78 469 (36.1) | 24 345 (29.1) | 16 405 (44.2) | 37 719 (39.0) |
| 2009–2013 | 83 888 (38.6) | 31 396(37.6) | 14 583 (39.3) | 37 909 (39.2) |
| 2014–2019[e] | 55 053 (25.3) | 27 782 (33.2) | 6106 (16.5) | 21 075 (21.8) |
| Quintiles of IMD | | | | |
| 1 (least deprived) | 48 282 (22.2) | 18 046 (21.6) | 7387 (19.9) | 22 861 (23.6) |
| 2 | 36 837 (16.9) | 14 013 (16.8) | 5904 (15.9) | 16 922 (17.5) |
| 3 | 41 815 (19.2) | 16 227 (19.4) | 7168 (19.3) | 18 419 (19.0) |
| 4 | 41 004 (18.9) | 15 888 (19.0) | 7317 (19.7) | 17 794 (18.4) |
| 5 (most deprived) | 49 472 (22.8) | 19 445 (23.3) | 9318 (25.1) | 20 707 (21.4) |
| Ethnicity | | | | |
| White | 77 085 (35.5) | 29 565 (35.4) | 14 105 (38.0) | 33 415 (34.6) |
| South Asian | 6509 (3.0) | 3173 (3.8) | 954 (2.6) | 2382 (2.5) |
| Black | 3150 (1.4) | 1674 (2.0) | 402 (1.1) | 1074 (1.1) |
| Other/mixed | 3105 (1.4) | 1586 (1.9) | 399 (1.1) | 1120 (1.2) |
| Missing | 127 561 (58.7) | 47 615 (57.0) | 21 234 (57.2) | 58 712 (60.7) |

Data are *n* (%) unless otherwise specified. IMD, Index of Multiple Deprivation; IQR, interquartile range; long duration, ≥28 days; short duration, <28 days. [a]Between 1 January 2004 and 31 July 2019, between the ages of 8 and 50 years, having not had an acne-related medication other than oral antibiotics in the previous 365 days prior to acne code. [b]Between 1 January 2004 and 31 July 2019. [c]Antibiotic prescription with durations of <28 days with prescription dates on the day of the acne code or after. Total course of therapy <28 days despite formation of continuous courses. [d]Antibiotic prescription for a minimum duration of 28 days prescribed with acne diagnostic code preceding or on the same day as the prescription. [e]To 31 July 2019.

### *First prescription of long-term antibiotic*

Most people, ($n=71\,544$, 74.0%) treated with a long-term antibiotic after acne diagnosis received their first course of antibiotic with a duration lasting between 28 and 90 days with a treatment gap of ≥28 days from course completion before receiving a further antibiotic prescription and 18 127 (18.7%) received their first antibiotic prescription for <6 weeks (Table 2).[4,5] The median duration of first antibiotic prescriptions after an acne diagnosis was 56 days (IQR 50–93).

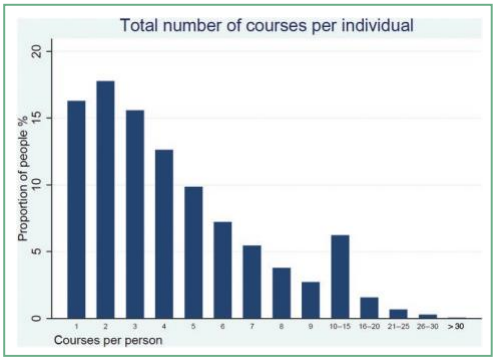


**Figure 3** Total number of courses per individual (proportion of people, $n=96\,703$). Median number of courses per person is five (interquartile range 2–6).

### *Second long-term antibiotic prescription*

Overall, 58.2% ($n=56\,261/96\,703$) of people who received a first course of antibiotic received a second course of antibiotic, with a gap of ≥28 days between consecutive courses of therapy (Table 5). Of those who received a first course of long-term antibiotic, 31–59% received a second course of antibiotic depending on first-line antibiotic class: tetracycline 58.6% ($n=47\,920$), macrolide 59.2% ($n=7796$); and trimethoprim 31.1% ($n=545$).

Most individuals who initiated tetracycline antibiotics who received a second course were subsequently treated with tetracyclines ($n=41\,211$, 86.0%); of those who were first treated with a macrolide, $n=3984$ (51.1%) subsequently received a tetracycline and $n=3672$ (47.1%) received a macrolide as their second course (Table 5). Of those who were first treated with trimethoprim, most were subsequently treated with either a tetracycline ($n=243$, 44.6%) or further trimethoprim ($n=242$, 44.4%).

Of the 56 261 people who received a second antibiotic, $n=11\,953$ (21.2%) were prescribed for <6 weeks and $n=31\,463$ (55.9%) were prescribed for between 6 weeks

**Table 2** Number of people ($n=96\,703$) and duration (treatment course length) category of first oral antibiotic exposure on the day of or after acne code, second antibiotic exposure ($n=56\,261$) and all antibiotic exposures ($n=248\,560$)[a]

| Antibiotic | People with prescription exposure length 28–41 days, *n* (%) | People with prescription exposure length 42–90 days, *n* (%) | People with prescription exposure length 91–180 days, *n* (%) | People with prescription exposure length 181–365 days, *n* (%) | People prescription exposure with length > 365 days, *n* (%) |
|---|---|---|---|---|---|
| First course | | | | | |
| All antibiotics ($n=96\,703$) | 18 127 (18.7) | 53 417 (55.2) | 18 170 (18.8) | 5658 (5.9) | 1331 (1.4) |
| Tetracycline ($n=83\,393$) | 14 162 (17.0) | 46 538 (55.8) | 16 362 (19.6) | 5155 (6.2) | 1176 (1.4) |
| Macrolide ($n=12\,075$) | 3654 (30.3) | 6164 (51.1) | 1677 (13.9) | 461 (3.8) | 119 (1.0) |
| Trimethoprim ($n=1235$) | 311 (25.2) | 715 (57.9) | 131 (10.6) | 42 (3.4) | 36 (2.9) |
| Second course | | | | | |
| All antibiotics ($n=56\,261$) | 11 953 (21.2) | 31 463 (55.9) | 9653 (17.2) | 2531 (4.5) | 659 (1.2) |
| Tetracycline ($n=47\,920$) | 10 024 (20.9) | 27 195 (56.8) | 8207 (17.1) | 2021 (4.2) | 471 (1.0) |
| Macrolide ($n=7796$) | 1811 (23.2) | 3970 (50.9) | 1371 (17.6) | 476 (6.1) | 168 (2.2) |
| Trimethoprim ($n=545$) | 118 (21.7) | 298 (54.7) | 75 (13.8) | 34 (6.2) | 20 (3.7) |
| All courses | | | | | |
| All antibiotics[b] ($n=248\,560$) | 53 804 (21.6) | 137 076 (55.1) | 42 826 (17.2) | 11 943 (4.8) | 2911 (1.2) |
| Tetracyclines ($n=204\,893$) | 39 850 (19.4) | 115 044 (56.1) | 37 000 (18.1) | 10 507 (5.1) | 2492 (1.2) |
| Macrolides ($n=38\,459$) | 12 489 (32.5) | 19 248 (50.0) | 5151 (13.4) | 1242 (3.2) | 329 (0.9) |
| Trimethoprim ($n=5208$) | 1465 (28.1) | 2784 (53.5) | 675 (13.0) | 194 (3.7) | 90 (1.7) |

Data are *n* (row %). [a]Treatment gap of ≥ 28 days between courses. Median duration of first course 56 days [interquartile range (IQR 50–93)], median duration of second course 56 days (IQR 50–93 days) and median duration all courses 56 days (IQR 47–88). Continuous courses from individual prescriptions were formed if an antibiotic within the same class was prescribed within 28 days of the start date of the current prescription unless the antibiotic class was changed – in this case two individual courses are described. [b]All antibiotic courses during follow-up.

and 3 months (Table 2). The median duration of second courses was 56 days (IQR 50–93 days). The median gap between the first and second course was 135 days (IQR 67–302 days).

## Sensitivity analysis

A sensitivity analysis (Tables S2–S4; see Supporting Information) altering the gap allowed between prescriptions to define continuous courses of therapy from 28 days to

**Table 3** Characteristics of individuals ($n=96\,703$) prescribed an oral antibiotic (overall and by antibiotic class) for ≥ 28 days between 1 January 2004 and 31 July 2019 (first prescription)

| | | Antibiotic class | | |
|---|---|---|---|---|
| Characteristic | All antibiotics ($n=96\,703$, 100%) | Tetracycline ($N=83\,393$, 86.2%) | Macrolide ($N=12\,075$, 12.5%) | Trimethoprim ($N=1235$, 1.3%) |
| Sex | | | | |
| Female | 57 229 (59.2) | 48 338 (58.0) | 7861 (65.1) | 1030 (83.4) |
| Male | 39 474 (40.8) | 35 055 (42.0) | 4214 (34.9) | 205 (16.6) |
| Age at diagnosis, years | | | | |
| 8–11 | 3378 (3.5) | 2325 (2.8) | 995 (8.2) | 58 (4.7) |
| 12–18 | 59 010 (61.0) | 51 565 (61.8) | 6930 (57.4) | 515 (41.7) |
| 19–25 | 15 506 (16.0) | 13 550 (16.2) | 1695 (14.0) | 261 (21.1) |
| 26–35 | 12 518 (12.9) | 10 585 (12.7) | 1697 (14.1) | 236 (19.1) |
| 36–50 | 6291 (6.5) | 5368 (6.4) | 758 (6.3) | 165 (13.4) |
| Calendar period[a] | | | | |
| 2004–2008 | 37 719 (39.0) | 31 336 (37.6) | 5807 (48.1) | 576 (46.6) |
| 2009–2013 | 37 909 (39.2) | 32 955 (39.5) | 4459 (36.9) | 495 (40.1) |
| 2014–2019 | 21 075 (21.8) | 19 102 (22.9) | 2809 (23.3) | 164 (13.3) |
| Quintiles of IMD | | | | |
| 1 (least deprived) | 22 861 (23.6) | 19 980 (24.0) | 2593 (21.5) | 288 (23.3) |
| 2 | 16 922 (17.5) | 14 754 (17.7) | 1960 (16.2) | 207 (16.8) |
| 3 | 18 419 (19.0) | 15 735 (18.9) | 2394 (19.8) | 290 (23.5) |
| 4 | 17 794 (18.4) | 15 127(18.1) | 2465 (20.4) | 201 (16.3) |
| 5 (most deprived) | 20 707 (21.4) | 17 794 (21.3) | 2663 (22.1) | 249 (20.2) |
| Ethnicity | | | | |
| White | 33 415 (34.6) | 28 800 (34.5) | 4081 (33.8) | 534 (43.2) |
| South Asian | 2382 (2.5) | 2111 (2.5) | 256 (2.1) | 15 (1.2) |
| Black | 1074 (1.1) | 940 (1.1) | 124 (1.0) | 10 (0.8) |
| Mixed/Other | 1120 (1.2) | 1006 (1.2) | 101 (0.8) | 13 (1.1) |
| Missing | 58 712 (60.7) | 50 536 (60.6) | 7513 (62.2) | 663 (53.7) |

Data are *n* (%). IMD, Index of Multiple Deprivation. [a]Calendar period during which antibiotic prescribed.

**Table 4** Population characteristics and time spent on oral antibiotics throughout follow-up[a]

| Characteristic | Denominator ($n=217\,410$ people with acne code) | People with ≥28 days of oral antibiotic ($n=96\,703$) |
|---|---|---|
| All, total person-years | 1 102 202 | 213 721 (19.4) |
| Sex | | |
| Female | 708 283 | 141 050 (19.9) |
| Male | 393 919 | 72 671 (18.4) |
| Age band,[b] years | | |
| 8–1 1 | 5708 | 2509 (44.0) |
| 12–18 | 356 339 | 101 332 (28.4) |
| 19–25 | 354 488 | 52 038 (14.7) |
| 26–35 | 230 272 | 33 881 (14.7) |
| 36–50 | 155 396 | 23 961 (15.4) |
| Calendar period[c] | | |
| 2004–2008 | 175 526 | 54 525 (31.1) |
| 2009–2013 | 456 566 | 102 544 (22.5) |
| 2014–2019 | 470 110 | 56 651 (12.1) |
| Quintiles of IMD | | |
| 1 (most deprived) | 241 285 | 49 632 (20.6) |
| 2 | 179 364 | 36 049 (20.1) |
| 3 | 208 237 | 40 109 (19.3) |
| 4 | 212 805 | 40 228 (18.9) |
| 5 (least deprived) | 260 511 | 47 704 (18.3) |
| Ethnicity | | |
| White | 378 553 | 74 596 (19.7) |
| South Asian | 26 937 | 4709 (17.5) |
| Black | 12 514 | 1848(14.8) |
| Other or mixed | 12 041 | 1993 (16.6) |
| Missing | 672 156 | 130 574 (19.4) |

IMD, Index of Multiple Deprivation. [a]Data are person-years (% of total person-time in specific strata). Denominators calculated from study population ($n=217\,410$). [b]Age band of recipient when antibiotic prescribed. [c]Calendar period during which antibiotic prescribed.

14 days when constructing consecutive courses is reported in Appendix S2 (see Supporting Information).

## Discussion

This descriptive study has highlighted that over 40% of people diagnosed with acne are prescribed an oral antibiotic for ≥28 days over a median follow-up of 4.3 years for the overall study population following acne diagnosis, and that almost 60% of people subsequently have a repeat course of long-term antibiotic with a median gap between the first and second course of 4.5 months. Our findings showed most people with acne who are treated with antibiotics receive a first antibiotic prescription of between 28 and 90 days of duration with a median duration of 56 days and almost 20% receive <6 weeks of oral antibiotics without a further prescription within 28 days of course completion. The median number of courses of long-term antibiotic was four (IQR 2–6) and 13.9% of people receiving long-term antibiotics had ≥5 courses during follow-up. The median cumulative duration spent on antibiotics per person during a median 5.3 years of follow-up was 255 days, or 8.5 months for those prescribed an oral antibiotic for ≥28 days. Our data showed a smaller percentage of males consult their GP and are coded for acne (34.3% males vs. 65.7% females), and of those coded for acne, fewer males were prescribed a long-term oral antibiotic than females (40.8% males vs. 59.2% females). We

**Table 5** Second course: the proportion of people with acne prescribed an antibiotic receiving a second course of antibiotic[a]

| First antibiotic course ($n=96\,703$) | Second antibiotic course ($n=56\,261$, 58.2%), people receiving second course of antibiotic for a minimum continuous exposure of 28 days, *n* (%) | |
|---|---|---|
| | Second antibiotic | *n* (%) |
| Tetracycline ($n=81\,777$) | | 47 920/81 777 (58.6) |
| | Tetracycline | 41 211/47 920 (86.0) |
| | Macrolide | 602/47 9205 (12.6) |
| | Trimethoprim | 684/47 920 (1.4) |
| Macrolide ($n=13\,175$) | | 7796/13 175 (59.2) |
| | Tetracycline | 3984/7796 (51.1) |
| | Macrolide | 3672/7796 (47.1) |
| | Trimethoprim | 140/7796 (1.8) |
| Trimethoprim ($n=1751$) | | 545/1751 (31.1) |
| | Tetracycline | 243/545 (44.6) |
| | Macrolide | 60/545 (11.0) |
| | Trimethoprim | 242/545 (44.4) |

[a]That is >28 days after the first course. Second antibiotic exposure relative to first with treatment gap of ≥28 days between courses.

found the majority of first prescriptions of long-term antibiotics in people with acne were for tetracyclines.

This is the first study to our knowledge to determine oral antibiotic prescribing practices over a 15-year period with a median follow-up of 5.3 years in UK primary care. Our study used a large, representative data source from general practices across the UK. Although the use of routinely collected health data provides real-world data, there are certain limitations. Given acne affects predominantly younger people, there may be a higher proportion of people transferring out of the practice, and hence who are lost to follow-up as they move to live elsewhere and this may be supported by the finding that the median follow-up of people who receive antibiotics (both $<$ or $\geq$ 28 days in duration) is longer (5.8 and 5.3 years, respectively) than for people who receive no antibiotic prescriptions (2.6 years). Young people may opt to stay registered with their original GPs if they are receiving longer-term treatment for their acne. Bias could be introduced if people were not registered with their GP for a sufficient duration to be prescribed long-term therapy and are prescribed antibiotics elsewhere – this would underestimate antibiotic exposure in this highly mobile population. People who were prescribed $\geq$ 10 courses had longer follow-up in the cohort, suggesting it is possible people with less follow-up may have further oral antibiotics for acne at another general practice where data are not recorded by the CPRD.

We defined our study population using acne diagnostic codes. It is possible that people in our population have acne coexisting with another condition requiring long-term oral antibiotic use of a similar class used to treat acne, for example recurrent urinary tract infections or hidradenitis suppurativa. In this situation, it would be difficult to ascertain what condition the long-term antibiotic was specifically prescribed for. We believe the number of people with two diagnoses requiring long-term antibiotics would be small and therefore unlikely to affect our results. Removing people with acne and a further diagnosis requiring long-term antibiotics of a similar class to acne may have introduced selection bias.

To define the antibiotic for acne, we ensured that the oral antibiotic classes used for acne needed to be prescribed for a minimum duration of 28 days thereby excluding some infective conditions for which the antibiotics could be prescribed for; however, this may mean we underestimate the use of shorter courses for acne. Given acne guidelines recommending longer courses (present and historic), shorter courses of antibiotic intended for acne would be rare. Additionally, trimethoprim may be prescribed long term for urinary tract infection prophylaxis, however, trimethoprim only accounts for 2.1% of all prescriptions.[23] The CPRD is broadly representative of the UK population in terms of ethnicity; however, data on ethnicity were incomplete with 60.7% missing or unknown in the long-term antibiotic use group, and hence conclusions about prescribing by ethnicity are limited.

Shorter treatment durations may be because repeat prescriptions are not obtained or people are unaware that the course is to be continued, or they do not request or are not issued their second prescription. People may not request a further prescription if they have already seen an improvement in their acne to a satisfactory level. Local prescribing policies, the patient's personal circumstances and the GP's personal prescribing preferences may influence the duration of each prescription. Shorter treatment durations per course may also reflect poor adherence, for example if people do not begin courses on the day of the prescription or miss doses therefore requesting their subsequent prescriptions later than expected. Shorter than recommended treatment durations may mean courses are less effective at treating acne, and therefore may mean courses need to be repeated and antibiotic exposures are higher than necessary. Such intermittent and prolonged use of antibiotics may contribute to selection pressure and give bacteria the opportunity to develop mechanisms to withstand the effects of antibiotics and therefore contribute to the overall burden of AMR.[11]

Our study assessed the number of courses and duration of oral antibiotics people with acne receive at the population level over time. Acne guidelines recommend a 3- to 4-month course of oral antibiotic to be repeated twice, and if there is no treatment response to refer the patient to specialist dermatology care.[9] In contrast to guideline recommendations, we found the median number of antibiotic courses prescribed was four, with a large proportion of individuals receiving five or more courses. We also noted a median duration between courses of 119 days. It is therefore unclear if the median number of courses prescribed reflects non-treatment response or relapse after remission.

The majority of first prescriptions for acne were with a tetracycline and this is consistent with clinical guidelines.[4–6] A possible explanation for fewer males being prescribed an oral antibiotic for acne than females may be that female patients are seeing their GP and seeking medical treatment for their acne more than male patients. A study using CPRD data in 2017 looked at prescriptions of all acne medication; however, patients were followed up for 1 year, so it may not have been possible to ascertain if people received a second course of oral antibiotic, and the duration of the second course.[19] A study using primary care date from The Health Improvement Network (THIN) found median duration of tetracycline therapy in people with acne between 12 and 22 years of age was 112 days, but we do not know if antibiotic courses were repeat prescribed for individuals during follow-up.[3] Given THIN and CPRD include similar populations, differences in findings may be because of how courses of therapy were defined. The THIN study, allowed further antibiotic prescriptions within 180 days of the start of the first prescription to be combined into one course. A US study of health insurance claims data found the number of courses of oral antibiotics per 100 individuals with acne was approximately 20 and the median duration of therapy was 129 days when antibiotics were prescribed by a nondermatologist.[10] Studies have previously looked at the concomitant prescription of topical acne therapy recommended in acne guidelines using UK primary care data therefore this work was not replicated here.[3,19]

In conclusion, this study found that people with acne have a median of 56 days of oral antibiotic per course and that a median of four courses are prescribed per person with a cumulative duration of oral antibiotic exposure of 8.5 months during follow-up. Given bacterial AMR is one of the leading causes of death worldwide, and the aetiology of acne is multifactorial and not a classic infectious disease, the widespread use of long-term antibiotics for acne in a relatively healthy, young population requires further investigation.[12,13] Alternative therapy for acne may reduce exposure to oral

antibiotics. Future work may include further describing the oral antibiotics prescribed for acne by subclass given varying subclasses of an antibiotic class may cause varying degrees of resistance.[24] High-quality prospective studies investigating the impact of long-term oral antibiotic use for acne and AMR are imperative, so that antibiotic prescribing practices for acne can be modified if needed. More rigorous prescribing practices and the implantation of algorithms or prescribing tools could be beneficial to ensure antibiotics are prescribed according to guidelines.

## Acknowledgments

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## Conflicts of interest

D.J.M. has consulting relationships with Janssen and Pfizer (the relationships are not related to acne or antibiotics; hidradenitis and venous dermatitis, respectively) and has funding from Pfizer (KIR genetics and atopic dermatitis). The other authors declare they have no conflicts of interest.

## Data availability

All codelists are available on datacompass.lshtm.ac.uk. Some investigators had access to the deidentified data in CPRD Gold to create the study population.

## Ethics statement

This study protocol has been approved by ISAC.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

**Covered day**

Any day upon which a prescription for an antibiotic would be taken if the antibiotic is dispensed, e.g. an antibiotic issued on the 1st of January 2022 for 28 days presumes the antibiotic is taken from 1st of January to the 28th of January.

**Antibiotic for acne**

Any oral antibiotic (Tetracycline, macrolide or trimethoprim) prescribed for a minimum duration of 28 days in someone with an acne code is presumed for acne in this study.

**Course**

Sequential covered days comprising a single acne treatment course, which could contain multiple prescriptions (Figure 1, part B). Each course is separated by at least 28 days where no antibiotics are prescribed and there are no covered days.

**Long-term antibiotic**

Any antibiotic prescribed for at least 28 days.

**Short-term antibiotic**

Any antibiotic prescribed for less than 28 days.

**Antibiotic switching**

Two distinct antibiotic classes are supplied without a gap of at least 28 days between covered days.

**Box 5.1:** Definitions of terms used in manuscript

## 5.4 Summary

- There were 217,410 people with a new acne diagnosis between the ages 8 and 50 years between January 1st 2004 to 31st July 2019 with a median follow up of 4.3 years (Interquartile range (IQR) 1.9–7.6 years).

- Of the people with a new acne diagnosis, 96,703 (44.5%) people received a prescription for a long-term antibiotic for a minimum duration of 28 days - median duration of follow up was 5.3 years (IQR 2.8 - 8.5).

- The median length of courses (including consecutive prescriptions comprising a single course) of oral antibiotics for acne was 56 days (Inter quartile range (IQR) 47 - 88). The median gap between the first and second course of oral antibiotic for acne was 135 days (IQR 67 - 302 days). The median gap between all courses was 119 days (IQR 64 – 260 days). The median cumulative duration spent on antibiotics for acne per person during follow up was 255 days (IQR 130 – 455).

- Overall, 58.2% (n=56,261/96,703) of people who received a long-term antibiotic received a second antibiotic prescription, with a gap of at least 28 days between consecutive courses of antibiotic therapy.

- During the median follow of up 5.3 years, participants had a median of four courses of oral antibiotic for acne (IQR 2-6); n=13,452 (13.9%) people were prescribed five or more courses and n=1,715 (1.8%) people were prescribed ten or more courses.

- If eligible, alternatives to prolonged courses of antibiotics over three months could be considered, for example with the use of oral isotretinoin or spironolactone for females.

# Chapter 6: The association between the long-term use of oral antibiotics for acne and subsequent antibiotic treatment failure – a cohort study

## 6.1 Introduction

In this paper I outline my cohort study to address objective three: the association between long-term oral antibiotics for acne and subsequent antibiotic treatment failure when oral antibiotics are used to treat lower respiratory tract infections, skin and soft tissue infections or urinary tract infections. This chapter comprises the final draft of the manuscript pre-submission to a journal.

Appendix 3 accompanying this chapter contains the Independent Scientific Advisory Committee (ISAC) and ethical approval document from the London School of Hygiene and Tropical Medicine which were both obtained before I started the study. Appendix 3 also contains the supplementary material (sensitivity analyses) to this research paper.

In the findings of my systematic review in chapter three, there were no studies addressing the relationship between oral antibiotics and infection with a resistant organism or evidence of AMR. In this study, I therefore aimed to address this gap by using one of the largest datasets from UK primary care to explore the association of long-term oral antibiotics for acne and subsequent antibiotic treatment failure. The data source I used for this study is described in chapter four.

## 6.2 Research paper four

Ketaki Bhate, Sarah-Jo Sinnott, David J Margolis, Kathryn E Mansfield, Nick Francis, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Sinéad M Langan, Rohini Mathur.

Long-term oral antibiotic for acne and antibiotic treatment failure: three population-based cohort studies in the United Kingdom.

Manuscript pre submission.

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

**SECTION A – Student Details**

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|---|---|---|---|
| **Student ID Number** | 1512948 | **Title** | Dr |
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**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

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| | |
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| Where is the work intended to be published? | British Journal of Dermatology |
| Please list the paper's authors in the intended authorship order: | Ketaki Bhate, Sarah-Jo Sinnott, David J Margolis, Kathryn E Mansfield, Nick Francis, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Sinéad M Langan, Rohini Mathur. |
| Stage of publication | **Not yet submitted** |

**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 of this paper. I wrote the protocol for this study, completed all the analyses and wrote the manuscript. The co-authors contributed to the design of the study and provided comments on the manuscript. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Ketaki Bhate |
| **Date** | 12.04.2023 |

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| **Supervisor Signature** | Sinéad Langan |
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## TITLE

Long-term oral antibiotic for acne and antibiotic treatment failure: three population-based cohort studies in the United Kingdom

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**4314**

## CONTRIBUTOR STATEMENT

Ketaki Bhate developed the initial protocol for the study. Sinéad Langan, and Rohini Mathur supervised the development of study design and writing process and contributed equally. Sarah-Jo Sinnott supervised the development of the study design and will review the draft manuscript. Kathryn Mansfield contributed to the study design, analysis code and will review the draft manuscript. Clemence Leyrat, Richard Stabler, Laura Shallcross, David

Margolis, Susan Hopkins and Nick Francis have acted as an advisory group, and contributed to the final study design and will review the manuscript.

## ABSTRACT

**Background**

We do not understand how long-term oral antibiotics for acne contribute to antibiotic treatment failure and antimicrobial resistance.

**Aims**

To investigate the association between long-term oral antibiotic use for acne and antibiotic treatment failure for Lower Respiratory Tract Infection (LRTI), Skin and Soft Tissue Infections (SSTI) and Urinary Tract Infection (UTI).

**Methods**

Using primary care data from the Clinical Practice Research Datalink for individuals with an acne diagnosis, we compared risk of antibiotic treatment failure between individuals who have and have not received a long-term oral antibiotic for acne. We undertook three cohort studies to estimate risk of antibiotic treatment failure within 30 days of receiving an antibiotic for LRTI, SSTI, or UTI.

**Results**

Of 847,760 people with acne, 114,770 had an LRTI, 73,648 had an SSTI, and 94,017 had a UTI. For LRTI, after adjusting for sex, deprivation, alcohol use, asthma and diabetes, oral antibiotics for acne were associated with an 8% increase in antibiotic treatment failure (Adjusted HR =1.08, (1.04, 1.13)). For SSTI, there was an 11% increase (HR=1.11, (1.07, 1.16)) and for UTI, oral antibiotics were associated with a 6% increase in treatment failure (HR= 1.06 (1.02, 1.10)). For LRTI, associations were greater for trimethoprim use (HR=1.77 (1.63, 1.93)) than macrolides (HR=1.13 (1.07, 1.20)) and tetracyclines (HR=0.99 (0.95, 1.04)) and shorter courses of oral antibiotics for acne were less strongly associated with antibiotic treatment failure than longer durations (duration 28-41 days (HR=1.07 (0.92, 1.24)), 42-90 days (HR=1.07 (1.03, 1.11)), 91-180 days (HR=1.06 (0.97, 1.15)), 181-365 days (HR=1.23 (1.06, 1.42)) and >366 days (HR=1.84 (1.48, 2.28)). Associations were also greater for trimethoprim use and longer durations of oral antibiotics for acne in the SSTI and UTI cohorts.

**Conclusion**

Findings suggest an association between oral antibiotics for acne and antibiotic treatment failure within five years. There is some evidence that trimethoprim is more strongly associated with antibiotic treatment failure and shorter durations of antibiotics for acne are associated with less antibiotic treatment failure.

## INTRODUCTION

Acne vulgaris is a chronic, inflammatory skin disorder with predominant onset in adolescence. Acne affects 80% of individuals between the ages 8 and 50 with 20% experiencing moderate to severe disease.(63) Long-term oral antibiotics are commonly prescribed for acne. Guidelines generally recommend that courses of oral antibiotics are continued for three months of daily exposure, with some guidelines stating that effectiveness of treatment for acne can be noted after six weeks.(45, 69, 70, 78) A previous study has found that antibiotics are prescribed for 40% of people diagnosed with acne in UK primary care and are prescribed for a median of 56 days (two months), with 60% of people receiving a second course of long-term antibiotic. The study also found that the median number of courses (sequential covered days comprising a single acne treatment course, which could contain multiple prescriptions) received per individual with acne is four.(140)

AMR (Antimicrobial Resistance) is one of the leading cause of death worldwide with almost five million deaths associated with bacterial AMR.(141) Without interventions, future infection-related deaths due to AMR are estimated at 10 million per year worldwide, and by 2050, the cost of AMR could reach 100 trillion US dollars.(13) The overuse of oral antibiotics is known to cause AMR as repeated and sustained antibiotic exposure allows microbes to develop mechanisms to avoid them.(97) The use of oral antibiotics for acne may also lead to antibiotic resistance of flora at other body sites.(97) The effectiveness of antimicrobial stewardship – a framework to ensure judicious use of antibiotics – has been demonstrated for infections such as urinary tract or respiratory tract infections in care homes, but not for acne and the younger population predominantly affected.(142) To ensure the successful implementation of an antimicrobial stewardship framework in acne treatment, we first need to understand how antibiotics for acne are associated with AMR. We do not yet fully understand how long-term oral antibiotics for acne impact bacterial flora elsewhere in the body and affect AMR.

Our overall aim was to investigate the association between long-term oral antibiotics for acne and antibiotic treatment failure for common infections in young, healthy people between ages 8 and 50 using UK primary care electronic health record data. Our hypothesis

was that prior long-term oral antibiotics for acne increase the risk of antibiotic treatment failure when oral antibiotics were prescribed for subsequent common infections and that the degree of association varies by antibiotic class prescribed for acne and type of common infection. We used antibiotic treatment failure as proxy measure for AMR given one of the causes of antibiotic treatment failure is AMR.

# METHODS

## Study design and setting

We conducted a cohort study using primary care health records from the UK Clinical Practice Research Datalink (CPRD GOLD). The CPRD contains anonymised routinely collected information from health records and contains information on diagnoses, prescriptions and demographics on 4.7% of the UK population. The CPRD is broadly representative of the UK population in terms of age, sex and ethnicity.(122, 128)

## Study population

Our overall study population included individuals with an acne diagnostic code at any time in their medical record. To be eligible for inclusion individuals needed to be: 1) aged between 8 and 50 at the time of acne diagnosis (the predominant age range that people get acne and may be prescribed oral antibiotics); and 2) registered with a CPRD practice at the start of study follow up. Individuals were eligible for inclusion from the latest of: 1) their current registration date plus one year (to allow for robust capture of baseline health status); 2) the day the practice was deemed to be up to standard plus 1 year; 3) the date the study started (CPRD began in 1987, however some acne diagnoses were entered as historic diagnoses backdated to 1953 - people were eligible for follow-up at any point after their first acne diagnosis (with earliest diagnosis dates going back to 1953) 4) the individual's 8$^{th}$ birthday; or 5) first record of a diagnostic code for acne. We included individuals with and without prior use of oral antibiotics commonly prescribed for acne (or any other prescribed antibiotic of any duration as excluding them may have introduced selection bias). From the study population comprising eligible people with an acne diagnosis, we identified three separate cohorts of individuals who had been diagnosed with a 1) a Lower Respiratory Tract Infection (LRTI); 2) a Skin and Soft Tissue Infection (SSTI) and 3) a Urinary Tract Infection (UTI) after their first acne diagnostic code (**Figure 6.1 – study diagram**). Further information about the identification of people with acne with infections is provided in **Appendix 3**).

## Exposure

The infection diagnosis could occur at any time point after an acne diagnosis. Our exposure of interest was a prescription of a long-term oral antibiotic for acne in the five years prior to the first oral antibiotic prescription for the infection of interest (LRTI, SSTI, or UTI).The exposure was defined as a prescription for oral tetracycline, macrolide or trimethoprim for a minimum duration of 28 days at any time on the day of or after an initial diagnostic code for acne.

## Outcome

Our primary outcome was a second prescription of oral antibiotic (within the same class of antibiotic or an alternate class) within 30 days of the first antibiotic prescription for an infective episode occurring during follow up (proxy for antibiotic treatment failure).(102, 104)

We required the oral antibiotic for infection to be initiated within seven days after the infection was diagnosed (**Figure 6.1 – study diagram**). The index date was the date of the oral antibiotic for the infection. Follow-up started the day after the oral antibiotic prescription for the first infection within each cohort. If two oral antibiotics were prescribed within seven days of an infection, we used the latest prescription date as the index date. The 30 day follow up period started the day after the oral antibiotic prescription for the first infection (index date – LRTI, SSTI or UTI). Individuals were followed up from their index date until the earliest of: 1) end of registration with the GP; 2) death; 3) the practice ceasing to contribute data towards the CPRD; 4) end of the study period 31$^{st}$ December 2019; or 5) study outcome, i.e., antibiotic treatment failure (or 30 days after index date if outcome not achieved).

## Covariates

We used a directed acyclic graph (DAG) provided in **Appendix 3**) and existing literature to a priori visualise relationships between long-term antibiotic use for acne and subsequent antibiotic treatment failure following a diagnosis of an LRTI, SSTI or UTI, to establish

potential confounding factors and effect modifiers of the relationship. Our DAG helped identify potential confounders, and where possible using electronic health record data, we adjusted for confounding variables in regression analyses. We considered the following as potential confounders of the relationship between long-term antibiotic prescribing for acne and antibiotic treatment failure: age; sex and socioeconomic deprivation (assessed using individual-level quintile of Index of Multiple Deprivation (IMD) and where this was not available, IMD at the practice level). In addition, we considered the following comorbidities as confounders - Type 1 and type 2 diabetes mellitus; asthma; harmful alcohol use (current/ex or none). All co-morbidities were defined at index date. Further details on covariate definitions and rationale for inclusion can be found in **Appendix 3.** All covariates were defined separately for each cohort as the index date differed for each infection (LRTI, SSTI and UTI).

## Statistical analyses

**Main analysis**

We described the characteristics of each infection cohort (LRTI, SSTI and UTI) by exposure status (oral antibiotic for acne use within the five years prior to index date). We used Cox regression with age as the underlying timescale to estimate hazard ratios with 95% confidence intervals for the association between oral antibiotics for acne and antibiotic treatment failure for an infection. Our first model was unadjusted including only the exposure variable (oral antibiotic for acne within five years of index date). Further models included (1) additionally adjusting for sex and Index of Multiple Deprivation (IMD); (2) additionally adjusting for harmful alcohol use and (3) further adjusting for asthma and type 1 and 2 diabetes. We did a complete case analysis and given data were unlikely to be missing at random and may be related to our outcome, we did not use multiple imputation.(143) We repeated our analyses in a series of sensitivity analyses to establish the robustness of our findings (**Appendix 3**). People who were prescribed a second antibiotic for infection on the same day as the index date were excluded from the Cox regression models. People with missing data on IMD were excluded. Previous antibiotic treatment failure prior to an acne diagnosis were not excluded to avoid introducing selection bias.

**Secondary analyses**

We investigated the associations between oral antibiotics for acne and antibiotic treatment failure for infections (LRTI, SSTI and UTI) by duration of acne antibiotic (28-41 days, 42 to 90 days, 91 to 180 days, 181 to 365 days and over 1 year) of the nearest and furthest oral antibiotic prescribed for acne within the five years prior to index date where there were multiple courses of oral antibiotic prescribed for acne (**Box 6.1**). We also investigated associations between oral antibiotics for acne and antibiotic treatment failure by the nearest and furthest antibiotic class (tetracycline, macrolide or trimethoprim) prescribed for acne within the prior five years of the index date. For each antibiotic duration and antibiotic class category, separate models were tested as in the main analyses (**Appendix 3**).

Our study was approved by the London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee and the Independent Scientific Advisory Committee (protocol 20_000229). Data were managed and analysed using Stata Version 17 MP (StataCorp, Texas, USA). All code lists will be made available on LSHTM data compass - datacompass.lshtm.ac.uk.

## RESULTS

Between 1st January 1953 and 31st December 2019 our study population comprised 847,760 individuals between the ages of 8 and 50 with an acne diagnosis. From our study population, after an acne diagnosis, there were 114,770 people with an LRTI with an oral antibiotic for LRTI prescribed within the subsequent seven days of infection diagnosis (diagnosed between 26th Nov 1985 and 31st Dec 2019) and similarly, 73,648 of people with an SSTI with an SSTI antibiotic within seven days of diagnosis (diagnosis made between 14th August 1987 and 31st Dec 2019) and 94,017 with a UTI and a UTI oral antibiotic within the subsequent seven days after diagnosis (diagnosed between 25th Sept 1986 and 31st Dec 2019) (**Table 6.1, Figure 6.2 - flowchart**). The predominant age category for an acne diagnosis across all three cohorts was between 12 and 18 years (LRTI cohort 54,060 (47.1%), SSTI cohort 36,346 (49.4%) and UTI cohort 42,063 (44.7%)). IMD distributions were broadly similar between the three cohorts as was the prevalence of type 1 and 2 diabetes (LRTI n=1,566 (1.4%), SSTI n=1,255 (1.7%), UTI n=1,029 (1.1%). Fewer people with an LRTI had a prior diagnosis of asthma (n=30,375 (26.5%) versus the SSTI cohort (n=15,322 (46.3%) and UTI cohort (n=19,904 (40.3%) and there was a lower prevalence of harmful alcohol use in those with a UTI (n=1,529 (3.6%) than LRTI (n=3,189 (6.4%) and SSTI (n=2,242 (6.8%). More women than men had a diagnosis of LRTI (n=30,962 / 72,186 (62.9%) and SSTI n=43,418 /73,648 (59.0%), however diagnoses of UTI were almost exclusively in women (n=88,567/94,017 (94.2%).

With regard to the total time spent from acne diagnosis to censoring, the median follow-up from acne diagnosis to outcome or index date +30 days (end of follow up) of the LRTI cohort was 13.6 years (Interquartile range (IQR) 8.3-20.4 years) and n=49,772 (43.4%) people were exposed to an oral antibiotic for acne before their LRTI diagnosis and n=64,998 (56.6%) were not. The median follow-up of the SSTI cohort from acne diagnosis to outcome or index date +30 days was 13.1 years (IQR 8.1-19.5) with n=33,096 (44.9%) people exposed to an oral antibiotic for acne before their SSTI diagnosis and n=40,552 (55.1%) not. The UTI cohort were followed for a median 11.9 years (IQR 7.1-18.2) from acne diagnosis and n=41,899 (44.6%) were exposed to an oral antibiotic for acne before their UTI diagnosis and n=52,118 (55.4%) were not (**Table 6.1**).In the LRTI cohort the median follow up was 30 days (IQR – 30 – 30 days) and there were 10,482 (9.1%) individuals (of n=114,770) with antibiotic

treatment failure. In the SSTI cohort the median follow up was 30 days (IQR 30-30 days) and there were 9,648 (13.0%) individuals (of n=73,648 people) with antibiotic treatment failure. In the UTI cohort the median follow up was also 30 days (IQR 30 – 30 days) and there were 9,646 (10.3%) people (of n=94,017) with antibiotic treatment failure.
In the LRTI cohort, 53,521 people had at least a five year duration from diagnosis of acne to index date, in the SSTI cohort 36,627 people had at least five years between acne diagnosis and index date and in the UTI cohort there were 39,708 people with at least five years between acne diagnosis and index date.

### Main analysis

An oral antibiotic for acne was associated with a small increased hazard of antibiotic treatment failure compared to no oral antibiotic for acne across the LRTI, SSTI and UTI cohorts in our age-adjusted Cox regression models (LRTI cohort HR 1.08 [1.04-1.12]; SSTI cohort HR 1.11 [1.07-1.16]; UTI cohort HR 1.06 [1.02-1.11]). After adjusting for potential confounders, the association between oral antibiotics for acne and antibiotic treatment failure was unchanged (LRTI cohort HR 1.08 [1.04-1.13]; SSTI cohort HR 1.11 [1.07-1.16]; UTI cohort HR 1.06 [1.02-1.10]) (**Table 6.2, Figure 6.3**).

### Secondary analyses

The median duration gap between the nearest antibiotic for acne to index date in the LRTI cohort was 515 days (1.4 years) (IQR 224 – 1000.3 days) and the median duration gap between the furthest antibiotic from the index date in the LRTI cohort was 971 days (2.7 years) [IQR 485.5-1450 days]. In the SSTI cohort, the median duration between the nearest antibiotic for acne to index date was 516.3 days (1.4 years) (IQR 220-1005 days) and the median duration gap between the furthest antibiotic for acne and the index date was 995.5 (2.7 years) (IQR 502.5 – 1482 days). In the UTI cohort, the duration between the nearest antibiotic for acne to the index date was a median 501.5 days (1.4 years) (IQR 216-971 days) and the duration between the furthest antibiotic for acne to the index date was a median 945 days (2.6 years) (IQR 469 – 1437 days) (**Figure 6.3**).

**Antibiotic class for acne**

Where there was more than one course of antibiotic for acne prescribed within the prior five years of index date we ran separate models for each nearest antibiotic class that was prescribed. Results were mixed and varied by infection cohort (LRTI, SSTI and UTI). In the LRTI cohort fully adjusted estimates were HR 0.99 [0.95-1.04] for tetracyclines, HR 1.13 [1.07-1.20] for macrolides and HR 1.77 [1.63-1.93] for trimethoprim. Fully adjusted estimated in the SSTI cohort across the three antibiotic classes were HR 1.08 [1.03-1.13] for tetracyclines; HR 1.13 [1.06-1.20] for macrolides and HR 1.32 [1.19-1.46] for trimethoprim. For the UTI cohort, tetracyclines and macrolides for acne were not associated with antibiotic treatment failure (tetracyclines HR 1.03 [0.99-1.08]; macrolides HR 0.97 [0.91-1.03]) and were more strongly associated for trimethoprim (HR 1.46 [1.35-1.58]) (**Table 6.3, Figure 6.3**). A similar pattern was seen in the models for the furthest oral antibiotic for acne within the prior five years of the index date– (LRTI cohort tetracyclines HR 1.0 [0.96-1.05]; macrolides HR 1.14 [1.07-1.21]; trimethoprim HR 1.69 [1.55-1.85], SSTI cohort tetracyclines HR 1.06 [1.02-1.11]; macrolides HR 1.17 [1.10-1.24] and trimethoprim HR 1.38 [1.24-1.53], UTI cohort tetracyclines HR 1.03 [0.99-1.08], macrolides HR 0.98 [0.91-1.04] and trimethoprim HR 1.43 [1.32-1.55] (**Table 6.4, Figure 6.3**).

**Duration of antibiotic for acne**

We investigated the association between the duration of oral antibiotic received for acne in each cohort with antibiotic treatment failure, specifically the nearest oral antibiotic prescribed for acne to the index date and the furthest. In our fully adjusted models for both the nearest and furthest antibiotic for acne prescribed, shorter durations of oral antibiotic for acne were less strongly, or not associated with antibiotic treatment failure than longer durations of oral antibiotic for acne across the LRTI, SSTI and UTI cohorts - (28-41 days) LRTI cohort HR 1.07 [0.92 - 1.24]; SSTI cohort HR 1.06 [0.91 - 1.24]; UTI cohort HR 1.16 [0.99 - 1.34]; for 181 – 365 days LRTI cohort 1.23 [1.06 – 1.42], SSTI 1.59 [1.39 – 1.81], UTI 1.10 [ 0.94 – 1.29], and for > 365 days LRTI cohort HR 1.84 [1.48 - 2.28]; SSTI cohort HR 2.44 [2.02 - 2.95] and UTI cohort 1.31 [0.98 - 1.75] (**Table 6.5, Figure 6.3**). Similar trends were seen for the duration categories of the furthest oral antibiotic prescribed for acne – 28-41 days LRTI cohort HR 1.05 [0.91 - 1.22]; SSTI cohort HR 1.15 [0.99 - 1.34] and UTI cohort HR 1.10 [0.94 - 1.28]; 181 – 365 days LRTI 1.25 [1.09 – 1.43], SSTI 1.48 [1.31 – 1.69], UTI 1.15 [1.0 - 1.33]

and for > 365 days of oral antibiotic for acne – LRTI cohort HR 1.64 [1.32 - 2.03]; SSTI cohort HR 1.60 [1.29 - 1.98] and UTI cohort HR 1.60 [1.29 - 1.98] (**Table 6.6, Figure 6.3**).

In our sensitivity analyses when we only investigated data entered by GPs on or after 1st January 2004 (including diagnoses of acne, prescriptions for oral antibiotics for acne, and infection diagnoses) the magnitude of the association between oral antibiotics for acne and antibiotic treatment failure increased (LRTI cohort HR 1.22 [1.15 - 1.29]; SSTI cohort HR 1.27 [1.20 - 1.34] UTI cohort HR 1.19 [1.13 - 1.26]. Findings from the remainder of our sensitivity analyses did not differ vastly from the results of our main analyses (**Appendix 3)**.

# DISCUSSION

## Summary

In this population-based study of over 800,000 people with acne diagnosed between the ages of 8 and 50, we found that long-term oral antibiotics for acne were associated with antibiotic treatment failure. We found the strongest risk was for longer durations of oral antibiotics, especially durations of six months and over for acne. Long term trimethoprim for acne was associated with a greater risk of antibiotic treatment failure than long-term oral tetracyclines or macrolides for acne. Furthermore, our findings suggest that the risk of antibiotic treatment failure, having previously had an oral antibiotic for acne, might persist for at least five years (median 2.7 years). We found that the hazard for antibiotic treatment failure may be greater with a more recent antibiotic course over one year in duration for acne than an earlier course over one year in duration within five years for individuals who have been prescribed more than one course of antibiotic and who subsequently developed an LRTI or SSTI.

### Findings in context

A systematic review investigating the evidence of long-term antibiotics for acne and AMR overall found weak evidence and was not conclusive.(144) None of the included studies investigated AMR as a result of long-term oral antibiotics directly - two studies investigated rates of infection, and three resistance or changes to microbial flora. Three of the included studies had 35 or fewer participants (range n=20-118 496). Two included studies found that rates of infection were higher in people who had oral antibiotics for acne than those with acne who had not.

An earlier systematic review looked at 24 studies investigating antibiotic resistance in individuals prescribed antibiotics in primary care. The authors found that longer durations and multiple courses of oral antibiotics were associated with higher rates of resistance and, in contrast with the findings of our study which found the effects of long-term oral antibiotics for acne on antibiotic treatment failure may last up to five years, the authors concluded that the effects of oral antibiotics on AMR could last up to 12 months.(145) This

study included people with all lengths of antibiotic prescriptions for various indications, and not exclusively the effect of long-term oral antibiotics for acne.

Currie et al investigated antibiotic treatment failure for first line antibiotic monotherapies associated with diagnoses of respiratory, skin and soft tissue infections and acute otitis media using the CPRD. The study used similar methodology as our study for detecting antibiotic treatment failure, while additionally assessing hospitalisations.(102) Though this study did not investigate antibiotic treatment failure as result of oral antibiotics for acne, rather antibiotic treatment failure within 30 days of an antibiotic monotherapy prescription for an infection, they found that the highest antibiotic treatment failure rates were in people given an oral antibiotic for a lower respiratory tract infection (16.9%). Further work by the group in people aged between 12 and 17 found the treatment non response rate for SSTI was 7.1% - and SSTIs were the most prominent infection being treated with antibiotics. Antibiotics for acne comprised more than half of the prescriptions studied (across respiratory tract infections, SSTI and acute otitis media.(146) Overall, there are no studies which have investigated oral antibiotics for acne and antibiotic treatment failure that we can directly compare the findings of our study to.

**Strengths and limitations**

To our knowledge this is the first study, to investigate the association between long-term oral antibiotics for acne and antibiotic treatment failure when oral antibiotics are prescribed common infections, LRTI, SSTI and UTI. In addition, our findings were robust across a range of sensitivity analyses.

A major strength of our study is that we used a large representative data source from general practices across the UK and therefore our results reflect real-world clinical practice and are likely to be generalisable to other healthcare settings. However, while routinely collected health data provides real world data there are some limitations when using these data to conduct cohort studies. Given acne affects younger people, there may be a higher proportion of people transferring out of the practice who are therefore lost to follow up as they move to live elsewhere. However, our median follow up across three cohorts was between 11.9 and 13.6 years (lowest 25$^{th}$ centile 7.1 years and maximum 75$^{th}$ centile 20.4 years) across the three infection cohorts. Bias may have also been introduced if people

were not registered with their GP for a sufficient duration of time to be prescribed an oral antibiotic for their acne after they received an acne diagnosis. Given our relatively long median follow up duration for the LRTI, SSTI and UTI cohorts, and our *a priori* maximum duration of five years during which we ascertained if oral antibiotics for acne were prescribed before index date, this is unlikely to have affected our results significantly. Young people may opt to stay registered with their original GPs if they are receiving longer term oral treatment for their acne, however across all three infection cohorts, the median follow up was slightly greater for people who had not received an oral antibiotic for their acne than those who had received one. As the CPRD has a benefit of a long follow up duration, we chose five years as the exposure window so we can fully capture antibiotic treatment failure that occurs in the years after long-term antibiotics for acne. It is possible that the effects of oral antibiotics for acne on antibiotic treatment failure last longer than five years. This would mean the unexposed cohort could also have antibiotic treatment failure as a result of long-term oral antibiotics for acne, not detected due to our study design, which could underestimate associations and bias our results towards the null. We did not opt to have a window of exposure for greater than five years due to the possibility of attrition bias, in that people who moved to another practice would not be included, and because acne predominantly affects adolescents and young adults, bias would be introduced if the people moving practices were those who moved away to study at a university or work elsewhere and therefore had to switch practices. A further point to note is that in our main analyses we chose to use diagnoses and prescriptions dated to when CPRD records began however practices and data quality have changed over time and data electronically recorded prior 1987 have been retrospectively added to the electronic health record; there is a possibility of transcription errors during this process. To overcome this, we conducted a sensitivity analysis where we only included diagnoses of acne and infections, and antibiotic treatment failure from the 1$^{st}$ of January 2004 (**Appendix 3**). The CPRD records information on prescriptions but we do not know if oral antibiotics were subsequently collected from pharmacies and then consumed as intended, on a daily basis. The non-adherence with prescribed antibiotics could cause the magnitude of effect to be lowered and be shifted towards the null (HR =1).

We defined our study population using acne diagnostic codes. People in our population could have acne co-existing with another condition requiring long-term oral antibiotic use of a similar class used to treat acne, for example, recurrent urinary tract infections or hidradenitis suppurativa, (HS). In this situation, it would be difficult to ascertain what condition the long-term antibiotic was specifically prescribed for. We believe the number of people with two diagnoses requiring long-term antibiotics would be small and therefore unlikely to affect our results (2.7% population prevalence for recurrent UTI and 0.77% population prevalence for HS).(147, 148) Trimethoprim may be prescribed long-term for urinary tract infection prophylaxis however trimethoprim only accounts for 3.7% of all prescriptions in our LRTI cohort, 3.5% of prescriptions in our SSTI cohort and 5.2% in our UTI cohort.(149) Removing people with acne who have a further diagnosis requiring long-term antibiotics (such as recurrent UTI) of a similar class to acne may have introduced selection bias.

To define antibiotic for acne, we ensured that the oral antibiotic classes used for acne needed to be prescribed for a minimum duration of 28 days thereby excluding some infective conditions for which oral antibiotics of similar classes as those prescribed for acne could be prescribed for - however this may mean we cannot assess the effects of shorter courses for acne. Given acne guidelines recommend longer courses (present and historic), shorter courses of antibiotic intended for acne would be rare. Acne guidelines generally recommend a tetracycline antibiotic first line and tetracyclines are predominantly prescribed first line in real world practice.(140) The majority of first prescriptions for acne were with a tetracycline, consistent with clinical guidelines.(45, 69, 77)

I could not exclude a de-novo infection occurring within the outcome period of 30 days, i.e., a completely treated first infection followed by a new second infection episode and hence that the second oral antibiotic prescription was not to treat the second de-novo infection, however, I believe this is unlikely to be common. I would expect such misclassification of outcome to be the same in both the exposed and unexposed groups and therefore the magnitudes of measured associations to be underestimated. The approach used in my study is in keeping with previous studies using the CPRD to investigate LRTI in various contexts where authors have regarded consultations within 28 as part of the same episode of

LRTI.(150) To ensure this is the correct approach, a validation study using bacterial culture methods alongside clinical assessments of patients during their illness would be required. Furthermore, recent infection surveillance studies require at least 91 days between Covid and influenza positive results (likely viral in origin) between episodes to regard them as separate infections.(151)

**Implications for future research**

Given bacterial AMR is one of the leading causes of death worldwide, and the aetiology of acne is multifactorial and it is not an infectious disease, the effect of widespread use of long-term antibiotics for acne in a relatively healthy, young population requires further investigation.(13, 141). Alternative therapy for acne may reduce exposure to oral antibiotics. Further work could include investigating differences in antibiotic treatment failure rates by the class of oral antibiotic prescribed for the infections (LRTI, SSTI and UTI) and how long the effect of oral antibiotics for acne persists in being associated with antibiotic treatment failure. We do yet not know if there is a difference in the magnitude of effect on antibiotic treatment failure is dependent upon the indication for long-term oral antibiotic. Additionally, characterising antibiotic treatment failure rates of the sub classes of tetracycline and macrolide antibiotics for acne may be useful in clinical practice if rates vary.(152) Further high quality prospective studies investigating the impact of long-term oral antibiotic use for acne and AMR are imperative, so that antibiotic prescribing practices for acne can be modified if needed.

**Conclusion**

In conclusion we found the long-term antibiotics for acne were associated with higher rates of antibiotic treatment failure when antibiotics are subsequently prescribed for LRTI, SSTI and UTI. We found that this association varied by the antibiotic class prescribed for acne, duration of oral antibiotic for acne and subsequent infection (LRTI, SSTI or UTI). Our work has found the effect of oral antibiotics for acne may last up to five years. More rigorous prescribing practices and the implantation of algorithms or prescribing tools could be beneficial to ensure antibiotics are prescribed according to guidelines, and not for longer or shorter durations. Further comparative studies assessing treatment outcomes of oral antibiotics for acne versus other topical and systemic treatments for acne such as

spironolactone or the earlier use of isotretinoin (a disease modifying acne treatment) would also be beneficial with view to finding efficacious antibiotic alternatives. Given the risks of oral antibiotics for acne and threat of AMR, there is also an impetus for the development of novel acne therapies.

# MAIN ANALYSIS

**Table 1**. Characteristics of the LRTI, SSTI and UTI study populations at cohort entry stratified by acne antibiotic exposure status. Values are numbers (percentages) unless stated otherwise.

| | LRTI | | | SSTI | | | UTI | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Study population** | **With oral antibiotic for acne** | **Without oral antibiotic for acne** | **Study population** | **With oral antibiotic for acne** | **Without oral antibiotic for acne** | **Study population** | **With oral antibiotic for acne** | **Without oral antibiotic for acne** |
| | n=114,770 | n=49,772 (43.4%) | n=64,998 (56.6%) | n=73,648 | n=33,096 (44.9%) | n=40,552 (55.1%) | n=94,017 | n=41,899 (44.6%) | n=52,118 (55.4%) |
| **Follow-up*** | | | | | | | | | |
| Total person-years | 1,704,070 | 678,578 | 1,025,492 | 1,054,645 | 437,111 | 617,533 | 1,250,025 | 530,444 | 719,580 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.4) | 12.4 (7.6-18.5) | 14.7 (9.0-21.6) | 13.1 (8.1-19.5) | 12.1 (7.4-17.8) | 14.1 (8.7-20.8) | 11.9 (7.1-18.2) | 11.3 (6.8-17.2) | 12.3 (7.2-19.0) |
| **Sex** | | | | | | | | | |
| Female (%) | 72,186 (62.9%) | 30,962 (62.2%) | 41,224 (63.4%) | 43,418 (59.0%) | 19,283 (58.3%) | 24,135 (59.5%) | 88,567 (94.2%) | 39,489 (94.2%) | 49,078 (94.2%) |
| **Age at acne diagnosis**** | | | | | | | | | |
| 8-11 | 1,646 (1.4%) | 673 (1.4%) | 973 (1.5%) | 1,164 (1.6%) | 501 (1.5%) | 663 (1.6%) | 1,472 (1.6%) | 682 (1.6%) | 790 (1.5%) |
| 12-18 | 54,060 (47.1%) | 23,255 (46.7%) | 30,805 (47.4%) | 36,346 (49.4%) | 15,955 (48.2%) | 20,391 (50.3%) | 42,063 (44.7%) | 18,768 (44.8%) | 23,295 (44.7%) |
| 19-25 | 24,501 (21.3%) | 9,777 (19.6%) | 14,724 (22.7%) | 15,932 (21.6%) | 6,785 (20.5%) | 9,147 (22.6%) | 21,979 (23.4%) | 9,017 (21.5%) | 12,962 (24.9%) |
| 26-35 | 23,465 (20.4%) | 10,337 (20.8%) | 13,128 (20.2%) | 13,902 (18.9%) | 6,460 (19.5%) | 7,442 (18.4%) | 20,270 (21.6%) | 9,213 (22.0%) | 11,057 (21.2%) |
| 36+ | 11,098 (9.7%) | 5,730 (11.5%) | 5,368 (8.3%) | 6,304 (8.6%) | 3,395 (10.3%) | 2,909 (7.2%) | 8,233 (8.8%) | 4,219 (10.1%) | 4,014 (7.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | | | | | | | |
| 1(least deprived) | 24,113 (21.0%) | 10,507 (21.1%) | 13,606 (20.9%) | 15,499 (21.0%) | 6,883 (20.8%) | 8,616 (21.3%) | 20,840 (22.2%) | 9,334 (22.3%) | 11,506 (22.1%) |
| 2 | 20,005 (17.4%) | 8,922 (17.9%) | 11,083 (17.1%) | 12,929 (17.6%) | 5,931 (17.9%) | 6,998 (17.3%) | 17,239 (18.3%) | 7,735 (18.5%) | 9,504 (18.2%) |
| 3 | 21,711 (18.9%) | 9,368 (18.8%) | 12,343 (19.0%) | 14,038 (19.1%) | 6,369 (19.2%) | 7,669 (18.9%) | 18,253 (19.4%) | 8,190 (19.6%) | 10,063 (19.3%) |
| 4 | 21,042 (18.3%) | 9,149 (18.4%) | 11,893 (18.3%) | 13,403 (18.2%) | 6,036 (18.2%) | 7,367 (18.2%) | 17,170 (18.3%) | 7,648 (18.3%) | 9,522 (18.3%) |
| 5(most deprived) | 27,899 (24.3%) | 11,826 (23.8%) | 16,073 (24.7%) | 17,779 (24.1%) | 7,877 (23.8%) | 9,902 (24.4%) | 20,515 (21.8%) | 8,992 (21.5%) | 11,523 (22.1%) |
| **Harmful alcohol use (%)***** | 3,189 (6.4%) | 1,235 (2.5%) | 1,954 (3.0%) | 2,242 (6.8%) | 938 (2.8%) | 1,304 (3.2%) | 1,529 (3.6%) | 641 (1.5%) | 888 (1.7%) |
| **Asthma (%)***** | 30,375 (26.5%) | 13,958 (28.0%) | 16,417 (25.3%) | 15,322 (46.3%) | 7,328 (22.1%) | 7,994 (19.7%) | 16,904 (40.3%) | 7,899 (18.9%) | 9,005 (17.3%) |
| **Diabetes (%)***** | 1,566 (1.4%) | 662 (1.3%) | 904 (1.4%) | 1,255 (1.7%) | 604 (1.8%) | 662 (1.6%) | 1,029 (1.1%) | 486 (1.2%) | 543 (1.0%) |
| **Ethnicity** | | | | | | | | | |
| White | 43,585 (38.0%) | 18,069 (36.3%) | 25,516 (39.3%) | 28,544 (38.8%) | 12,313 (37.2%) | 16,231 (40.0%) | 37,726 (40.1%) | 16,186 (38.6%) | 21,540 (41.3%) |
| South Asian | 2,529 (2.2%) | 1,016 (2.0%) | 1,513 (2.3%) | 1,944 (2.6%) | 861 (2.6%) | 1,083 (2.7%) | 2,126 (2.3%) | 888 (2.1%) | 1,238 (2.4%) |
| Black | 928 (0.8%) | 349 (0.7%) | 579 (0.9%) | 813 (1.1%) | 301 (0.9%) | 512 (1.3%) | 755 (0.8%) | 287 (0.7%) | 468 (0.9%) |
| Other | 525 (0.5%) | 190 (0.4%) | 335 (0.5%) | 365 (0.5%) | 148 (0.4%) | 217 (0.5%) | 468 (0.5%) | 170 (0.4%) | 298 (0.6%) |
| Mixed | 470 (0.4%) | 179 (0.4%) | 291 (0.4%) | 306 (0.4%) | 117 (0.4%) | 189 (0.5%) | 471 (0.5%) | 188 (0.4%) | 283 (0.5%) |
| Not stated or missing | 66,733 (58.1%) | 29,969 (60.2%) | 36,764 (56.6%) | 41,676 (56.6%) | 19,356 (58.5%) | 22,320 (55.0%) | 52,471 (55.8%) | 24,180 (57.7%) | 28,291 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure.
** Age at acne diagnosis - eligibility for entry to study population.
*** Based on records closest to index date.
LRTI Lower respriatory tract infection
SSTI Skin and soft tissue infection
UTI Urinary tract infection

**Table 2.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI, SSTI and UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.

Fitted to patients with complete data for all variables included in each model*

| | | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|---|
| **Infection** | | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| LRTI | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 49,572 | 384,215 | 5,096 | **1.08 (1.04, 1.12)** | **1.09 (1.05, 1.13)** | **1.09 (1.05, 1.14)** | **1.08 (1.04, 1.13)** |
| SSTI | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 32,944 | 218,780 | 4,841 | **1.12 (1.07, 1.16)** | **1.12 (1.07, 1.16)** | **1.12 (1.08, 1.16)** | **1.11 (1.07, 1.16)** |
| UTI | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 41,656 | 288,595 | 4,790 | **1.06 (1.02, 1.11)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** |

* Unadjusted model.

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale).

# SECONDARY ANALYSIS

**Table 3.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI, SSTI and UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (nearest antibiotic class prescribed for acne from index date^*).

Fitted to patients with complete data for all variables included in each model*

| | | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** |
|---|---|---|---|---|---|---|---|---|
| **Antibiotic for acne** | | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| **LRTI** | | | | | | | | |
| Tetracycline | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 32,992 | 263,279 | 3,145 | **0.99 (0.95, 1.03)** | **1.01 (0.96, 1.05)** | **1.01 (0.97, 1.06)** | **0.99 (0.95, 1.04)** |
| Macrolide | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 12,233 | 92,803 | 1,351 | **1.14 (1.07, 1.21)** | **1.13 (1.07, 1.20)** | **1.13 (1.07, 1.20)** | **1.13 (1.07, 1.20)** |
| Trimethoprim | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,347 | 28,133 | 600 | **1.77 (1.62, 1.92)** | **1.66 (1.53, 1.81)** | **1.66 (1.53, 1.81)** | **1.77 (1.63, 1.93)** |
| **SSTI** | | | | | | | | |
| Tetracycline | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 21,722 | 146,574 | 3,115 | **1.09 (1.04, 1.14)** | **1.09 (1.05, 1.14)** | **1.10 (1.05, 1.15)** | **1.08 (1.03, 1.13)** |
| Macrolide | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 8,563 | 56,714 | 1,322 | **1.13 (1.07, 1.20)** | **1.13 (1.07, 1.20)** | **1.13 (1.07, 1.20)** | **1.13 (1.06, 1.20)** |
| Trimethoprim | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 2,659 | 15,492 | 404 | **1.35 (1.22, 1.49)** | **1.31 (1.18, 1.45)** | **1.30 (1.18, 1.44)** | **1.32 (1.19, 1.46)** |
| **UTI** | | | | | | | | |
| Tetracycline | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 26,320 | 185,868 | 2,964 | **1.03 (0.99, 1.08)** | **1.02 (0.98, 1.07)** | **1.03 (0.98, 1.07)** | **1.03 (0.99, 1.08)** |
| Macrolide | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 10,405 | 73,228 | 1,138 | **0.97 (0.91, 1.03)** | **0.97 (0.91, 1.04)** | **0.97 (0.91, 1.03)** | **0.97 (0.91, 1.03)** |
| Trimethoprim | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,931 | 29,499 | 688 | **1.47 (1.36, 1.59)** | **1.48 (1.37, 1.60)** | **1.48 (1.36, 1.60)** | **1.46 (1.35, 1.58)** |

^* Where two oral antibiotics for acne are prescribed.

* Unadjusted model.

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale).

**Table 4.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI, SSTI and UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (furthest antibiotic class prescribed for acne from index date

| | | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** |
|---|---|---|---|---|---|---|---|---|
| **Antibiotic for acne** | | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| **LRTI** | | | | | | | | |
| Tetracycline | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 33,245 | 265,890 | 3,197 | **1.00 (0.96, 1.05)** | **1.02 (0.98, 1.07)** | **1.03 (0.98, 1.07)** | **1.00 (0.96, 1.05)** |
| Macrolide | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 12,287 | 91,921 | 1,359 | **1.14 (1.07, 1.21)** | **1.13 (1.07, 1.20)** | **1.13 (1.07, 1.20)** | **1.14 (1.07, 1.21)** |
| Trimethoprim | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,040 | 26,404 | 540 | **1.69 (1.55, 1.85)** | **1.59 (1.46, 1.74)** | **1.59 (1.46, 1.74)** | **1.69 (1.55, 1.85)** |
| **SSTI** | | | | | | | | |
| Tetracycline | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 22,200 | 151,096 | 3,136 | **1.07 (1.02, 1.12)** | **1.08 (1.03, 1.13)** | **1.08 (1.03, 1.13)** | **1.06 (1.02, 1.11)** |
| Macrolide | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 8,216 | 53,171 | 1,313 | **1.18 (1.11, 1.25)** | **1.17 (1.10, 1.24)** | **1.17 (1.10, 1.24)** | **1.17 (1.10, 1.24)** |
| Trimethoprim | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 2,528 | 14,513 | 392 | **1.41 (1.27, 1.56)** | **1.36 (1.23, 1.51)** | **1.36 (1.22, 1.51)** | **1.38 (1.24, 1.53)** |
| **UTI** | | | | | | | | |
| Tetracycline | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 26,701 | 188,098 | 2,982 | **1.04 (0.99, 1.09)** | **1.03 (0.98, 1.07)** | **1.03 (0.98, 1.07)** | **1.03 (0.99, 1.08)** |
| Macrolide | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 10,110 | 70,796 | 1,137 | **0.98 (0.92, 1.04)** | **0.98 (0.92, 1.05)** | **0.98 (0.92, 1.05)** | **0.98 (0.91, 1.04)** |
| Trimethoprim | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,845 | 29,701 | 671 | **1.44 (1.33, 1.56)** | **1.45 (1.34, 1.57)** | **1.45 (1.34, 1.57)** | **1.43 (1.32, 1.55)** |

^* Where two oral antibiotics for acne are prescribed.

* Unadjusted model.

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^^ Estimated hazard ratios from Cox regression with current age as underlying timescale).

**Table 5.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI, SSTI and UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for 28 days for acne to those who have not by duration of oral antibiotic for acne (nearest oral antibiotic for acne within five years prior to index date^*).

Fitted to patients with complete data for all variables included in each model*

| Duration acne antibiotic | | Number | Person years at risk | Events | Unadjusted model* Hazard ratio (95% CI)^ | Model 1** Hazard ratio (95% CI)^ | Model 2*** Hazard ratio (95% CI)^ | Model 3**** Hazard ratio (95% CI)^ |
|---|---|---|---|---|---|---|---|---|
| **LRTI** | | | | | | | | |
| 28-41 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,726 | 14,271 | 183 | **1.07 (0.92, 1.24)** | **1.08 (0.93, 1.25)** | **1.08 (0.93, 1.25)** | **1.07 (0.92, 1.24)** |
| 42-90 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 40,126 | 310,624 | 4,065 | **1.07 (1.03, 1.11)** | **1.07 (1.03, 1.12)** | **1.07 (1.03, 1.12)** | **1.07 (1.03, 1.11)** |
| 91-180 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 5,500 | 42,632 | 570 | **1.05 (0.96, 1.15)** | **1.07 (0.99, 1.17)** | **1.08 (0.99, 1.18)** | **1.06 (0.97, 1.15)** |
| 181 - 365 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,653 | 12,640 | 193 | **1.22 (1.06, 1.41)** | **1.26 (1.09, 1.46)** | **1.27 (1.10, 1.47)** | **1.23 (1.06, 1.42)** |
| > 365 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 567 | 4,047 | 85 | **1.85 (1.49, 2.29)** | **1.94 (1.56, 2.40)** | **1.94 (1.57, 2.41)** | **1.84 (1.48, 2.28)** |
| **SSTI** | | | | | | | | |
| 28-41 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,143 | 7,957 | 167 | **1.07 (0.92, 1.25)** | **1.07 (0.92, 1.25)** | **1.07 (0.92, 1.25)** | **1.06 (0.91, 1.24)** |
| 42-90 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 26,283 | 175,946 | 3,681 | **1.06 (1.02, 1.11)** | **1.06 (1.02, 1.11)** | **1.06 (1.02, 1.11)** | **1.06 (1.01, 1.10)** |
| 91-180 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 3,958 | 25,308 | 650 | **1.22 (1.13, 1.33)** | **1.23 (1.13, 1.34)** | **1.24 (1.14, 1.34)** | **1.22 (1.12, 1.32)** |
| 181-365 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,140 | 7,066 | 232 | **1.58 (1.39, 1.81)** | **1.60 (1.40, 1.82)** | **1.61 (1.41, 1.83)** | **1.59 (1.39, 1.81)** |
| > 365 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 420 | 2,503 | 111 | **2.44 (2.02, 2.95)** | **2.49 (2.06, 3.01)** | **2.50 (2.07, 3.03)** | **2.44 (2.02, 2.95)** |
| **UTI** | | | | | | | | |
| 28-41 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,425 | 9,964 | 177 | **1.16 (1.00, 1.35)** | **1.16 (1.00, 1.35)** | **1.16 (1.00, 1.35)** | **1.16 (0.99, 1.34)** |
| 42-90 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 34,066 | 237,498 | 3,883 | **1.06 (1.02, 1.11)** | **1.06 (1.01, 1.10)** | **1.06 (1.01, 1.10)** | **1.06 (1.01, 1.10)** |
| 91-180 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,538 | 30,473 | 522 | **1.01 (0.92, 1.10)** | **0.99 (0.90, 1.08)** | **0.99 (0.90, 1.08)** | **1.00 (0.91, 1.10)** |
| 181-365 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,271 | 8,317 | 162 | **1.11 (0.95, 1.30)** | **1.08 (0.93, 1.27)** | **1.09 (0.93, 1.27)** | **1.10 (0.94, 1.29)** |
| >365 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 356 | 2,343 | 46 | **1.33 (1.00, 1.78)** | **1.28 (0.95, 1.71)** | **1.27 (0.95, 1.70)** | **1.31 (0.98, 1.75)** |

^* Where two courses of antibiotics are prescribed with at least 28 days between the end of the previous course and the beginning of the next course

* Unadjusted model.

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale).

LRTI Lower Respiratory Tract Infection

SSTI Skin and Soft Tissue Infection

UTI Urinary Tract Infection

**Table 6.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI, SSTI and UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not by duration of oral antibiotic for acne (furthest oral antibiotic for acne within five years prior to index date^*).

Fitted to patients with complete data for all variables included in each model*

| Duration | | Number | Person years at risk | Events | Unadjusted model* Hazard ratio (95% CI)^ | Model 1** Hazard ratio (95% CI)^ | Model 2*** Hazard ratio (95% CI)^ | Model 3**** Hazard ratio (95% CI)^ |
|---|---|---|---|---|---|---|---|---|
| **LRTI** | | | | | | | | |
| 28-41 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,713 | 14,238 | 182 | **1.05 (0.91, 1.22)** | **1.06 (0.91, 1.23)** | **1.06 (0.92, 1.23)** | **1.05 (0.91, 1.22)** |
| 42-90 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 39,234 | 305,042 | 3,993 | **1.07 (1.02, 1.11)** | **1.07 (1.03, 1.11)** | **1.07 (1.03, 1.12)** | **1.07 (1.03, 1.11)** |
| 91-180 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 6,064 | 46,200 | 619 | **1.07 (0.98, 1.16)** | **1.09 (1.00, 1.19)** | **1.10 (1.01, 1.19)** | **1.07 (0.98, 1.16)** |
| 181-365 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,915 | 14,166 | 216 | **1.25 (1.09, 1.43)** | **1.28 (1.12, 1.47)** | **1.29 (1.12, 1.48)** | **1.25 (1.09, 1.43)** |
| > 365 days | unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 646 | 4,569 | 86 | **1.65 (1.33, 2.04)** | **1.72 (1.39, 2.13)** | **1.73 (1.40, 2.14)** | **1.64 (1.32, 2.03)** |
| **SSTI** | | | | | | | | |
| 28-41 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,072 | 7,405 | 169 | **1.16 (1.00, 1.36)** | **1.16 (1.00, 1.35)** | **1.17 (1.00, 1.36)** | **1.15 (0.99, 1.34)** |
| 42-91 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 25,760 | 172,751 | 3,648 | **1.07 (1.03, 1.12)** | **1.07 (1.03, 1.12)** | **1.07 (1.03, 1.12)** | **1.07 (1.02, 1.12)** |
| 91- 180 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 4,341 | 27,465 | 686 | **1.18 (1.09, 1.28)** | **1.19 (1.10, 1.29)** | **1.20 (1.11, 1.30)** | **1.18 (1.09, 1.28)** |
| 181-365 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,324 | 8,247 | 254 | **1.49 (1.32, 1.70)** | **1.51 (1.33, 1.71)** | **1.52 (1.33, 1.72)** | **1.48 (1.31, 1.69)** |
| > 365 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 447 | 2,912 | 84 | **1.60 (1.29, 1.99)** | **1.64 (1.32, 2.04)** | **1.64 (1.32, 2.04)** | **1.60 (1.29, 1.98)** |
| **UTI** | | | | | | | | |
| 28-41 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,402 | 10,008 | 171 | **1.09 (0.94, 1.27)** | **1.09 (0.94, 1.27)** | **1.10 (0.94, 1.28)** | **1.10 (0.94, 1.28)** |
| 42 -90 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 33,209 | 232,607 | 3,791 | **1.06 (1.02, 1.11)** | **1.06 (1.01, 1.10)** | **1.06 (1.01, 1.10)** | **1.06 (1.01, 1.10)** |
| 91-180 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 5,108 | 33,557 | 580 | **1.02 (0.93, 1.11)** | **1.00 (0.92, 1.09)** | **1.00 (0.92, 1.09)** | **1.01 (0.93, 1.10)** |
| 181-365 days | unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 1,535 | 9,898 | 198 | **1.16 (1.01, 1.34)** | **1.13 (0.98, 1.31)** | **1.14 (0.99, 1.31)** | **1.15 (1.00, 1.33)** |
| > 365 days | unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | exposed | 447 | 2,912 | 84 | **1.60 (1.29, 1.99)** | **1.64 (1.32, 2.04)** | **1.64 (1.32, 2.04)** | **1.60 (1.29, 1.98)** |

^* Where two courses of antibiotics are prescribed with at least 28 days between the end of the previous course and the beginning of the next course.

* Unadjusted model.

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

LRTI Lower Respiratory Tract Infection

SSTI Skin and Soft Tissue Infection

UTI Urinary Tract Infection

**Antibiotic for acne**

Any oral antibiotic (Tetracycline, macrolide or trimethoprim) prescribed for a minimum duration of 28 days in someone with an acne code is presumed for acne in this study.

**Course**

Sequential covered days comprising a single acne treatment course, which could contain multiple prescriptions. Each course is separated by at least 28 days where no antibiotics are prescribed and there are no covered days.

**Long-term antibiotic**

Any antibiotic prescribed for at least 28 days.

**Index date**

The date of oral antibiotic prescription classically prescribed for infection (LRTI, SSTI, UTI) within seven days of the diagnostic code for the infection.

**Antibiotic treatment failure**

A second prescription of oral antibiotic classically prescribed for an infection within 30 days of index date.

**Box 6.1:** Definitions of terms used in manuscript

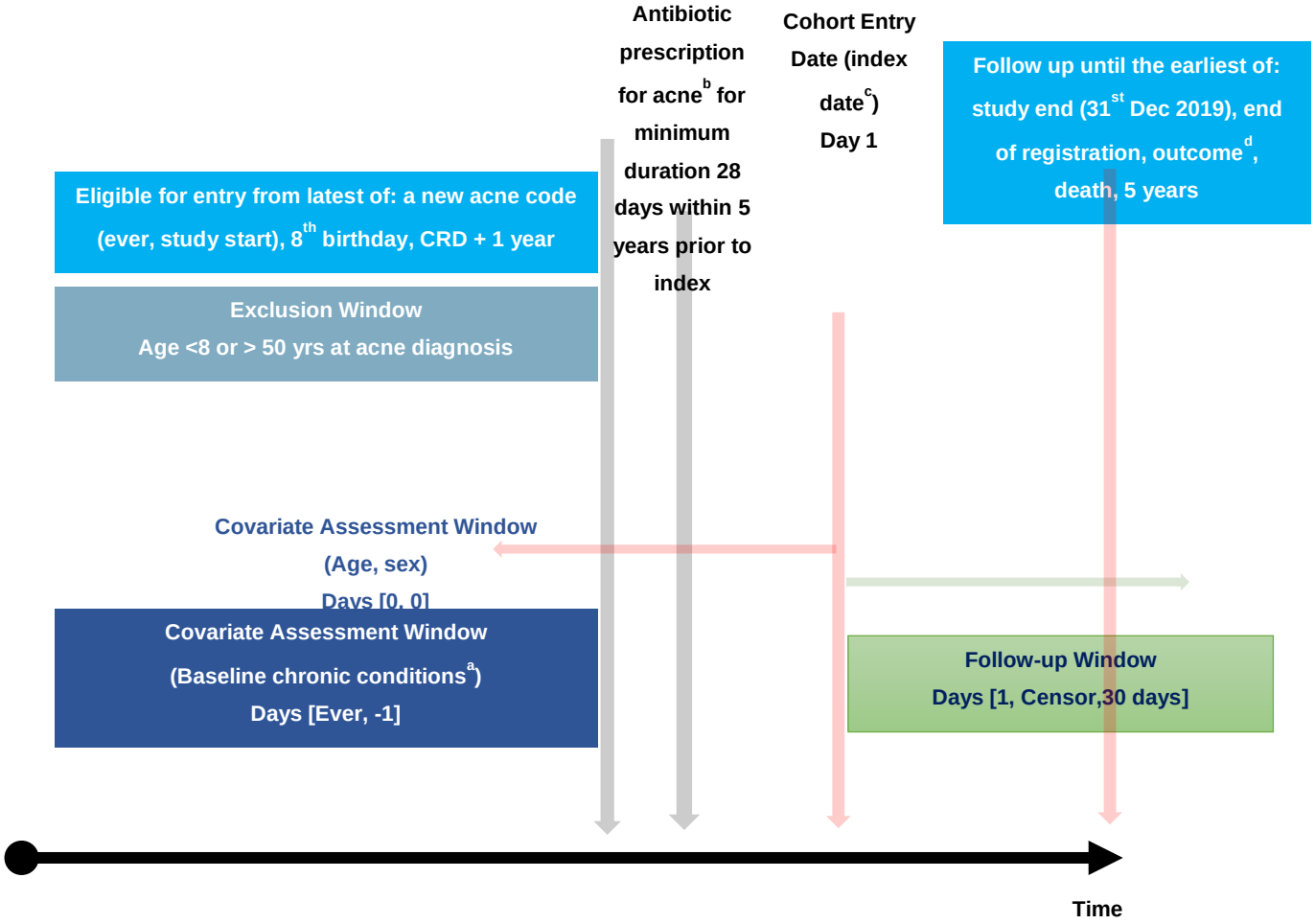

Antibiotic prescription for acne[b] for minimum duration 28 days within 5 years prior to index
Cohort Entry Date (index date[c]) Day 1
Follow up until the earliest of: study end (31st Dec 2019), end of registration, outcome[d], death, 5 years
Eligible for entry from latest of: a new acne code (ever, study start), 8th birthday, CRD + 1 year
Exclusion Window
Age <8 or > 50 yrs at acne diagnosis
Covariate Assessment Window
(Age, sex)
Days [0, 0]
Covariate Assessment Window
(Baseline chronic conditions[a])
Days [Ever, -1]
Follow-up Window
Days [1, Censor,30 days]
Time

**Figure 6.1:** Cohort study design describing study population, cohort entry, covariate assessment period, follow up and cohort exit

a. Baseline conditions included: harmful alcohol use, asthma, diabetes types 1 and 2 (for secondary analysis this further describes the exposure status but does not change the index date)
b. Antibiotic classes for acne – tetracycline, macrolide or trimethoprim
c. First oral antibiotic for LRTI, SSTI or UTI prescribed within 7 days of infection diagnosis
d. Prescription of a second antibiotic course within 30 days of the first antibiotic for an infective episode

SSTI = skin and soft tissue infection
LRTI = lower respiratory tract infection
UTI = urinary tract infection
BNF = British National Formulary
CRD = current registration date with practice
CPRD = Clinical Practice Research Datalink

**Figure 6.2**: flowchart showing the inclusion and exclusion criteria applied to the study population and the LRTI, SSTI and UTI cohort studies.

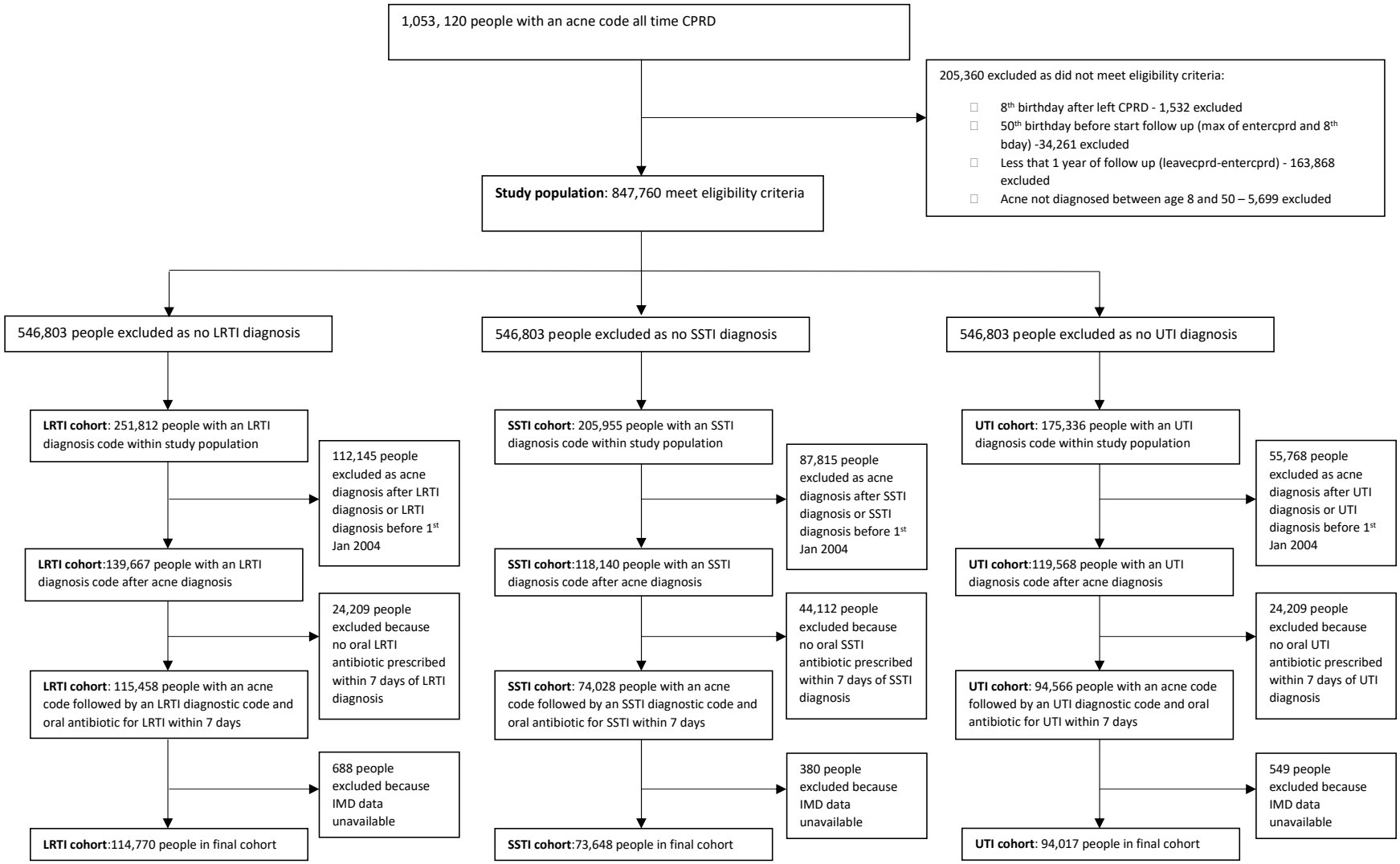
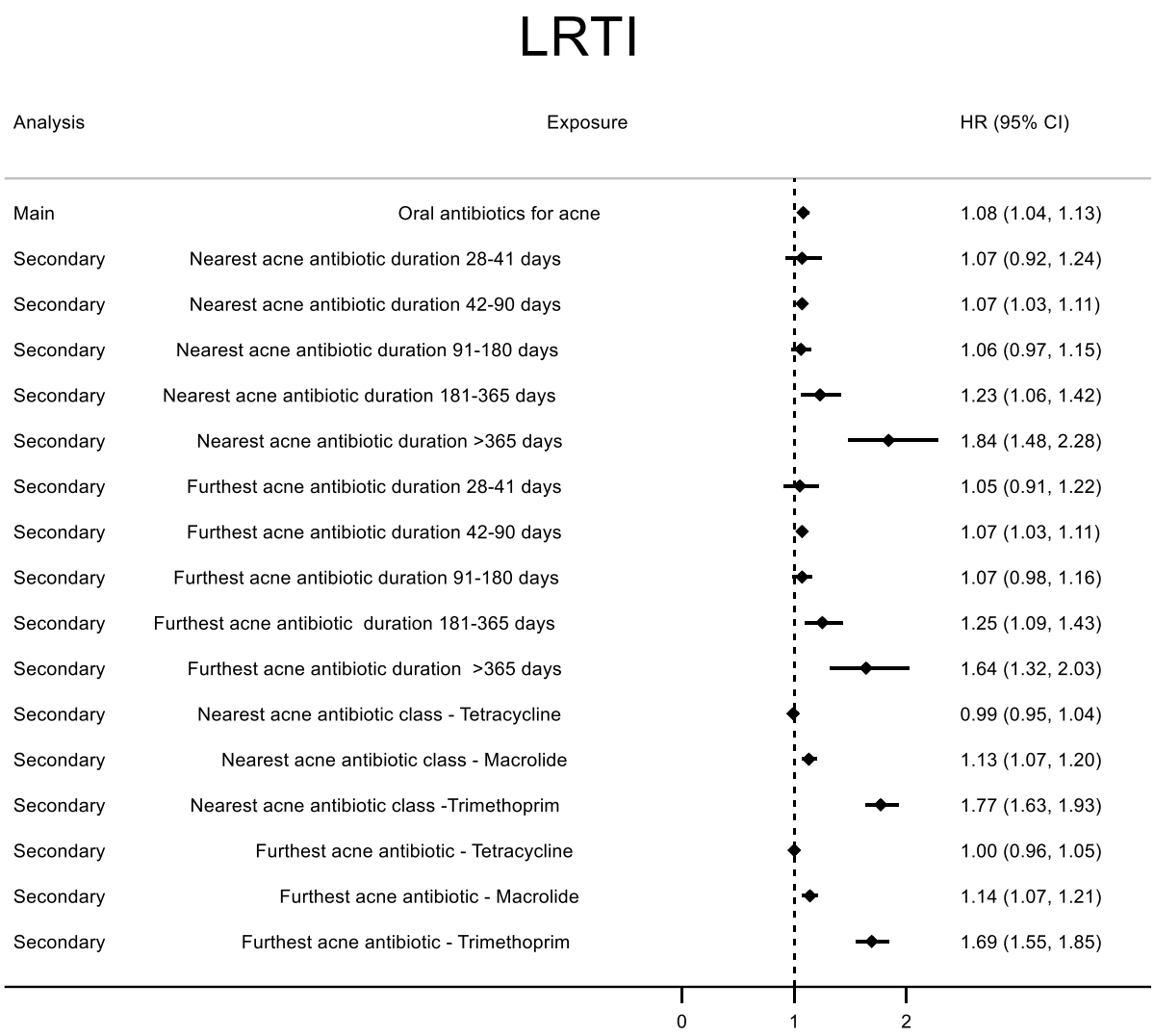
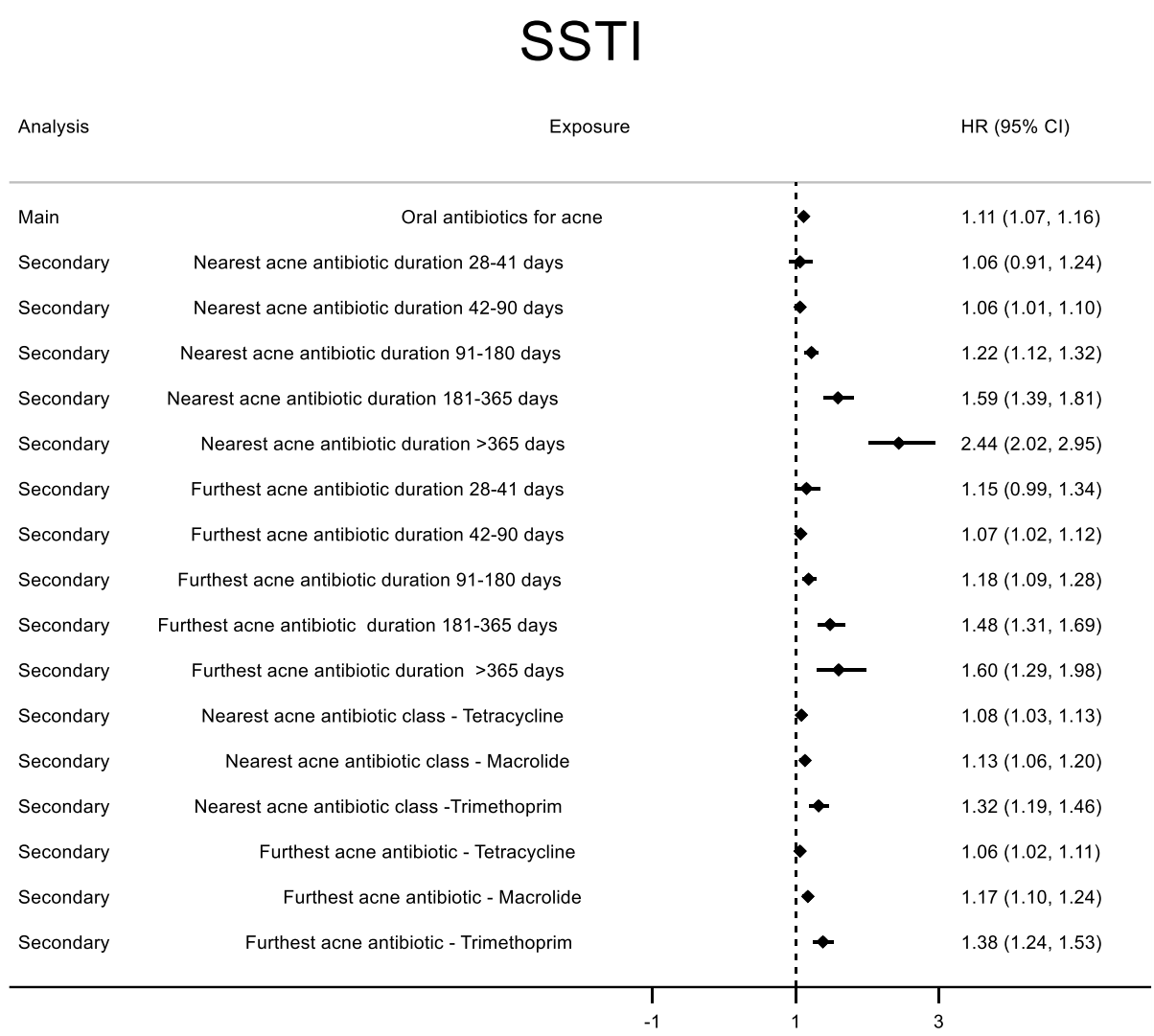


**Figure 6.3 (A):** association of oral antibiotics for acne and antibiotic treatment failure for Lower Respiratory Tract Infection (LRTI).



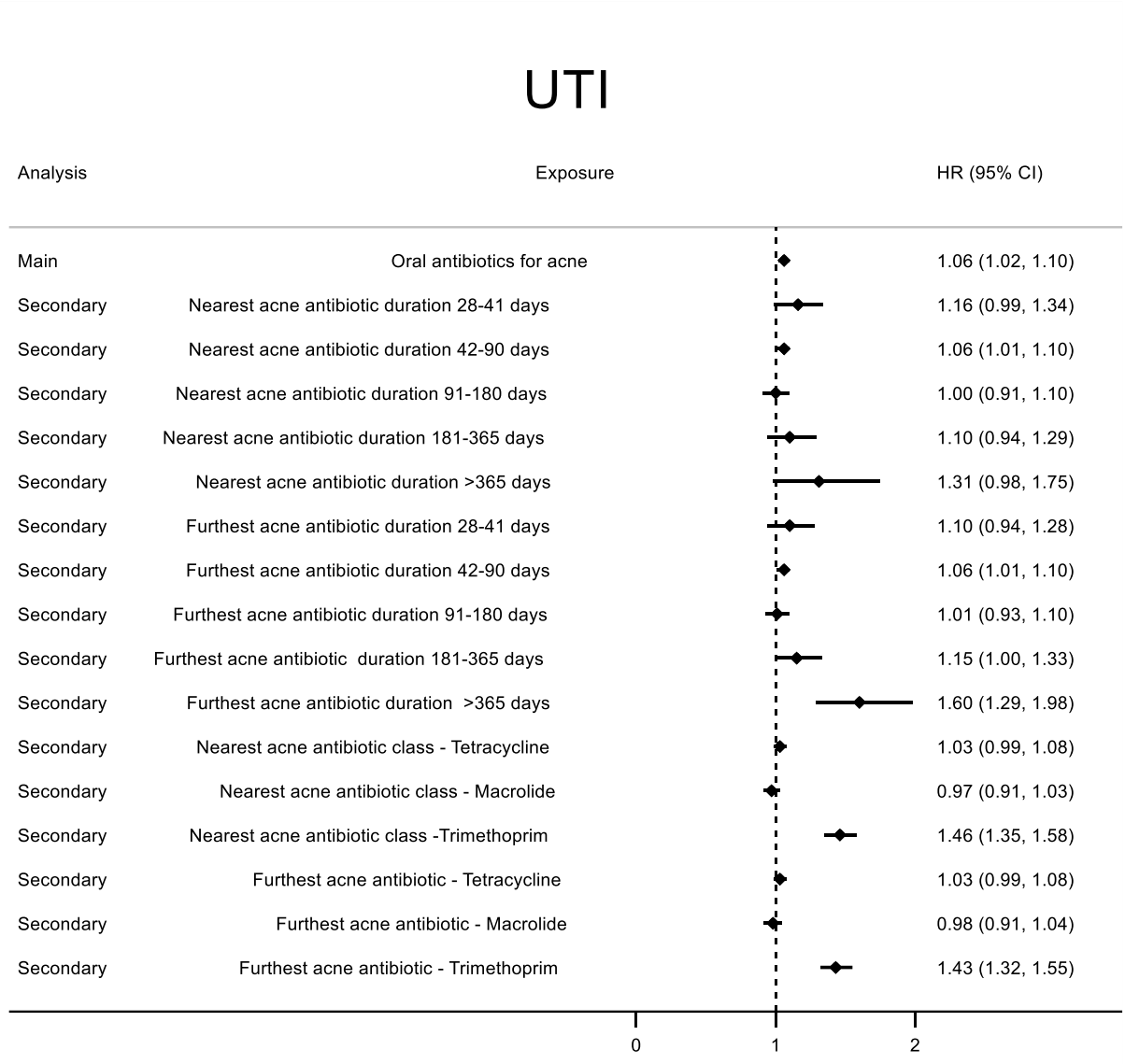

Fully adjusted models adjusted for age, sex, deprivation, harmful alcohol use, diabetes and asthma. Secondary analyses further characterise oral antibiotic for acne into nearest and furthest oral antibiotic prescribed within the five-year period prior to index date, split by duration of antibiotic course and class of antibiotic for acne prescribed.

**Figure 6.3 (B):** association of oral antibiotics for acne and antibiotic treatment failure for Lower Respiratory Tract Infection (SSTI).




Fully adjusted models adjusted for age, sex, deprivation, harmful alcohol use, diabetes and asthma. Secondary analyses further characterise oral antibiotic for acne into nearest and furthest oral antibiotic prescribed within the five-year period prior to index date, split by duration of antibiotic course and class of antibiotic for acne prescribed.

**Figure 6.3 (C):** association of oral antibiotics for acne and antibiotic treatment failure for Lower Respiratory Tract Infection (UTI).




Fully adjusted models adjusted for age, sex, deprivation, harmful alcohol use, diabetes and asthma. Secondary analyses further characterise oral antibiotic for acne into nearest and furthest oral antibiotic prescribed within the five-year period prior to index date, split by duration of antibiotic course and class of antibiotic for acne prescribed.

**Sensitivity analyses**

To test the robustness of our findings we conducted a series of sensitivity analyses summarised in **Table 6.7**. The results of these sensitivity analyses can be found in **Appendix 3**.

| Analysis | Description | Justification |
|---|---|---|
| Sensitivity analysis 1 | Investigate individuals with a new acne code and an oral antibiotic prescription restricted to January 2004 and December 2019. | This is to assess the impact of acne antibiotic prescribing guidelines that were introduced in 2004 on prescribing practices and also to account for the changes in coding practices after the introduction of the 2004 Quality Outcomes Framework (QOF). While QOF did not include specific points for the recording of acne diagnoses or prescribing, overall recording practices may have improved with it's introduction. |
| Sensitivity analysis 2 | Reducing the gap used to definite continuous courses of antibiotics from 28 days to 14 days. This shortens the time for a new prescription to be issued by the GP and the time taken | To explore the sensitivity of our results to an alternative definition of our exposure (long-term oral antibiotic for acne). |

| | | |
|---|---|---|
| | for the patient to collect the antibiotic from a pharmacy. | |
| Sensitivity analysis 3 | Excluding primary immunodeficiency (e.g. common variable immunodeficiency) recorded at any time in medical record prior to index date. | To explore if excluding individuals who may be more at risk of developing an infection affects estimates. |
| Sensitivity analysis 4 | Excluding any cancer within 6 months of index date. | To explore the effect of recent cancer treatment on our main analysis estimates. Cancer treatment may require immunosuppressive medication (e.g., chemotherapy or corticosteroids) making individuals more likely to suffer with infections. |
| Sensitivity analysis 5 | Additionally adjusting for ethnicity, as a confounder related to being prescribed an antibiotic and also seeking treatment for an infection. | We knew a priori from previous work that 58% of data of data on ethnicity are missing so we conducted a complete case analysis limited to January 2004 to December 2019 (given ethnicity data is more completely recorded after this date) in order to examine if excluding ethnicity on our main |

| | | |
|---|---|---|
| | | analysis introduced bias and changed our estimates. We categorised ethnicity into White, Black, South Asian, Other/Mixed.(128) |
| Sensitivity analysis 6 | Restrict our study cohorts to people who have had a GP appointment in the one year prior to index date. | To exclude people who are practice non-attenders and therefore may have differential recording of exposure, co-variates and outcomes compared to practice attenders (ascertainment bias). For example, people who regular attend their GP (e.g. to request antibiotic prescriptions for their acne) maybe more likely to attend and consequently get a second antibiotic prescription for an infection (antibiotic treatment failure). |
| Sensitivity analysis 7 | Limit the infection cohort to include only people with an oral antibiotic prescription on the same day as the diagnostic code for infection (LRTI, SSTI or UTI) | To explore an alternate definition of our outcome, antibiotic treatment failure on the sensitivity of our results. |

| | | |
|---|---|---|
| Sensitivity analysis 8 | Study population limited to women only in the UTI cohort | To ascertain if UTIs in women only affect the estimates in the main analysis given UTIs are rare in men.(153) |

## 6.3 Summary

- The World Health Organisation has that AMR Is one of the top ten global public health threats facing humanity.(1)

- Oral antibiotics are commonly used to treat acne and acne treatment guidelines generally recommend they are continued for at least three months of daily exposure.

- My cohort study aimed to investigate the association between long-term oral antibiotics for acne and antibiotic treatment failure for LRTIs, SSTIs and UTIs using routinely collected primary health care records.

- Oral antibiotics for acne were associated with an 8% increase in antibiotic treatment failure for LRTI; an 11% increase for SSTI; and a 6% increased risk of antibiotic treatment failure for UTI.

- Associations were greater for trimethoprim use for acne than macrolides and tetracyclines and longer durations of oral antibiotic for acne over six months were more strongly associated with antibiotic treatment failure for LRTI and SSTI than shorter durations.

# Chapter 7: Discussion

## 7.1 Introduction

My thesis explored the association between long-term oral antibiotics for acne and antimicrobial resistance (AMR). This chapter aims to summarise the key findings of my research by providing an overview by chapter. I will also discuss the biological plausibility of my findings within the framework of the Bradford Hill Criteria for causality. I will then explain the findings of my research in the context of previous studies in the literature that have investigated long-term oral antibiotics and AMR and then discuss the strengths and limitations of my methodology. I conclude by discussing the implications of my research for prescribing and public health policy and my recommendations for future research.

## 7.2 Summary of key findings (by chapter) / overview of research

*Research question 1: What is the evidence for an association between the long-term use of oral antibiotics for acne and the subsequent risk of antibiotic treatment failure, infection caused by a resistant organism or other evidence of antimicrobial resistance?*

In chapter three, I described my systematic review which included five studies. None of these studies addressed the primary outcome of antibiotic treatment failure or infection caused by a resistant organism. All five studies investigated secondary outcomes: three used bacterial culture methods to investigate the carriage of resistant bacteria in people treated with oral antibiotics for acne, and two investigated the rate of infection following use of oral antibiotics for acne. There was only one randomised controlled trial which compared topical clindamycin 1% along with a tablet placebo, and tetracycline 250 mg twice a day orally along with a topical placebo, where the outcome was the quantity and resistance patterns of skin and intestinal flora.(154) The remaining four studies were cohort studies: Two of the cohort studies by the same leading author investigated the rate of infections following the use of antibiotics for acne.(155, 156) The earliest of the two in 2005 used routinely collected electronic health records from the CPRD (at the time of the study the CPRD was called General Practice Research Datalink or GPRD) to evaluate the association between oral antibiotics prescribed for acne and subsequent upper respiratory tract

infections and UTIs.(155) The second study in 2012 investigated the risk of developing pharyngitis in students with acne receiving antibiotic treatment who were based on one university campus in North America.(156) The final two studies investigated changing resistance patterns among flora following exposure to oral antibiotics for acne. One studied the changing pattern of bowel flora resistance in patients with acne receiving oral erythromycin and tetracycline and family members living in the same household as the patient with acne (157), and the other aimed to investigate changes in the microbial flora of the nose, oropharynx, and faeces following use of systemic isotretinoin and oral antibiotic therapy.(158) The included studies were heterogeneous, particularly with regard to outcomes, hence, it was not possible to perform a meta-analysis. Therefore, I reported the results of the systematic review narratively.

Overall, using Grading of Recommendations Assessment, Development and Evaluation (GRADE), I found low (cohort studies) or very low (randomised controlled trial where there were serious concerns about the randomisation process, deviations from the intended interventions and an overall high risk of bias) quality of evidence to support long-term oral antibiotics for acne being associated with infectious outcomes or AMR.
This systematic review highlighted the dearth of high-quality scientific research on the implications of long-term oral antibiotic use for acne on infectious or AMR sequelae and confirmed a need for further, high quality studies.

*Research question 2: What are the prescribing patterns of oral antibiotics for acne over a five-year time period?*

For research question 2, I used routinely collected health record data from the Clinical Practice Research Datalink (CPRD), to describe the prescription of oral antibiotics for acne in a population of people diagnosed with acne during the five years following initial diagnosis. I found that in a population of 217,410 people diagnosed with acne aged 8 to 50 between January 1st 2004 to 31st July 2019, 96,703 people were prescribed an oral antibiotic for their acne for a minimum duration of 28 days during a median follow up of 5.3 years (Inter quartile range (IQR) 2.8 - 8.5 years). The median duration of each course was 56 days (two months) (IQR 47 – 88 days). I found that 58.2% (n=56,261/96,703) of people who received a

first antibiotic received a second antibiotic prescription, with a gap of at least 28 days between consecutive courses of antibiotic therapy. The median cumulative duration spent on antibiotics for acne per person during follow up was 255 days (IQR 130 – 455). During a median follow of up 5.3 years, participants had a median of four courses of oral antibiotic for acne (IQR 2-6); n=13,452 (13.9%) people were prescribed five or more courses and n=1,715 (1.8%) people were prescribed ten or more courses. The median length of courses of oral antibiotics for acne was 56 days (Inter quartile range (IQR) 47 - 88). The median gap between the first and second course of oral antibiotic for acne was 135 days (IQR 67 - 302 days). The median gap between all courses where more than two courses were prescribed was 119 days (IQR 64 – 260 days).

In summary, I established how oral antibiotics are prescribed in UK general practice for people with acne over a median time period of 5.3 years. Acne guidelines recommend prescribing a three month course of oral antibiotics; I found that people were usually prescribed shorter courses lasting approximately 2 months.(45, 69, 70) My study highlighted the need to understand the consequences of oral antibiotic use for acne, in particular the long-term sequelae of how they may impact upon subsequent antibiotic treatment failure and AMR.

*Research question 3: Using antibiotic treatment failure in infections as a proxy for antibiotic resistance, what are the rates of antibiotic treatment failure in patients with acne who have been treated with long-term oral antibiotics in comparison to patients with acne who have not been exposed to long-term oral antibiotic treatment for their acne?*

In chapter 6, using the CPRD I undertook three cohort studies to investigate the association between oral antibiotics for acne and subsequent antibiotic treatment failure as measured by a repeat prescription of an antibiotic within the following 30 days of an initial prescription for a lower respiratory tract infection (LRTI), skin and soft tissue infection (SSTI) or urinary tract infection (UTI). I found that, after adjusting for confounders, that there was a 6-11% increased risk of subsequent antibiotic treatment failure when being treated with an oral antibiotic for a LRTI (HR 1.08 [1.04-1.13); SSTI HR 1.11 [1.07-1.16]; and UTI HR 1.06

[1.02-1.10] having previously had a long-term oral antibiotic for acne within the previous five years.

Between 1st January 1953 and 31st December 2019, my study population comprised 847,760 individuals between the ages of 8 and 50 with an acne diagnosis. From my study population, after an acne diagnosis, there were 114,770 people with an LRTI treated with an antibiotic and similarly, 73,648 of people with an SSTI receiving antibiotic and 94,017 with a UTI and antibiotic.

**Antibiotic class for acne**

In a series of secondary analyses, I further categorised the oral antibiotic prescribed for acne by (1) duration of treatment and (2) by antibiotic class. Results were mixed, and varied by infection cohort (LRTI, SSTI and UTI). For the nearest antibiotic class in the LRTI cohort, tetracyclines were not associated with antibiotic treatment failure, however there was a 13% increased hazard for macrolides and 77% for trimethoprim. In the SSTI cohort, I observed associations across all three antibiotic classes, with an 8% increased risk of antibiotic treatment failure for tetracyclines, a 13% increased risk for macrolides and 32% increased risk for trimethoprim. In contrast to the LRTI and SSTI cohorts, tetracyclines and macrolides for acne were not associated with antibiotic treatment failure in the UTI cohort, however trimethoprim was associated with a 46% increased risk. A similar mixed pattern of results was seen in the fully adjusted models for the furthest oral antibiotic for acne within the prior five years of the index date. In the LRTI cohort, tetracyclines for acne were not associated with antibiotic treatment failure, however macrolides were associated with a 14% increased risk of antibiotic treatment failure, and trimethoprim a 69% increased risk. In the SSTI cohort, tetracyclines were associated with mildly increased risk of antibiotic treatment failure of 6%, 17 % for macrolides and 38% for trimethoprim. Similar to the LRTIs, tetracyclines for acne were not associated with antibiotic treatment failure for UTIs and were also not associated for macrolides. Trimethoprim for acne however, had a 43% increased risk for antibiotic treatment failure for UTI.

**Duration of antibiotic for acne**

I investigated the association between the duration of oral antibiotic received for acne in each cohort with antibiotic treatment failure, specifically the nearest oral antibiotic

prescribed for acne to the index date and the furthest. In my fully adjusted models for both the nearest and furthest antibiotic, shorter durations of oral antibiotic for acne were less strongly associated with antibiotic treatment failure than longer durations across the LRTI, SSTI and UTI cohorts particularly for durations over six months. For the nearest antibiotic for acne to the index date, for durations of 181 days to 365 days (six months to one year), there was an increased risk of 23% in the LRTI cohort and 59% in the SSTI cohort. There was no association for the UTI cohort in this duration category. For durations greater than 365 days, there was an 84% increased risk of antibiotic treatment failure in the LRTI cohort, 144% increased risk in the SSTI cohort and no association in the UTI cohort.

I found similar trends for the duration categories of the furthest oral antibiotic prescribed for acne. For durations of 181 – 365 days there was a 25% increased risk of antibiotic treatment failure in the LRTI cohort, 48% increased risk in the SSTI cohort and no association in the UTI cohort. There was an increased risk of antibiotic treatment failure in the LRTI and SSTI cohorts for durations of > 365 days: 64% in the LRTI cohort and 60% in both the SSTI and UTI cohorts.

To summarise, I found that there was a small association between long-term oral antibiotics for acne and antibiotic treatment failure when antibiotics are prescribed for LRTI, SSTI and UTI within five years. I found that this association varied by the duration of exposure to oral antibiotic for acne and by the class of antibiotic prescribed for acne.

## 7.3 Biological plausibility – (Bradford Hill Criteria)

In 1965, British statistician Sir Austin Bradford Hill proposed a set of criteria to help establish if a relationship between an environmental factor and a disease is causal or simply an association. In this section, I will apply these criteria to my individual research questions where appropriate.

**Strength of association**

It is generally understood that a large effect estimate provides stronger evidence for an association than a smaller effect estimate. This reason is that small, unrecordable factors which influence results are unlikely to change markedly stronger associations compared to weaker ones and it is possible that a small study could be quite heavily influenced by unmeasured confounding. The hazard ratios (HRs) in the main analyses of my cohort study which investigated long-term oral antibiotics for acne and antibiotic treatment failure were between 1.06 to 1.11 across the LRTI, SSTI and UTI cohort studies with confidence intervals between 1.02 to 1.16. The often-cited example is the ratio of the death rate among cigarette smokers to that among lifelong non-smokers of comparable age for men under 70 years being 2:1.(159, 160) With this in mind, the HRs in my study are lower, and therefore represent a weaker strength of association.

**Dose response relationships**

The demonstration of a dose-response relationship strengthens the argument for causality. In my cohort studies, across most infections, I found that longer durations of oral antibiotics for acne had higher hazard ratios than lower durations for both the nearest oral antibiotic for acne prescribed as well as the furthest. There are no studies in the literature that have examined a dose response relationship between the duration of oral antibiotic prescribed for acne and the risk of antibiotic treatment failure. It was not possible to assess dose response relationships to antibiotic class and type of subsequent infection given the categorical nature of these variables, however using linked secondary care data (HES), I

could investigate the severity of subsequent infections or antibiotic treatment failure as a result of prior exposure to long-term oral antibiotics for acne.

**Consistency**

When several studies conducted at different times, in different settings all show the similar results, according to the Bradford Hill Criteria, this helps strengthen evidence for a causal relationship. Studies of varying designs strengthen the case for causality further, given studies of the same design may be flawed in similar ways. It has not been possible to assess consistency, given my study is novel and there are no other studies investigating the same research question with a similar outcome (antibiotic treatment failure).

**Temporality**

All of the included studies in my systematic review were longitudinal, albeit no studies investigated my primary outcome of AMR or infection with a resistant organism. It is not plausible that people with acne are more likely to develop an infection or AMR when an antibiotic is prescribed for an infection (LRTI, SSTI or UTI) in the absence of antibiotic treatment for acne, therefore this reduces the possibility of findings being due to reverse causality. When identifying my study population for my cohort study, I did not exclude people with an infection code and antibiotic treatment failure prior to their acne code, because of the possibility of introducing selection bias in that there may have been differences in the people who have previously had infections or antibiotic treatment failure to those who have not. However, I used the first diagnostic acne code recorded for all individuals in the CPRD to identify the study population, and only defined people as exposed if they were prescribed a long-term oral antibiotic on the day of, or after their acne code thereby making it more likely that the long-term antibiotic was for acne. Furthermore, exposure status was assigned in the prior five years of the index date.

**Biological plausibility**

While the pathophysiological pathways of bacterial AMR are still being investigated and revised, broadly speaking there are four main mechanisms by which bacterial resistance can develop: 1) by limiting the update of a drug 2) by the modification of a drug target 3) by inactivating a drug and 4) by efflux of a drug.(161) A plausible biological mechanism is that

prior, prolonged, exposure to oral antibiotics for acne, may modify otherwise harmless host bacteria such that they become pathogenic, causing infections and develop one of the aforementioned mechanisms to avoid the effects of antibiotics. Epidemiological studies do not investigate pathophysiological mechanisms, more the clinical manifestations long-term oral antibiotics for acne have. My systematic review found limited evidence for AMR sequelae secondary to oral antibiotics for acne, however there have been studies that have investigated the impact of longer courses of oral antibiotics prescribed for pneumonia and the association with infection recurrence rates and the emergence of AMR, though the duration of courses investigated are shorter than courses typically prescribed for acne.(162, 163) My cohort study showed that longer courses of antibiotics for acne, over 181 days of continuous exposure have higher hazard ratios for the development of antibiotic treatment failure across the LRTI and SSTI cohorts, in keeping with the studies that have found that prolonged exposure to oral antibiotics may provide the selective pressure to drive antimicrobial resistance.(106) Another plausible mechanism is that the use of oral antibiotics for acne could exert selection pressure on non-target, commensal bacteria elsewhere in the body which could develop resistance or provide an environment for opportunistic pathogens to flourish.(10, 97)

**Specificity of association**

To fulfil this criterion of causality, antibiotic treatment failure to infections would only be caused by long term oral antibiotics for acne and by no other mechanism. However, as for many outcome and exposure associations, antibiotic treatment failure could also be caused by other factors such as patient non-adherence with the prescribed antibiotic, a misdiagnosis of a viral infection where antibiotics would be ineffective, or primary infection with a resistant organism. Additionally, antibiotic treatment failure may be multifactorial, with environmental and behavioural factors at play, and as such may have several different aetiological risk factors. It is therefore unlikely that antibiotic treatment failure is caused by a single risk factor.

**Coherence**

While there are no other studies specifically investigating the association between oral antibiotics for acne and antibiotic treatment failure, the positive association I have found is

compatible with laboratory studies that have investigated duration of antibiotic exposure and antibiotic treatment failure. The findings of my cohort study showed that longer courses of antibiotic for acne for durations over six months were more strongly associated with antibiotic treatment failure than shorter courses. Similarly, in a prospective study of 171 children with community acquired pneumonia randomised to a short (five day) or standard (10 day) course of beta-lactam antibiotic, the number of beta-lactam and multi-drug efflux resistant genes per prokaryotic cell was lower in the children who has received the short duration of antibiotics compared to the standard duration.(164)

There have been no observational studies that have investigated antibiotic treatment failure as a result of oral antibiotics for acne. There have however, been studies that have found that longer antibiotic courses are more associated with antibiotic treatment failure than shorter courses.(106) Palin et al found that people who received over six days of antibiotic were more at risk of infection related hospitalisations within 30 days of an infection diagnosis. In summary, there is coherence with other studies investigating antibiotic treatment failure or AMR secondary to antibiotics, however no studies specifically investigate the effects of long-term antibiotics for acne.

**Experiment**

There is no existing evidence in the literature on the association of long-term oral antibiotics for acne and antibiotic treatment failure that have been conducted in observational studies, the finding of which I can compare to my cohort study. In order to provide more evidence in support of a causal link, robust, well conducted interventional studies would be required. I have further discussed the nature of these studies in the final section of the discussion section.

**Analogy**

The risk of antibiotic treatment failure has been studied in the context of short courses of oral antibiotic monotherapies for upper and lower respiratory tract infections, skin and soft tissue infection and acute otitis media.(104) where antibiotic treatment failure was captured using the outcome of a prescription of a second antibiotic within 30 days of the first line antibiotic for the infection. My study specifically investigated the relationship

between antibiotic treatment failure to an infection and previously having been exposed to an antibiotic for acne. Therefore, while there have been no observational studies investigating oral antibiotics for acne and subsequent antibiotic treatment failure, the methodology used in my cohort study is supported by other studies that have investigated antibiotic treatment failure in other contexts.

**Summary**

The Bradford Hill criteria were examined and applied to my cohort study to gather evidence for a causal relationship between long-term oral antibiotics for acne and antibiotic treatment failure. There is some evidence of a dose response relationship, temporality, biological plausibility, coherence and analogy. At present, there is a lack of other studies specifically investigating the resistance sequelae of oral antibiotics for acne. To strengthen the evidence-base for a causal link, further, robust intervention studies are required as well as laboratory studies with evidence of antibiotic resistance at the cellular level.

## 7.4 Explanation of findings in context of previous studies

There have been no previous studies directly investigating long-term oral antibiotics for acne and antibiotic treatment failure or antimicrobial resistance as outlined in my systematic review in chapter 3. My thesis therefore comprises two novel studies, one that is the first to describe how oral antibiotics for acne are prescribed in the UK over five years and the second, a study which investigated the effect of oral antibiotics for acne and antibiotic treatment failure. The methodology I have used and the findings of my studies will be discussed in the context of the previous literature.

**Comparison with other acne drug utilisation studies**

Francis et al described consultation rates, referrals to secondary care and prescriptions for new diagnoses of acne, including oral antibiotics, using the CPRD.(80) The definition of long-term antibiotic was 28 days and similar to my methodology, the authors also excluded people who had been prescribed an acne medication listed in the BNF acne chapter in order to best capture new diagnoses. Their study population comprised 318,535 people aged over

eight years of which 277,250 were prescribed an acne related medication as listed in the BNF acne section. Because only acne medications in the BNF chapter were described, the use of only oxytetracycline, tetracycline, doxycycline, lymecycline, minocycline and erythromycin were described. A total of 167,573 people with new acne diagnoses were included in the study, however oral antibiotic prescribing during the entire one year of follow up was not reported, only oral antibiotic prescriptions provided during the index consultation (date of acne diagnosis). While this information is useful, particularly in terms of assessing adherence to acne guidelines, no conclusions on the overall burden of oral antibiotic prescribing over time could be made.

In comparison to my drug utilisation study, the list of diagnostic codes I complied to identify oral antibiotics for acne was more extensive and included trimethoprim and other macrolide antibiotics for example azithromycin – two antibiotics which are recommended in some guidelines and are prescribed by GPs for acne.(70-72) Acne prescribing practice is region dependent with local practices varying across Primary Care Trusts (PCTs) or Clinical Commissioning Groups (CCGs). There is no single national guideline used (72, 73), (PCTs and CCGs are regional bodies accountable for local care; CCGs replaced PCTs following the Health and Social Care Act in 2012 coming into effect in April 2013). The study by Francis et al also followed people with a new acne diagnosis for one year.(80) Guidelines often recommend a stepwise approach for mild to moderate acne, for example, beginning with topical medication, and if insufficient clinical improvement, to progress to oral antibiotics. Investigating oral antibiotics for acne, therefore requires a longer period of follow up, reflecting the chronicity of the disease, to fully estimate the burden of antibiotic prescribing. My drug utilisation study was therefore conducted with a longer duration of follow-up (median follow up 5.3 years (IQR 2.8 – 8.5 years). Overall, given the differences in study objectives, follow-up, age range of participants and methodology, direct comparisons between this study and my drug utilisation study cannot be made.

**Comparison with other studies using routinely collected health data to investigate AMR**

The methodology of this thesis was inspired by the work of Currie et al who used the CPRD to investigate antibiotic treatment failure in upper and lower respiratory tract infections, skin and soft tissue infections and acute otitis media. (102) The study identified antibiotic

'monotherapies' in the CPRD, that is, prescriptions of an antibiotic separated by no more than 30 days and comprising a single antibiotic agent. The study group investigated antibiotic treatment failure using a prescription of a different antibiotic within 30 days of the first line outcome as one of their outcomes. Antibiotic treatment failure rates across the study period were between 12 and 21%.

Further work by the same group investigated antibiotic non-response rates in adolescents aged between 12 and 17 to upper and lower respiratory tract infections, skin and soft tissue infections and acute otitis media. Over half of the SSTI prescriptions in this study were for acne (acne was included in the SSTI category of infection although it is not an infection, more rather a multifactorial chronic skin disease),(63) however, unlike my study which looked at antibiotic treatment failure as a result of oral antibiotics for acne, this study used the prescription of an alternative antibiotic within 30 days of the first prescribed antibiotic as evidence of antibiotic treatment failure. Given acne is not an infection, and the efficacy of oral antibiotics to treat acne cannot be assessed until six weeks at the earliest, this methodology may not have been optimal because clinically, non-response to acne would not be possible to assess within 30 days.(77) Across the infections studied, using several EHR proxy measures for antibiotic treatment failure, antibiotic non response rates varied between 7.1% and 11.9%.

Lastly, shorter and longer durations of antibiotics prescribed for infection episodes in the CPRD in England were analysed for associations with antibiotic treatment failure using risk of infection related hospitalisations within 30 days of primary antibiotic prescription as the outcome.(106) While the main aim of this study was to assess differences between shorter and longer durations of antibiotic courses (courses lasting up to 30 days), the study found that the overall incidence of infection related hospitalisations was 0.15% and hospitalisation was most likely to occur in the first week following GP consultation. Patients who received antibiotic course durations of 8-15 days were most likely to be hospitalised, and the greatest rate of hospitalisation were for LRTI (LRTI 0.39% vs UTI 0.08%). My cohort study aimed to specifically investigate long-term oral antibiotics for acne (defined by a continuous course of oral antibiotic therapy for a minimum duration of 28 days), therefore the results of this study cannot be directly compared to my study.

## 7.5 Strengths and limitations

I have outlined the strengths and limitations of each study within the manuscripts in chapters 3, 6 and 7. In the section below, I expand on these as well as discuss the specific strengths and limitations of using routinely collected health data for epidemiological studies.

**Strengths**

A major strength to using electronic health records is the large sample size, which meant I had greater precision of effect estimates and sufficient power to study my exposure and outcome combination. As discussed in chapter three, all five studies included in my systematic review were rated as having 'serious' problems with imprecision. Conducting a large cohort study of the same size where people are recruited prospectively into clinical trials versus my cohort study, where data for health records are collected routinely and in real time, over five years for the specific purpose of my study would be very expensive and time consuming.

For the cohort study I used routinely collected health records which means data from consultations during routine care are entered onto IT systems are used to conduct studies. Given data are collected for the primary purpose of medical health records and not for research purposes, healthy participant bias, where healthier and health conscious individuals are able to, or opt into participating in research studies, would be less likely. However, it is possible that GP records may miss individuals who are less able to access care, or are more mobile geographically (e.g. students or people who are homeless) or who have lower English literacy and cannot register with a general practice.

Using routinely collected health data for cohort studies is more likely to reflect what happens in realistic conditions in real world practice.(165) The CPRD is broadly representative in terms of age, sex and ethnicity so therefore results from studies are more likely to generalisable the UK population.(122)

**Limitations**

The studies I conducted using electronic health records used one data source – the Clinical Practice Research Datalink. Strength would be added to my studies if my findings were replicated using alternative data sources. Replicating findings in another data source is applicable to the cohort study, where triangulation would help further determine the strength of evidence for this association. Furthermore, there may be biases using just one data source (described below), and replicating my findings using another data source would increase confidence in my conclusions.

Misclassification

Misclassification is a common limitation of using EHR data to conduct observational studies. GPs enter diagnostic codes onto record systems for a given medical condition. Medical conditions however, may have several code options reflecting varying subtypes of disease or severity and therefore the list of diagnostic codes used can vary across studies using the same data source to investigate the same condition. As such, there is a possibility that some important diagnostic codes are missed or are incorrect. To counteract inaccuracies related to diagnostic codes, I used several steps to formulate my diagnostic code lists (outlined in appendices 2 and 3) which included 1) obtaining previously used lists of diagnostic codes from authors investigating acne and similar infective outcomes; 2) including search terms for both diagnoses and prescriptions within the CPRD and 3) by cross checking terms with a second clinician familiar with CPRD coding. It is also possible that conditions are misdiagnosed by GPs.

Misclassification of *exposure*

While prescriptions of antibiotics for acne are well captured within the CPRD, I do not know if medications were dispensed, then subsequently obtained and consumed by individuals. Individuals incorrectly categorised as exposed would lead to misclassification of exposure - which would bias the results of my cohort study towards the null. Furthermore, my drug utilisation study outlined in chapter 5 found that the median duration of antibiotic courses was 56 days (IQR 47-88), suggesting that some people who were prescribed 28 days of oral antibiotic for acne, contacted their GP for a further second prescription if they were not prescribed 56 days (or two months) from the outset. Lastly, because acne is a chronic skin

condition, and GPs do not necessarily recode a diagnosis of acne with each prescription of an acne medication, I could not be certain that the oral antibiotic prescribed is for acne. There are only a few medical conditions that would require the prescription of a long-term oral antibiotic for similar antibiotic classes in 8 – 50 year old individuals similar to those prescribed for acne: hidradenitis suppurativa (tetracyclines or macrolides) and recurrent UTIs (trimethoprim) are two such examples and the prevalence of both conditions are so low they are unlikely to bias results overall.(147, 148, 166)

Misclassification of *outcome*

There is potential for misclassification of study outcomes, which could have underestimated and biased estimates towards the null. People with viral infections may have visited their GP, and have been prescribed an antibiotic which by default, given the nature of viruses would not have worked to improve the illness. The patient therefore, may have been prescribed a further antibiotic and be classified with the outcome of antibiotic treatment failure. To reduce misclassification of LRTI, I did not include generic codes for respiratory infections, or include codes for upper respiratory tract infection, as most of those are viral in origin. Misclassification would likely to be non-differential and independent of acne or oral antibiotic for acne status (exposure) and so would bias effect estimates towards the null.
In addition, infections are often diagnosed without microbiological samples in primary care, making the likelihood of misdiagnosis higher. To reduce the likelihood of including incorrectly diagnosed infections, my study required people with an infection to have also been prescribed an oral antibiotic on the day the diagnosis was made (or diagnostic code entered) or within the subsequent seven days. While an oral antibiotic prescription linked to an infection diagnosis was a requisite to investigate the outcome of antibiotic treatment failure, using both an oral antibiotic prescription as well as an infection diagnostic code ensured a degree of certainty in the infection diagnosis - as it would be less likely for a GP to prescribe an oral antibiotic for infection if there was diagnostic uncertainty.
People with an SSTI may have been prescribed a topical antibiotic first, then an oral antibiotic later if their infection worsened. In this situation, only more severe SSTIs would be captured for entry into the SSTI cohort. In my study, I required the oral antibiotic to be prescribed within seven days. Given other similar studies using the EHR data have defined infections with the prescription of an oral antibiotic on the same day as the infection code, I

undertook a sensitivity analysis where I limited the infection cohort to include only people with an oral antibiotic prescription on the same day as the index date (same day as the diagnostic code for LRTI, SSTI and UTI), the results of which did not reveal major differences in effect estimates compared to the main analysis (**Appendix 3**).

*Covariates*

There is potential bias for misclassification of covariates. GPs are not required to update lifestyle choices or diagnoses of chronic conditions during patient consultations. For example, a patient could be diagnosed with heavy alcohol use previously however this would be an historic diagnosis and the patient may be abstaining from alcohol at the time of index date and start of follow up. Another example is diabetes, if the patient was diagnosed with diabetes however has subsequently reversed their high sugar levels with dietary modification such that they no longer meet diagnostic criteria for diabetes type 2, then they will still be classified as diabetic in my cohort study. There is argument however, that such patients are 'pre-diabetic' and are more likely to become diabetic and contribute to the covariate effect of diabetes to the association between antibiotics for acne and antibiotic treatment failure, which may go undiagnosed.(167)

Additionally, confounding variables were only included up until the index date across the three infection cohorts. Given follow up duration for the outcome was 30 days from the index date, it is unlikely that misclassification of confounding variables for people with new diagnoses of the covariate in the relatively short time between the index date and 30 days thereafter would have a marked effect on estimates.

<u>Missing data</u>

It is not uncommon for electronic health record data to be missing. For the cohort study, given missingness was independent of the outcome, I conducted a complete case analysis whereby only individuals without missing data were included in my crude and unadjusted analyses.(143) This meant that I made the assumption that missing data for IMD, harmful alcohol use, asthma and diabetes (%) was not associated with antibiotic treatment failure. Multiple imputation requires data to be missing at random. In my cohort study, missing data were unlikely to be missing at random because it is plausible that people who have

symptoms or evidence of a diagnosis are more likely to have it recorded. For example, a patient with symptoms of asthma, is more likely to have that diagnosis recorded by their GP than if they did not experience any symptoms of asthma. Diagnoses in EHR are made by entering a clinical code onto software programmes. The absence of a diagnosis may imply that there is no particular diagnosis present. However, there is a possibility that the diagnosis is present and the data are not entered on to the recording software, or are entered incorrectly. Absent diagnoses would not be accounted for in my analyses.

In my a *priori* protocol I did not place a date restriction on diagnosis of acne (entry into study population) or diagnosis of infection (entry into cohort). Some diagnoses were electronically entered by GPs retrospectively which may contribute to recall bias. Additionally, there may be recording and misclassification biases if diagnoses were not transcribed accurately from paper to electronic medical records which could overall underestimate hazard ratios (bias results towards the null). In sensitivity analysis 1, I restricted entry to my study population by including only individuals who had been diagnosed with acne between January 2004 and December 2019 to assess the impact of acne antibiotic prescribing guidelines introduced in 2004 and to account for changes in recording after the introduction of the 2004 QOF (Quality Outcomes Framework) which may have improved overall recording quality.

Residual confounding

The *a priori* confounding variables I included in my study (harmful alcohol use, asthma and diabetes) were included as binary variables. There are varying degrees of severity of these confounding variables and as such their management, including prescribed medication vary markedly according to severity. This variation in severity may lead to residual confounding which is unaccounted for in my analyses.

Statistical power

I used EHR data for the cohort study to investigate long-term oral antibiotics for acne and antibiotic treatment failure which has the benefit of a large dataset which confers statistical power. Despite this, some secondary analyses had very wide confidence intervals reflecting

lower statistical power to detect associations. For example, when analysing the nearest and furthest oral antibiotic duration for acne, the > 365 days duration of acne nearest antibiotic group for both SSTI and UTI yielded wide confidence intervals. These wide confidence intervals reflected the relatively low number of people who had been prescribed >365 days of oral antibiotic for their acne (SSTI exposed n=420, HR = 2.44 (2.02, 2.95); UTI exposed n=356, HR = 1.31 (0.98, 1.75)).

Generalisability

The CPRD study population contains data on individuals residing in the UK. The UK has a higher incidence of acne and has better access to healthcare services in order to obtain oral antibiotic prescriptions for acne than in some LMICs. The results of my cohort study therefore may be generalisable to individuals residing in high income countries however further studies would be needed to investigate associations in LMICs.(63, 86) Furthermore, in some high income countries where healthcare is insurance based, there may also be disparity in access to prescriptions of antibiotics for acne. Lastly, there has been a shift in GP recording software use in previous years, with some practices switching to EMIS from Vision as outlined in chapter four. This switch in software provider has altered the representativeness of CPRD GOLD.

## 7.6 Implications for future research

My thesis includes two novel studies: the first investigated how oral antibiotics for acne are prescribed long-term over several years reflecting the chronicity of acne, at the population level; and the second, investigated antibiotic treatment failure as a result of long-term oral antibiotics in a population of young people with acne.

I have used the use of oral antibiotics in people with acne, a relatively young, healthy population, as a model to investigate antibiotic treatment failure. As previously described, there are several different causes of antibiotic treatment failure, one of which is AMR. Though there are insufficient data in the literature to conclude a direct causal link with oral antibiotics for acne and antibiotic treatment failure or antimicrobial resistance, given the

imminent global threat of antimicrobial resistance my thesis has highlighted the urgent need to further understand the consequences of oral antibiotics for acne in terms of AMR. Furthermore, my thesis has highlighted the need for the implementation of antibiotic stewardship initiatives surrounding the use of oral antibiotics for acne and additionally the need for establishing effective antibiotic alternative treatments for acne.(13) I will further discuss future research agenda below.

*Understanding the potential causal link between oral antibiotics for acne and antibiotic treatment failure*

As outlined earlier in the discussion section, there are various ways in which a potential causal link between oral antibiotics for acne and antibiotic treatment failure can be strengthened. Replicating findings, using similar methodology from another population such as in Denmark or Sweden where routinely collected EHR data are available would further strengthen the case for causality.

*Further using the CPRD and linked data sources to investigate other outcomes of antibiotic treatment failure*

To further capture antibiotic treatment failure, I could use other outcome measures in EHR data. The CPRD has linked secondary care data for people living in England. Additional measures of antibiotic treatment failure may include: 1) a GP record of admission to hospital with an infection related diagnosis within 30 days of antibiotic initiation using the Hospital Episode Statistics (HES) Admitted Patient Care linked data; 2) a GP referral to an infection related specialist service within 30 days of initiation; 3) a GP record of an emergency department visit within three days of initiation (the shorter time window being selected here to increase the probability that the emergency event was related to the infection) using the HES Accident and Emergency linked data and 4) a GP record of death with an infection related diagnostic code within 30 days of initiation of a prescription for a different antibiotic drug within 30 days of the first line antibiotic using the Office for National Statistics (ONS) mortality linked data.(102, 104, 146) Using other proxy measures of antibiotic treatment failure in the CPRD would further add strength to a causal argument. It should be noted however, that Hospital Episode Statistics (HES) data only provides linkage for people living in England, and ONS mortality data only provide linkage for people living in

England and Wales therefore sample sizes would be reduced. CPRD Aurum is a database which includes data on 883 general practices and had data on about 23 million people. Data are collected using EMIS recording software unlike the CPRD GOLD which uses Vision. Antibiotic prescribing in CPRD GOLD and CPRD Aurum are similar.(168) Further using the CPRD Aurum to replicate the same study would contribute to strength of association because CPRD Aurum has data on 23.1 million people and would include people registered with GPs not in the same practices as those included in CPRD GOLD.(168)

*Optimising the use of oral antibiotics for acne*

Long-term oral antibiotics are the mainstay of treatment for moderate to severe acne in primary care, however there is relatively little research on their optimum use in terms of timing, healthcare setting and duration of continuous courses.(45, 69, 70, 77, 81, 97). There is also relatively little evidence about the long-term effectiveness of oral antibiotics for acne. Further prospective studies are required to understand the relapse rate of acne treated with oral antibiotics over a long period of follow up reflecting the chronicity and intermittent nature of acne. Cohort studies using data sources where individuals are objectively assessed by health care professionals over several years in a physical examination would be ideal. The Avon Longitudinal Study of Parents and Children (ALSPAC) is a cohort of pregnant mothers in the early 1990's whose offspring have been followed up for over 30 years. Data in ALSPAC include yearly skin examinations on a subset who are invited to attend a physical examination, where acne is described morphologically and with an overall grade of severity by trained health professionals. Because over-the-counter and prescribed treatments are readily available for people with acne, there are relatively few studies that describe the natural history of acne. Such descriptive data on the natural history of acne could provide valuable hypothesis generating directions for the optimal timing of oral antibiotics for acne in the disease process.(63, 86, 169)

*Investigating the relationship between long-term oral tetracyclines for acne and the rate of subsequent MRSA infection and antibiotic treatment failure.*

Doxycycline is recommended in the treatment of MRSA infection.(91) Literature suggests that exposure to oral antibiotics is clearly associated with MRSA.(90) Further work could

therefore specifically investigate the use of oral antibiotics for acne and the risk of subsequent MRSA infection.

*Need for oral antibiotic alternatives for acne management*

While my thesis focuses on antibiotic treatment failure to infections after having had a long-term oral antibiotic for acne, there are other side effects of long-term oral antibiotics. There is a potential association with oral antibiotics for acne and with inflammatory bowel disease.(170) A cohort study using the THIN database (The Health Improvement Network) comprising primary care electronic health records found an association between antibiotics for acne and inflammatory bowel disease, in particular doxycycline for acne and Crohn's disease (adjusted HR = 2.25; 95% CI, 1.27–4.00), however it is not clear if acne or acne severity is related to Crohn's disease. There have also been suggestions of an association with both colorectal carcinoma (odds ratio (OR) 1.26, 95 % CI 1.11-1.44) and colorectal adenoma - a precursor to colorectal carcinoma OR 1.36 (95% CI 1.03 - 1.79) for use of antibiotics ≥ two months in women aged 20-39 and in women aged 40-59 OR 1.69 (95% CI 1.24 - 2.31)). (171, 172) Finally, there have also been associations described with antibiotics and breast cancer (OR 1.45 (1.24 - 1.69) with 1-50 cumulative days of antibiotic use.(173) While there are insufficient data for a causal association between oral antibiotics and other disease processes, there is growing evidence in favour of establishing alternative forms of non-antibiotic acne treatment for moderate to severe acne.(97) Isotretinoin, an orally taken vitamin A derivative, is the gold standard acne treatment for acne and is usually reserved for people with acne refractory to oral antibiotic treatment, or, earlier in the case of acne scarring. At present, isotretinoin is reserved for secondary care and in the UK, can only be prescribed by dermatologists. There is however, insufficient evidence to supports its earlier, intermittent or low dose use in terms of clinical effectiveness and relapse rates.(174-178) Further work would involve an observational or randomised controlled trial with long-term follow up to investigate how to use oral isotretinoin for acne optimally, particularly it's earlier use given it is the only known disease modifying drug in use for acne.

Isotretinoin, while having lower relapse rates than other medicines licensed for acne, has a relatively unfavourable side effect profile, including being highly teratogenic and therefore

necessitating monthly pregnancy tests for females. Such frequent secondary care medical encounters are expensive and arduous for the young population who are treated, particularly in terms of missed days from work or school. Spironolactone, an aldosterone receptor antagonist, is used to treat women with acne and is unlicensed. Though there is a study ongoing in the UK comparing spironolactone to placebo (179), further studies to establish the efficacy and risk profile of spironolactone in comparison to oral antibiotics, isotretinoin and the combined oral contraceptive are key to understand relative efficacy and to compare side effect profiles. Lastly, there have been no new classes of medical acne treatment for acne for over 40 years. Newly released drugs have involved combination treatments of existing drugs or topical forms of orally taken drugs such as clascoterone (topical androgen receptor antagonist, derived from spironolactone).(180) Greater funding of drug development for acne is essential to create oral antibiotic alternatives.

*Better understanding of the modifiable risk factors for acne*

The aetiology of acne is multifactorial and is likely to be a complex interaction between genetic and environmental factors.(63, 86, 181) Several studies have investigated modifiable risk factors particularly the association of chocolate, high-glycaemic diets and high fat foods with acne, however definitive evidence is lacking, given the inherent difficulties and biases with conducting robust dietary studies. The ALSPAC (Children of the 1990's) cohort carries information on skin examinations and dietary data from questionnaires and food diaries. A cohort study investigating diet and acne could be undertaken using ALSPAC data. Further studies on diet and acne would add to the growing body of data on modifiable risk factors for acne. A greater understanding of modifiable risk factors would highlight certain behaviours or diets that worsen acne, which could be included in treatment plans that in turn, could lead to reduced exposure to oral antibiotics for acne.

*The relationship between particular antibiotic classes for acne and the class of antibiotic prescribed for the subsequent infection*

There is some evidence of 'cross resistance' where if a patient is treated with antibiotic A, resistance develops to antibiotic B during subsequent treatment (**Figure A3.3,** Supplementary material for cohort study, page 262).(97, 182) Cross resistance could occur within classes but also between classes.

In the secondary analyses of my cohort study outlined in chapter 6, when investigating antibiotic classes for acne and subsequent antibiotic treatment failure, I found that trimethoprim for acne had higher hazard ratios in support of antibiotic treatment failure for both the nearest and furthest antibiotic for acne, across all three infection cohorts. I also noted varying hazard ratios of antibiotic treatment failure by the infection being treated in my main analyses (LRTI HR 1.08 [1.04-1.13], SSTI HR 1.11 [1.07=1.16] and UTI HR 1.06 [1.02-1.10]. It would be clinically useful to understand if particular antibiotic classes for acne in combination with certain antibiotic classes for an infection have a greater or lesser likelihood of antibiotic treatment failure and AMR, and if this varies by the type of infection being treated. This could be investigated using EHR data using the CPRD.

*Investigating the relationship between long-term oral tetracyclines for acne and the rate of subsequent MRSA infection and antibiotic treatment failure*

Doxycycline is recommended in the treatment of MRSA infection.(90) Literature suggests that exposure to oral antibiotics is clearly associated with MRSA.(90) Further work could therefore specifically investigate the use of oral antibiotics for acne and MRSA infection.

## 7.7 Implications for prescribing and public health policy /clinical practice

Antibiotic resistance poses a significant threat to public health.(183) To help prevent the development of bacterial resistance, it is important to prescribe antibiotics according to the principles of antimicrobial stewardship, for example, by limiting unnecessary and prolonged exposure to antibiotics. While several definitions of antimicrobial stewardship exist, one of

the more widely used is a 'strategy, or a coherent set of actions which promote using antimicrobials responsibly, where the specific action depends on the role of the individuals within the healthcare system'.(108) My study in chapter 5 found a median of four courses of long-term oral antibiotic are prescribed for people with acne and that each course has a median duration of 56 days (IQR 47 - 88 days), which is not in keeping with three months as recommended in major acne treatment guidelines.(45, 69, 70). My findings indicate a requirement for a stewardship initiative to improve the use of oral antibiotics to treat acne.

*Implementation of an intervention followed by quality improvement / national audit*

The implementation of algorithms, prescribing tools or alerts appearing on online prescribing interfaces that GPs use could ensure more rigorous prescribing practices of oral antibiotics for acne in keeping with prescribing guidelines. A similar system could alert the patient on the NHS app with a popup when they login to request a repeat prescription of oral antibiotic. Such an alert may work to limit the duration of prolonged courses, but also inform patients with acne that three months of oral antibiotic are recommended to complete the course. After the implementation of an intervention to encourage better prescribing of oral antibiotics for acne in line with guidance, a national audit would highlight prescribing shortfalls nationally and to individual practices so that practice can be modified to be more adherent with acne treatment guidelines.

## 7.8 Conclusions

My thesis has focused on the use of oral antibiotics for acne and antimicrobial resistance. Firstly, my systematic review gathered evidence on the use of long-term oral antibiotics for acne and the association with antibiotic treatment failure, infection with a resistant organism or antimicrobial resistance. My findings were inconclusive, and found weak evidence in support of an association. Secondly, in my drug utilisation study of oral antibiotics for acne, I established how oral antibiotics are being prescribed for acne over a median 5.3 years in UK primary care, thus identifying the burden of long-term oral antibiotic prescribing for acne. Lastly, I tested the hypothesis that long-term oral antibiotics for acne are associated with subsequent antibiotic treatment failure to when treating infections. To my knowledge, there have been no other studies that have described the use of long-term oral antibiotics for acne in the UK with follow-up greater than one year, and there have been no studies investigating the association between oral antibiotics for acne and subsequent antibiotic treatment failure.

My findings have shown that oral antibiotics for acne are prescribed for over 40% of people diagnosed with acne in the UK, and that 60% are prescribed a second course of antibiotic. A median of four courses were prescribed for acne with a median cumulative duration of 255 days (8.5 months). I found that each course duration is prescribed for a median 56 days of intended daily exposure. My cohort study revealed a positive association with long-term oral antibiotics for acne and subsequent antibiotic treatment failure when oral antibiotics are used to treat lower respiratory tract infections, skin and soft tissue infections and urinary tract infections. Longer duration courses of oral antibiotic for acne and trimethoprim for acne were associated more strongly than shorter duration courses of oral antibiotic for acne and tetracyclines and macrolides for acne.

Before oral antibiotic prescribing for acne in clinical practice can be changed, further rigorous and large-scale population-based studies that investigate the association between long-term oral antibiotics for acne and antibiotic treatment failure or antimicrobial resistance are required to deepen our understanding on whether there is evidence to

support a causal link and to investigate if reducing exposure to long-term oral antibiotics reduces or mitigates any associated risk of antibiotic treatment failure.

# Appendix 1 – supplementary material to chapter three – systematic review

Published paper 1:

Ketaki Bhate, Liang-Yu Lin, John S Barbieri, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Liam Smeeth, Nick Francis, Rohini Mathur, Sinéad M Langan, Sarah-Jo Sinnott. Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review protocol *BMJ Open* 2020;10**:**e033662. doi: 10.1136/bmjopen-2019-033662

Published paper 2:

Ketaki Bhate, Liang-Yu Lin, John S Barbieri, Clemence Leyrat, Susan Hopkins, Richard Stabler, Laura Shallcross, Liam Smeeth, Nick Francis, Rohini Mathur, Sinéad M Langan, Sarah-Jo Sinnott. Is there an association between long-term antibiotics for acne and subsequent infection sequelae and antimicrobial resistance? A systematic review BJGP Open 9 March 2021; BJGPO.2020,0181 DOI: 10.3399/BJGPO.2020.0181

## CONTENTS

## A1.1 Supplementary tables of systematic review publication

| First author, publication year | Sponsorship | Design | Aims and objectives | Study period | Setting | Study population at recruitment and sampling methods | General study population characteristics | Inclusion criteria (study population at recruitment) | Exclusion criteria (study population at recruitment) | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome category | Outcome definition and ascertainment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Borglund 1984 | Non declared. | Randomised controlled trial. | To study the impact of topical clindamycin compared with oral tetracycline on the skin and intestinal flora in patients with acne vulgaris. | 8 weeks of treatment and 8 weeks of observation with pre treatment observation as well. | Not specified - presume Karolinska, (Dermatology clinic, Sweden). | 20 people from an outpatients department. Study population, recruitment and sampling methods not specified. | 20 otherwise healthy patients (13 female and 7 males aged 16-33 years with a mean age of 18 years) from out-patient department with moderate to severe inflammatory acne of a mean duration of 5 years were included. Patients had received no systemic antibiotics within two months before starting the investigation. | People with moderate to severe inflammatory acne of a mean duration of 5 years were included. Patients had received no systemic antibiotics within two months before starting the investigation.Topical treatment was stopped at least 2 weeks before starting the study. | Not stated | Exposed tetracycline capsules 250mg BD and placebo propylene glycol 5% (BD). | 1% clindamycin phosphate in hydroalcoholic solution and placebo capsules (BD). Ascertainment not described. | Secondary outcome. Minimum Inhibitory Concentration (defined as the lowest concentration of the drug inhibiting growth completely) from faecal and skin samples. Detecting the resistant microbial flora change. | Faecal and skin samples taken for clinical assessment and microbiological sampling 1 week before treatment and at weeks 4 and 8 during treatment. Samples taken at weeks 12 and 16 for microbiological sampling only. Agar pressed against skin on cheek for 10 seconds. |

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| Margolis 2005 | This study was supported by the centers for Education and Research on Therapeutics which is adminstered as a cooperative agreement by the agency for Healthcare Research and Quality (grant HS10399) by grant K24-AR02212 from the National Institutes of Health, Behesda, Md (Dr Margolis); and by a summer student research award from the American Academy of Dermatology Association (Ms Bowe). | Historical Cohort study. | To determine if the long-term use of antibiotics for the treatment of acne results in an increase in either upper respiratory tract infections (URTI) or urinary tract infections (UTI). | 1987 - 2002. | GPRD (General Practice Research Database) - UK primary care. | 5% UK population registered with the GPRD. Data broadly represenative in terms of age, sex and geographical distribution. 1500 GPs and 500 practices across the United Kingdom participated in the GPRD between 1987 and 2001. | 15 - 35 years. 33519 with no antibiotic used, 8499 with an antibiotic used. | One Reed code for acne and a code from the BNF consistent with the use of oral erythromycin and oral tetracycline. Age from 15 - 35 years. | Not specifically stated. Less than 12 months of follow up. | Antibiotic for 6 weeks or more ascertained with a BNF code. Exposure always ascertained before outcome. Exposure determined by BNF code for oral erythromycin or tetracycline for a duration of 6 weeks or more. | Compared to people with an acne code not receiving an antibiotic - oral or topical. | Secondary outcome. Development of 1) URTI eg pharyngitis or 2) UTI. | Clinically diagnosed pharyngitis or UTI within 12 months after the patient was enrolled in the cohort. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Margolis 2012 | NIH R01AR051185. | Prospective cohort study. | To evaluate the association between antibiotics used to treat acne and pharyngitis. | 2007 - 2008 academic year. | Participants recruited throughout campus of University of Pennsylvania in one single academic year. | Participants recruited through the campus of U Penn, urban campus of 10,000 students. All were fulltime undergraduate or graduate students with access to student health services. | Taken from a population of 10,000 individuals approx. Post graduate and undergraduate students. People with acne n=306 and of those n=36 took an oral antibiotic. 273 participants without acne. | Students with and without acne were eligible for this study. Participants were defined as having acne based on 1 of 3 criteria: (1) if they were determined by a trained expert on the day of the visit to have acne, (2) if they were currently using oral or topical treatments specifically for acne, or (3) if they had evidence of acne elsewhere on the body (eg, chest) besides the face. | Isotretinoin use. Enrollement in concomitant cross sectional study (by same authors and reported in the same paper). | Antibiotic exposure had to be documented on the survey prior to the report of pharyngitis. Ascertained via survey. | People without acne, or people with acne receiving no antibiotic - recruited in the same way as those with acne. | Secondary outcome. Rate of pharyngitis infection. | Questionnaires issued to participants at the beginning of fall semester, end of fall semester and near the end of Spring semester. Each time a throat swab for Group A streptococcus (GAS) and a distal tongue swab for Streptococcus salivarius was taken. In the questionnaires they were asked whether they were currently or had recently (within the past 60 days for the first survey and then since the last survey) used antibiotics, and if they had been recently evaluated for pharyngitis (ie, ❽ave you seen a health care provider because you were sick with a sore throat or have you been evaluated for a sore throat within the last 30 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Basak 2013 | None declared. | Prospective cohort study. Authors state study is an RCT however methodology consistent with a cohort study. | To investigate the effects of systemic isotretinoin and antibiotic therapy on the microbial floras of the nose, oropharynx and faces in patients with acne vulgaris. | Cultures from nose, oropharynx and faeces taken at baseline and once a month during 4-6 months of treatment period. | Not specified. | Not specified. | General population not specified. 35 patients were included, 24 female and 11 male patients with moderate to severe inflammatory acne between the ages of 15 and 24 years (20.14 +/- 2.02). | The duration of acne ranged from 4 months to 10 years (55.37 +/- 27.96 months). This study included thirty-[illegible] patients with acne vulgaris who have no history of infectious or systemic diseases and had not been using systemic or topical antibiotics or antiacne therapy for 4 weeks prior to study start. | No systemic or topical antibiotic and antiacne therapy for 4 weeks preceding study entry. | Eleven patients treated with azithromycin [illegible] for three consecutive days, three times a month for 3 months, and 4 patients were treated with doxycycline [illegible] for 3 months. Clinical assessments were performed and severity of disease was determined by using global acne grading system. No information on ascertainment. | Systemic isotretinoin 0.5-1mg/kg/day until cumulative dose of 120mg/kg achieved for 20 patients. Ascertainment not described. | Secondary outcome. Changes to microbial flora of the oropharynx, nose and faeces. | Oropharynx, nose and faeces cultures were taken at baseline and once a month during 4[illegible] 6 months of treatment period. Outcomes were measured using laboratory methods. |
| Adams 1985 | Non declared. | Cohort study. | To assess the effect of tetracycline and erythromycin adminsitration on aerobic bowel flora of acne patients and their relatives. | 1984 - study period approx 14 months. | Not specified - Eleven families. | Not specified. | 26 people, six taking erythromycin and 5 tetracycline each at 500mg/day dose. 7 Women, 4 men, the 15 relatives comprised 1 grandparent, 11 parents, 1 sibling and 2 spouses. All relatives formed part of the same household as the acne patient. | No relatives received antibiotics during the period of assessment. Relatives must have been in the same household as the acne patient. | See previous. | Exposure defined as either 500mg OD erythromycin or tetracycline for acne. Ascertainment not defined. | Relatives who live with the acne patients - not treated for acne who had not had any antibiotic in the previous 1 year. Ascertainment not fully described. | Secondary outcome. Bowel flora resistance to antibiotics. | Resistance of E coli in stool samples to tetracycline, ampicillin, streptomycin, chloramphenicol, neomycin and sulfafurazole using laboratory techniques. Stool samples were obtained before antibiotic therapy started and at monthly intervals between 4 and 14 months. Laboratory methods described in paper. |

**Supplementary table 1:** Study characteristics (author year, design, study period, Setting, Study population at recruitment, exposure definition and ascertainment, Comparator definition and ascertainment, Outcome type, Outcome definition and ascertainment).

| First author, publication year | Population size (n), follow-up time (months) | Enrolled study population characteristics (age) | Enrolled study population (other inc sex) | Participants with the outcome (n, %) or exposure for case-control studies) | Loss to follow up or withdrawing from trials | Statistical analysis method used | Main reported crude results (RR, OR, HR and CI) | Main reported adjusted results | Is dose response seen? | Confounders /covariates measured | Confounders/ covariates adjusted for? | Other additional stratified anaysis/subgroup analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Borglund 1984 | 20 people followed up for 17 weeks (1 week prior to study start, 8 weeks of treatment and 8 weeks post treatment). | 16-33 mean age 18 years. | 13 females and 7 males. | n/a. | 1 participant lost to follow up, individual dropped out after 8 weeks. | Not reported. | Numbers of patients with various bacteria and log reduction in bacterial counts reported. T**etracycline group:** Colon - pronounced changes in colon flora and new colonisation wih tetracycline resistant strains, flora normalised eight weeks after treatment stopped. The numbers of streptococci and enterococci decreased two to three log numbers in 7 patients receiving tetracycline during the treatment period. Enterobacteria also decreased two to three log cycles in 5 patients. Four patients were colonised by new bacterial strains which were all resistant to tetracycline (MIC >4mg/l). The anaerobic bacteria, mainly fusobacteria were also suppressed two-three log cycles in 4 patients during the period of | None reported. | Not reported. | Not reported. | No. | None. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | tetracycline administration. In other patients no significant changes in the number of anaerobic bacteria were observed. After 8 weeks the aerobic colon flora was normalised. Skin - tetracycline resistant staphylococci and entercocci were found before during and after treatment. Resistance to tetracycline during treatment was seen in 40% of the staphylococcal and enterococcal isolates. **Topical clindamycin group:** Colon no changes to colon flora and no diarrhoea. Skin - increase in the number of clindamycin resistant staphylococci during therapy but number decreased after treatment had stopped. Clindamycin-resistant strains among staphylococcal and enterococcal isolates were seen in 60% during treatment. | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Margolis 2005 | 118,496 individuals. Follow up at least 12 months. 33,519 used no antibiotic, 84,977 used an antibiotic. | Average age of the cohorts was 21.4 (5.76 SD) among acne antibiotic users and 21.7 (5.74 SD) among the non users. Median age was 19 (25%-17, 75%-26) among the acne antibitoic users and 20(25%-17, 75%-26) among the non antibiotic users. | 118,496 individuals with acne between 15 and 35. 84,977 were treated with an antibiotic and 33,519 were not. N=1,121 (1.3%) has an oral antibiotic only. 78,650 had an oral and topical antibiotic (92.6%). 44,725 (52.6%) of the acne antibiotic users were female and 21,507 (64.1%) of the non antibiotic users were female. (Antibiotic users includes, oral antibiotic alone, oral and topical antibiotic and topical antibiotic alone). Sex distribution was not reported for oral antibiotic users alone. | Not reported by subtype of antibiotic alone. Within the first year of observation, 18,281 (15.4%) had at least one URTI that was diagnosed by a GP and 4,270 (3.6%) had a UTI diagnosed by a GP. 372 males (0.61% males with acne) and 4976 females (6.40% of females with acne) had a UTI. 3096 (9.2%) vs 15,185 (18.6%) had an URTI in no antibiotic used vs antibiotic used cohorts. | None. | Logistic regression with both single and multiple (multivariate logistic regression) independent variables. Variables described using simple percentages or means with standard deviations. | Only reported for no antibiotic vs antibiotic user so therefore includes topical only. The OR of a URTI developing within the first year of observation among those using antibiotics compared with those not using antibiotics was 2.15 (95% confidence interval [CI], 2.05-2.23; P<0.001). The OR of a UTI developing within the first year of observation in women using antibiotics compared with those not using antibiotics was 1.11 (95% CI, 1.03-1.19; P=.002). | OR oral only compared to non users 2.75 (2.37-3.18). OR topical and oral 1.88 (1.80, 1.96). No interaction between gender, age, frequency of acne associated office visits and the use of acne antibiotics and URTI. Re UTI, OR with antibiotic use in males 1.88 (1.27, 2.78, p<0.002) and in females was 1.87 (1.38, 2.53) oral only and 1.26 (1.16, 1.36) for oral and topical. In men OR was 1.84 (1.23, 2.72) for both oral and topical and 2.22 (0.51, 9.65) oral only. No UTI reported in topical antibiotic use group only. | Not reported. | Yes: age, year of diagnosis, sex, contraceptive use or contraceptive counselling (only for UTIs) practice, history of diabetes, history of asthma. Visit frequency for acne (number office visits for treatment of acne) and the number of prescriptions for acne antibitoics during the 12 months of observation. May not strictly be risk factors but more factors to rule out ascertainement bias i.e. more visits to healthcare providers may happen when a patient is treated with antibiotics. | Yes. | The study split antibiotics with the following categories: topical only, oral only and oral and topical combined. When the cohort with the antibiotic non users was compared with the hypertension cohort, after age and sex were adjusted for, the OR was 0.97 (95% CI, 0.93-1.01), and when the cohort with the acne antibiotic users was compared with the hypertension cohort, the OR was 2.12 (95% CI, 2.00-2.27). |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Margolis 2012 | Population size: n = 579, n=306 with acne and 273 without acne. Follow up time 9 Months approx, early fall semester and end of the spring semester. A total of 579 students participated in the first survey, 359 (62.0%) participated in the second survey, and 312 (53.9%) took part in the third survey. A total of 285 of the students (49.2%) participated in all 3 survey periods, and 193 (33.3%) participated only in the first visit. | Mean 21.7 years. Range 16 - 38 years. (SD 3 years). | 358 female and 218 male. | 11.3% of those receiving oral antibiotic treatment reported pharyngitis (n= 4 approx), compared to 3.3% (n=2 approx) of participants who were not receiving oral antibiotics. | A total of 579 students participated in the first survey, 359 (62.0%) participated in the second survey, and 312 (53.9%) took part in the third survey. A total of 285 of the students (49.2%) participated in all 3 survey periods, and 193 (33.3%) participated only in the first visit. | To account for repeated measures in the longitudinal design mixed-effect logistic regression was used, allowing the repeated measures from the study participants to be expressed as random effects. The selection of variables for the multivariable model was based on purposeful selection (ie, variables thought to be clinically important) and a confounder that altered the effect estimate by more than 10%. | Adjusted OR 95% CI. | OR 4.34 associating oral antibiotic use with pharyngitis adjusted CI 1.51-12.47. Estimated relative risk 3.91. | Not reported. | Yes: age, sex, ethnicity, presence and severity of acne, teeth flossing habits, teeth brushing habits, face washing habits, number of cavities, presence of diabetes mellitus, alcohol use, tobacco use (chewing or smoking). Body piercings (reported in table). | Yes. | None. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Basak 2013 | 35 patients. Follow up for 4-6 months. | 15-24 years (20.14 +/- 2.02). | 24 female and 11 male patients. The duration of acne ranged from 4 months to 10 years (55.37 +/- 27.96 months). The two treatment groups were assigned as isotretinoin treated group (n=20) and age and gender-match antibiotic treated group (n=15). | Re systemic antibiotic: 1 of 15 oropharynx, 1 of 15 nose, and 3 of 15 faeces had differentiation of microbial flora in at least one of all culture samples throughout the treatment period. Before and after the treatment with antibiotic, no patients before and no patients after were colonised with S. aureus in the oropharyngeal and nasal cultures and 3 before (20%) and 5 after (33.3%) had ESBL positive E. coli in the faecal floras before and after the treatments. | Non reported. | Pearson chi-squared, McNemar, logistic regression and Fisher's exact tests were used with the significance level set at P<0.05. Though the results of all these tests are not reported. Table 1 reports the number and % of patients with differentiation of microbial flora in at least one of all culture samples throughout the treatment period using Fisher's exact test and Pearson chi-squared test. Table 2 reports the number and percentage of patients colonised with S. aureus in the oropharyngeal and nasal cultures and ESBL poitive E. coli in the faecal floras before and after hte treatments using the McNemar test. | Number and percentage of patients colonised with S. aureus in the oropharyngeal and nasal cultures and ESBL poitive E. coli in the faecal floras before and after the treatments: Isotretinoin group: Oropharynx: before 3 (15%) after 8 (40%) / Nose: before 3 (15%) after: 14 (70%) / Faeces: before 0 (0%) after 4 (20%) Antibiotic group: Oropharynx: before 0 after 0 / Nose: before 0 after: 0 / Faeces: before 3 (20%) after 5 (33.3%). | None reported. | n/a. | Unclear - not stated. | In results section states isotretinoin and antibitoic group were age and sex matched but this is not clearly reported. | None. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adams 1985 | 26 people from 11 families, six taking erythromycin, 5 tetracycline. Dose 500mg / day. 15 relatives of above antibitoic treated group. Follow up was between 5 and 14 months. | Patients aged between 15 and 24 years (mean 17.6 years). 7 women and 4 men. 15 relatives comprised 1 grandparent, 11 parents, 1 sibling and 2 spouses. All relatives from same household as the patient. No age data from relatives provided. | 7 women and 4 men. Sex distribution of relatives not described. | Percentage E coli resistant individuals in both tetracycline and erythromycin groups changed from baseline pre antibiotic treatment to during treatment: In the erythromycin group tetracycline resistant isolates decreased in patients 5/8 (63%) before treatment to 19/41 (46%) during treatment and increased in relatives 3/11 (27%) before treatment to 26/60 (43%) during treatment. Conversely in the tetracycline treated group, patients 2/6 (33%) before treatment to 61/61 (100%) during treatment and relatives 3/9 (33%) before treatment to 63/69 ( 91%) during treatment. Percentage of patients and relatives resistant (to E coli) to Tetracycline, sulfonamide, ampicillin, chloramphenicol, and neomycin | Non reported. | Not described. Number of antibiotics to which resistant isolates found, n and % resistant to particular antibiotic in the erythromycin and tetracycline group described, and overall % of erythromycin and tetracycline resistant isolates before and during treatment described. "p<0.01" for tetracycline resistance; "p<0.01" for "general increase in antibiotic resistance" with respect to sulfonamide, ampicillin, chloramphenicol, and streptomycin. | n and %. | Non reported. | Not reported. | No. | No. | Number of antibiotics E coli resistant to before therapy compared to during therapy in the erythromycin and tetracycline resistant groups reported in table II. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | increased in the tetracycline group of both acne patients and their relatives before therapy compared to during therapy; streptomycin decreased slightly 15% - 14%. | | | | | | | | |

**Supplementary table 2:** Study results (First author and publication year, design, population size (N), follow up time, people with outcome [or exposure for case-control studies] (N, %), statistical analysis methods used, main reported results, adjusted for).

**Appendix A**: Excluded studies with reasons for exclusion

| Editorial/review | Wrong intervention | Wrong study design | Contacted author – no reply | Contacted author – not relevant | Study related to P. acnes | Wrong indication of antibiotic | Wrong patient population | Wrong outcome | Wrong route of administration of antibiotic | Wrong comparator | Wrong intervention |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Abeck et al, 2003<br>Adams et al, 1995<br>Adler et al, 2017,<br>Chan et al, 2005<br>Chon et al, 2012<br>Del Rosso et al 2007<br>Garrett et al,2012<br>Patel et al, 2010<br>Walsh et al, 2016 | Adetutu et al, 2017<br>Batard et al, 2018 (and wrong indication of antibiotic)<br>Cetin et al, 2014 | Akers et al, 1976<br>Becker et al, 2017<br>Bettoli et al, 2016<br>Bjornberg et al, 1972<br>Bolognia et al, 1997<br>Bromberg et al, 1980<br>Crawford et al, 1990<br>Cremer et al, 1986<br>Cronk et al, 1956<br>Dawson et al, 1998<br>Del Giudice et al 2012<br>Del Rosso et al, 2016<br>Delost et al, 2015<br>Delost et al 2016<br>Fanelli et al, 2011<br>Gloor et al, 1995<br>Goitz et al, 1966<br>Levy et al, 2003<br>Moon et al, 2012<br>Nakase et al, 2014<br>Nakase et al, 2019<br>Ochsendorf et al, 2006<br>Ochsendorf 2006<br>Pierard et al, 1999<br>Santer et al, 2018<br>Sardana et al, 2014<br>Shalita et al, 1972<br>Sitohang et al, 2019<br>Valtonen et al, 1976 | Akamatsu et al, 2001 Bettoli et al, 2011 (also wrong patient population and wrong study design) | Bowe et al, 2004 | Alvarez - Sanchez et al, 2016 (also looking at topical abx), Bahar et al, 2004 (also wrong study design) Cooper et al, 1998 Dreno et al, 2016 | Bernie et al, 2016 ( also wrong intervention) | Miller et al, 1996<br>Moller et al, 1977<br>Rashid et al, 2015 | Bowe et al, 2007<br>Bowe et al, 2006<br>Haas et al, 2018<br>Jackson et al, 2018<br>Lee et al, 2017<br>Moore et al, 2014<br>Moore et al, 2018<br>Moore et al, 2015 | Forssman et al, 1995<br>Forssman et al, 1994 | Eady et al, 1990 | Kieffer et al, 2008<br>Totte et al, 2016 (and wrong study design) |

| First author, publication year | Domain 1: Bias due to confounding | | | Domain 2: Bias in selection of participants into the study | | | Domain 3: Bias in classification of interventions | | | Domain 4 ITT: Bias due to deviations from intended interventions: effects of assignment to intervention | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LYL | JB | KB | LYL | JB | KB | LYL | JB | KB | LYL | JB | KB |
| Margolis 2005 | | Low | Low | | Low | Low | | Low | Low | | NI | NI |
| Margolis 2012 | | Low | Low | | Moderate | Moderate | | Low | Low | | NI | NI |
| Basak 2013 | Critical | Critical | | Moderate | Moderate | | Low | Low | | NI | NI | |
| Adams 1985 | Critical | Critical | | NI | NI | | Low | Low | | NI | NI | |

| Domain 4 PP: Bias due to deviations from intended interventions: Effect of starting and adhering to intervention | | | Domain 5: Bias due to missing data | | | Domain 6: Bias in measurement of outcomes | | | Domain 7: Bias in selection of the reported result | | | Overall bias assessment across all domains | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LYL | JB | KB | LYL | JB | KB | LYL | JB | KB | LYL | JB | KB | LYL | JB | KB |
| | NI | NI | | Low | Low | | Low | Low | | Low | Low | | Low | Low |
| | NI | NI | | Moderate | Moderate | | Serious | Serious | | Low | Low | | Moderate | Moderate |
| NI | NI | | Low | Low | | Low | Low | | Serious | Serious | | Serious | Serious | |
| NI | NI | | NI | NI | | Moderate | Moderate | | Moderate | Moderate | | Serious | Serious | |

**Table 1:** Risk of bias summary showing judgements about each risk of bias domain in ROBINS I and overall bias assessment.

**Borglund 1984 RoB2**

| | LYL | KB |
|---|---|---|
| **Domain 1 Randomisation process** | High | High |
| **Domain 2 Deviations from intended interventions** | High | High |
| **Domain 3 Missing outcome data** | Low | Low |
| **Domain 4 Measurement of the outcome** | Some concerns | Some concerns |
| **Domain 5 Selection of the reported results** | Some concerns | Some concerns |
| **Overall Risk of bas** | High | High |

**Table 2:** Rob2 Risk of Bias assessment for randomised controlled trial: Borglund 1984 et al.

## Summary of findings

| No' studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No' patients | Quality |
|---|---|---|---|---|---|---|---|---|
| **Rate of infection** | | | | | | | | |
| 2 | Cohort | Not serious | Not serious | Not Serious | Serious | No: publication bias, large effect, plausible confounding, dose response gradient | Intervention Total: 79807, Control total: 33792 | ⊕⊕ LOW a,b |
| **Detection of resistant organisms without an infection / Changes to flora/microbiota** | | | | | | | | |
| 3 | 1 RCT and 2 cohort studies | Serious | Not serious | Not serious | Serious | No: publication bias, large effect, plausible confounding, dose response gradient | Intervention total: 36, Control total: 45 | ⊕ VERY LOW c,d,e,f,d,g |

**Explanations**

a. Selection bias - students selected from one university campus.
b. Imprecise estimates: wide 95% confidence intervals.
c. Patients not randomised to treatment - selection bias.
d. Confounding factors not reported or incorporated in analysis.
e. Follow up inconsistent between treatment groups.
f. Confidence intervals not reported and small sample size.
g. No 95% confidence intervals reported: predominantly numbers and percentages reported.

**Table 3:** Summary of findings (GRADE assessment of quality of evidence).

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 4 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 7 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 7 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 8 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | attached |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 18, 9, 10 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 10 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Supplementary Table 1 and 2, pg 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 10, 11 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 10, 11 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Supp Table 1, 2 and table 1 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | n/a |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1, appendix A |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Supp Table 1 and 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supp Table 1,2,and table 1, 2 and 3. Pg 12 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 3 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | n/a |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Table 3 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | n/a |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 2 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

A1.2 Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 31, 2019>

Search Strategy:

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1 acne.mp. (17491)
2 exp Acne Vulgaris/ (11259)
3 1 or 2 (17491)
4 antibiotic*.mp. (355427)
5 exp Antibiotic Prophylaxis/ (13110)
6 exp Anti-Bacterial Agents/ (700080)
7 tetracycline*.mp. (45045)
8 exp Tetracycline/ (19631)
9 exp Tetracyclines/ (46884)
10 lymecycline*.mp. (168)
11 exp Lymecycline/ (119)
12 minocycline*.mp. (8527)
13 exp Minocycline/ (5724)
14 doxycycline*.mp. (16071)
15 exp Doxycycline/ (9287)
16 oxytetracycline*.mp. (8262)
17 exp Oxytetracycline/ (6279)
18 macrolide*.mp. (22555)
19 Macrolides/ (11795)
20 exp Erythromycin/ (24397)
21 erythromycin*.mp. (25510)
22 clarithromycin*.mp. (10167)
23 exp Clarithromycin/ (6062)
24 azithromycin*.mp. (8538)
25 exp Azithromycin/ (4820)
26 dihydrofolate reductase inhibitor*.mp. (346)
27 exp Folic Acid Antagonists/ (57013)

28 trimethoprim*.mp. (21485)
29 exp Trimethoprim/ (11693)
30 exp Trimethoprim, Sulfamethoxazole Drug Combination/ (6696)
31 penicillin*.mp. (82869)
32 exp Penicillin-Binding Proteins/ (3293)
33 exp Penicillin G/ (38077)
34 cephalosporin*.mp. (32358)
35 exp Cephalosporins/ (41273)
36 exp beta-Lactamases/ (22172)
37 fluoroquinolone*.mp. (22199)
38 exp Fluoroquinolones/ (31393)
39 exp Ciprofloxacin/ (12824)
40 aminoglycoside*.mp. (23235)
41 exp Aminoglycosides/ (151256)
42 exp Gentamicins/ (18634)
43 antimicrobial*.mp. (154537)
44 exp Antimicrobial Stewardship/ (725)
45 exp Disk Diffusion Antimicrobial Tests/ (1536)
46 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (1080981)
47 resistance*.mp. (827828)
48 exp beta-Lactam Resistance/ (26155)
49 exp Drug Resistance, Microbial/ or exp Microbial Sensitivity Tests/ (231349)
50 exp Drug Resistance, Multiple/ (33795)
51 exp Drug Resistance, Bacterial/ (83040)
52 exp Methicillin Resistance/ (10188)
53 exp Multidrug Resistance-Associated Proteins/ (14320)
54 exp Vancomycin Resistance/ (3263)
55 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 (900383)
56 43 or 44 [antimicrobial altogether] (154537)
57 55 and 56 [antimicrobial AND resistance] (70921)
58 46 and 55 [antibiotic AND resistance] (248811)

59 infect*.mp. (2131927)

60 exp Escherichia coli/ (270735)

61 exp Bacteriophages/ (56525)

62 exp Infection/ (760393)

63 infection*.mp. (1804659)

64 59 or 60 or 61 or 62 [infection altogether] (2649927)

65 55 or 57 or 58 [resistance OR antimicrobial resistance OR antibiotic resistance] (900383)

66 64 or 65 [infection OR resistance altogether] (3306493)

67 3 and 66 [combined with acne] (3142)

# Appendix 2 – supplementary material to chapter five - drug utilisation study

Published paper:

Bhate K, Mansfield KE, Sinnott SJ, Margolis DJ, Adesanya E, Francis N, Leyrat C, Hopkins S, Stabler R, Shallcross L, Langan SM, Mathur R. Long-term oral antibiotic use in people with acne vulgaris in UK primary care: a drug utilization study. Br J Dermatol. 2022 Dec 13:ljac084. doi: 10.1093/bjd/ljac084. Epub ahead of print. PMID: 36670540.

## CONTENTS

# A2.1 ISAC study protocol

Medicines & Healthcare products Regulatory Agency

CPRD

1 General information

**Protocol reference Id**

19_168

**Study title**

Understanding the use of long-term antibiotics for acne in the United Kingdom

**Research Area**

Drug Utilisation

Pharmacoepidemiology

**Does this protocol describe an observational study using purely CPRD data?**

No

**Does this protocol involve requesting any additional information from GPs, or contact with patients?**

No

## 2 Research team

| | |
|---|---|
| **Role** | Chief Investigator |
| **Title** | Professor of Clinical Epidemiology |
| **Full name** | Sinead Langan |
| **Affiliation/organisation** | London School of Hygiene & Tropical Medicine ( LSHTM ) |
| **Email** | sinead.langan@lshtm.ac.uk |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Corresponding Applicant |
| **Title** | Clinical research fellow |
| **Full name** | Ketaki Bhate |
| **Affiliation/organisation** | London School of Hygiene & Tropical Medicine ( LSHTM ) |
| **Email** | ketaki.bhate@lshtm.ac.uk |
| **Will this person be analysing the data?** | Yes |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Collaborator |
| **Title** | Professor of Primary Care Research |
| **Full name** | Nicholas Francis |
| **Affiliation/organisation** | Cardiff University |
| **Email** | francisna@examplef.ac.uk |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Collaborator |
| **Title** | Clinical Senior Lecturer / Deputy Director, AMR PHE |
| **Full name** | Susan Hopkins |
| **Affiliation/organisation** | Public Health England |
| **Email** | susan.hopkins@phe.gov.uk |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

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3

## Access to data

### Sponsor

London School of Hygiene & Tropical Medicine ( LSHTM )

### Funding source for the study

**Is the funding source for the study the same as Chief Investigator's affiliation?**
No
**Funding source for the study**
National Institute for Health Research - NIHR London Office

### Institution conducting the research

**Is the institution conducting the research the same as Chief Investigator's affiliation?**
Yes
**Institution conducting the research**
London School of Hygiene & Tropical Medicine ( LSHTM )

### Method to access the data

**Indicate the method that will be used to access the data**
Institutional multi-study licence
**Is the institution the same as Chief Investigator's affiliation?**
Yes
**Institution name**
London School of Hygiene & Tropical Medicine ( LSHTM )

### Extraction by CPRD

**Will the dataset be extracted by CPRD**
No

### Multiple data delivery

**This study requires multiple data extractions over its lifespan**
No

### Data processors

## 4 Information on data

**Primary care data**

CPRD GOLD

**Do you require data linkages**

No

**Patient level data**

**NCRAS data**

**Covid 19 linkages**

**Area level data**

**Do you require area level data?**

Yes

**Practice level (UK)**

Practice Level Index of Multiple Deprivation

**Patient level (England only)**

Patient Level Index of Multiple Deprivation

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5

Protocol information

**Lay Summary**

Antimicrobial resistance (AMR) may lead to antibiotics used to treat infections in humans not working. This is because we are using them too frequently and for too long, so bacteria develop ways to avoid attack from antibiotics. Scientists have predicted by 2050, 10million people/year will die because antibiotics won't work.

Antibiotics, tablets and skin applications (e.g. creams), are commonly used to treat of acne or 'spots' in primary-care, sometimes for months at a time. Acne is common, affecting almost everyone to some degree, however it is moderate to severe in 20% of adolescents and it is those people who are prescribed antibiotics. Guidelines recommend that courses of antibiotics are repeated, each course duration being 3-6 months. Treatment courses can be given over many years intermittently. Most find antibiotics work for their acne, but this is not because acne is an infection, but because antibiotics lessen the redness of spots (anti-inflammatory). This approach does not stop spots coming back again in the future.

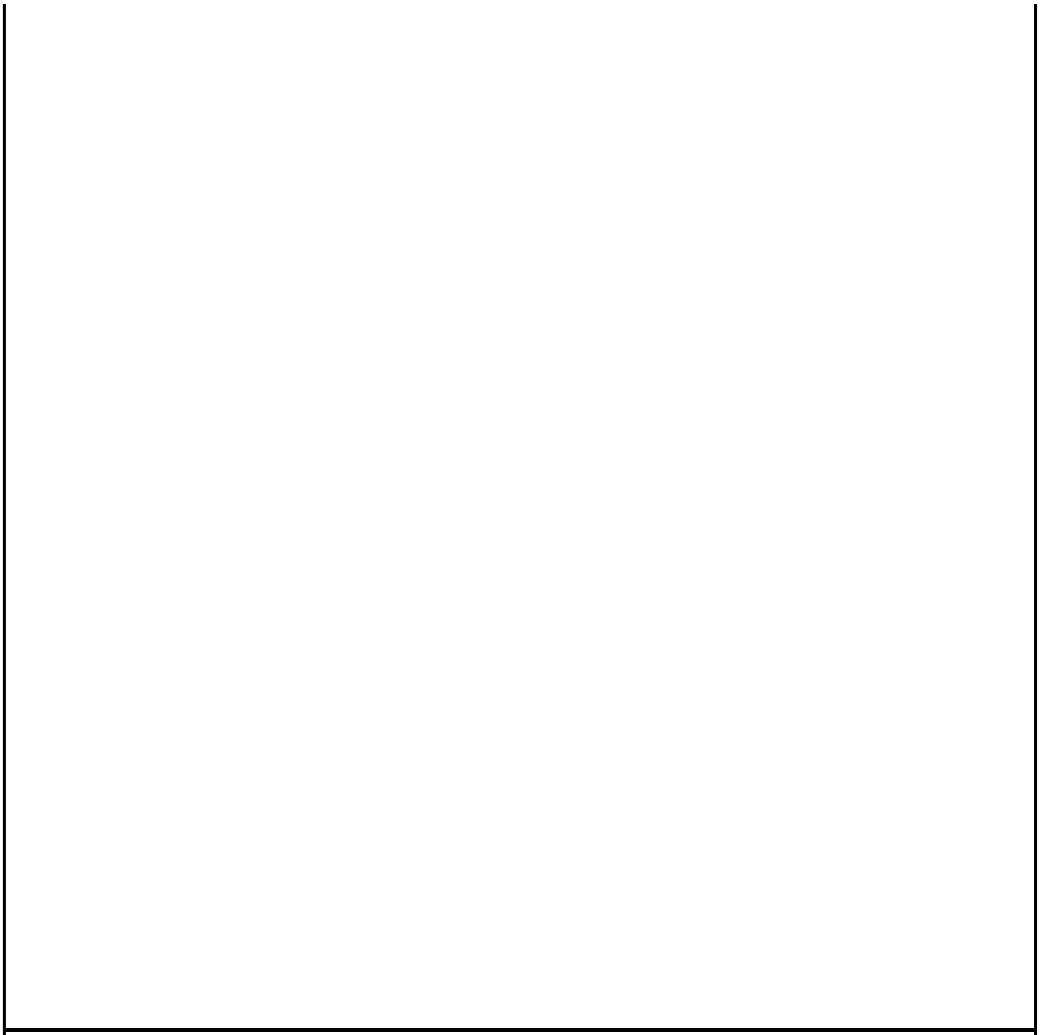
Antibiotics are recommended in all treatment guidelines for acne. We know from international studies that antibiotics are used frequently to treat acne, so there is a concern that they may be contributing to the problem of AMR. To fully understand the scale of antibiotic prescribing for acne in the UK, it is necessary to explore how these drugs are used by looking at antibiotic prescriptions over five-years, to determine the antibiotic prescribed, the duration of each individual course of antibiotic and the number of repeat courses.

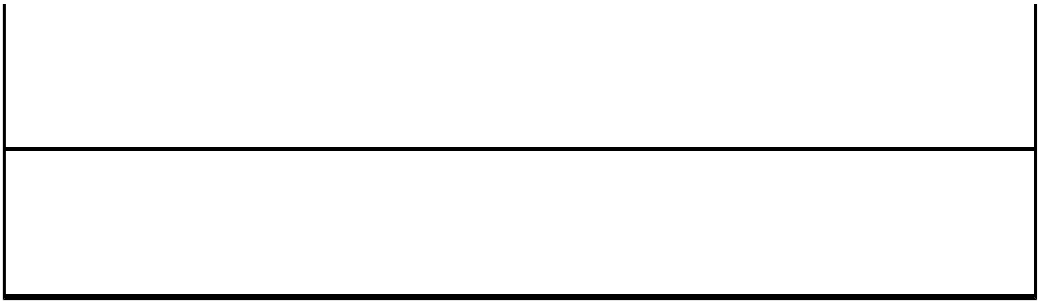
**Technical Summary**

The World Health Organisation declared the threat of Antimicrobial Resistance (AMR) a most urgent crisis. Without intervention, it is expected up to 10 million deaths/year from infections will occur by 2050 and the cost could reach 100 trillion USD. The overuse of antibiotics is a known driver of AMR as repeated and sustained exposure allows microbes to develop mechanisms to avoid the effects of drugs designed to defeat them.

Acne vulgaris is a chronic skin disorder with onset predominantly in adolescence. Prevalence studies show that 80-100% of adolescents have acne and 20% are moderately-severely affected. Duration is variable with 5% of people in their 50s with acne. Topical/oral antibiotics are commonly prescribed for the treatment of acne for several months. Tetracyclines and macrolides are the two most common oral antibiotic classes prescribed with dihydrofolate-reductase inhibitors (trimethoprim) prescribed second-line.

The pathophysiology of acne is multifactorial and although Cutibacterium acnes is associated in the development of acne, acne is not an infection, and antibiotics are used predominantly for their anti-inflammatory effects over antimicrobial. We do not understand how long-term antibiotics for acne attenuate flora elsewhere, nor how they influence the ability of bacteria at other infective sites to withstand their effects, which may contribute to AMR. Antibiotic prescribing is not generalisable across countries, as practices vary, therefore studies investigating antibiotic use elsewhere may not be applicable to the UK. While a previous study aimed to establish how acne medications are prescribed in the UK, follow up was restricted to one year. Given the chronicity of acne and the common practice of using antibiotics intermittently over several years, further study over a longer period is warranted. The overall aim of this study is to use the CPRD to elucidate how people with acne are managed with long-term oral/topical antibiotics in primary care for up to five-years follow-up.





# A2.2 LSHTM ethics approval

## LSHTM Ethics Application & CARE Form

### Project Information

Staff members/students based at:

- (•) LSHTM
- ( ) MRCG@LSHTM

1. Full project title

Understanding the use of long-term antibiotics for acne in the United Kingdom

2. Is this Project in fulfillment of a degree?

(•) Yes ( ) No

2a. Degree registered for

PhD

2b. Have you completed upgrading?

- ( ) Yes
- (•) No

2b (ii). If you have not yet completed upgrading, please state when upgrading is likely to take place, as well, detail why you are submitting to the ethics committee at this stage.

Upgrading 13th September 2019. This study has been approved by ISAC.

2f(deg). Is this an original submission, or are you responding to a request for clarification from the LSHTM ethics committee?

- ( ) Original submission
- (•) Responding to request for clarification

2f(i-deg) Please upload a covering letter responding to the committee's request for clarification (please use the same format as that shown in the template cover letter available under Help-Templates). Please upload all amended documents in the relevant section of the form.

Documents

| Type | Document Name | File Name | Version Date | Version | Size |
|---|---|---|---|---|---|
| Covering Letter | LEO Cover letter 18.10.19 | LEO Cover letter 18.10.19.docx | 18/10/2019 | 1 | 14.9 KB |
| Covering Letter | LEO Cover letter 31.10.19 | LEO Cover letter 31.10.19.docx | 31/10/2019 | 1 | 15.1 KB |

## Student Details

3a. Student details

Title First Name Surname

[redacted]

Address [redacted]

[redacted]

City [redacted]

Postcode [redacted]

Telephone [redacted]

Email [redacted]

3c. Supervisor's name.

[redacted]

3c (i). Supervisor's email address (if more than one, please only provide the email address of your main supervisor)

Email [redacted]

3 c(ii). Supervisor's institution

- (•) LSHTM
- ( ) MRC Gambia or Uganda
- ( ) Other

3e. Supervisor status

Confirmed

## Project Type

Note: Completing the filter will enable and disable sections of the form so you may not see all questions.

4. Does the research involve primary data collection, analysis of data/samples that have already been collected, or a mix of both?

- ○ Primary
- ◉ Previously collected data/samples
- ○ Mixed

4a(iii). Select type of project:

Project using data from secondary sources

6. Is this project being undertaken by Chariot Innovations or by the Rapid Support Team?

- ○ Yes
- ◉ No

## Samples

6a. Does this research project involve the collection, or use of previously collected, human tissue samples e.g urine, stool, blood etc? (Please select yes even if the samples are not considered relevant material under the Human Tissue Act)

- ○ Yes
- ◉ No

6b. Will this project involve living animals (either laboratory, livestock or wild animals) AND/OR biological material that has been obtained from animals in the experiments planned?

- ○ Yes
- ◉ No

## Fast-Track

7. Does this project use anonymised and unlinkable secondary datasets only?

- (•) Yes
- ( ) No

7a. Will this project be conducted within the NHS?

- ( ) Yes
- (•) No

7b. Is this application for fast-track? Note: MSc applications are not currently available for fast-track

- (•) Yes
- ( ) No

7c. Select reason for fast-track

Using anonymised and unlinkable secondary datasets only

## Vulnerable Groups

8c. Does this research project involve vulnerable groups? Vulnerable groups include: children, individuals with mental disability or learning difficulties, pregnant women, prisoners etc (see information icon for full description).

- ( ) Yes
- (•) No

## Security Sensitive Research Material

9. Does this research involve access to and/or storage of security sensitive research material? (please see information icon for what is considered security sensitive material)

- ( ) Yes
- (•) No

## Geography

10. List the countries where the research project is to be conducted (For example: if you are conducting a secondary data analysis for your project and you will be based in the UK, select UK regardless of where the original data has come from):

United Kingdom

10. List the countries where the research project is to be conducted (For example: if you are conducting a secondary data analysis for your project and you will be based in the UK, select UK regardless of where the original data has come from):

United States of America

Please be aware that all primary health research conducted in the UK requires a sponsor. Please contact the RGIO at RGIO@lshtm.ac.uk for more information on sponsorship.

## Outline

Note: Please do not copy and paste directly from the protocol. Applications where large portions of text have been copied and pasted directly from the protocol, and therefore do not properly answer the question, will be invalidated

12. Give an outline of the proposed project, including background to the proposal. Include information from any systematic reviews that have been conducted. Sufficient detail must be given to allow the Committee to make an informed decision without reference to other documents.

A. Study Background

The future effectiveness of antibiotics is in jeopardy with the World Health Organisation declaring the threat of Antimicrobial Resistance (AMR) a most urgent crisis. (3) Without intervention, future deaths from infections as a result of AMR is estimated at 10 million per year and by 2050, the cost of AMR could reach 100 trillion USD.(4)

The overuse of antibiotics is a known cause of AMR as repeated and sustained exposure allows microbes to develop mechanisms to avoid the effects of the drugs designed to defeat them.

Topical and oral antibiotics are commonly prescribed for the treatment of acne vulgaris, a chronic skin disorder with onset predominantly in adolescence. Given the psychosocial consequences and potential for permanent disfigurement with scarring, it is imperative that people with acne receive effective treatment.(5, 6) Prevalence studies show that 80-100% of teenagers have acne and that 20% are moderately to severely affected. The high prevalence of acne means that both topical and oral antibiotics are used in a large proportion of the adolescent population and for variable durations ranging from 6 weeks to many months, and in some cases, several years.(7, 8) Differences between international guidelines regarding duration of treatment is one of the reasons that antibiotics for acne are used for significantly longer than recommended .(8-13) Tetracyclines and macrolides are the two most common oral antibiotic classes prescribed for acne with varying durations of average use depending on treatment setting and between different countries.(8, 14)

Although acne is not an infectious disease and aetiologically is multifactorial, we already know that some strains of Cutibacterium acnes (formally Propionibacterium acnes or P. acnes), the bacteria pathophysiologically associated with acne, are now resistant to commonly used antibiotics in acne, making their initial use as anti-microbial agents futile.(15, 16) However, we do not know how these long-term antibiotics for acne may attenuate microbiota elsewhere, and the ability of other bacteria at other infective sites to withstand the effect of antibiotics. Despite this, the anti-inflammatory effect of antibiotics ensures their continued use as their clinical effectiveness is demonstrated (17), albeit their effects may not be sustained. Considering the relationship between long term exposure to antibiotics and AMR, and the burden of acne vulgaris at the population level, this practice may not be optimal.

To understand the extent of any AMR as a result of antibiotics for acne in the UK, it is first necessary to establish how the antibiotics are used. Acne is a chronic disease and there are no studies with follow up longer than one year in data sources representative of the UK population to establish current prescription practice of acne treatment with antibiotics over its chronic disease course in primary care. Data from the US suggests 20% of those with acne are treated with antibiotics, however, international treatment patterns are not always generalisable, especially amid inconsistent guidelines and differing health systems.(11-14) A recent study using CPRD data found that topical or oral antibiotics were prescribed in over 50% of people who visited their GP with acne, but we do not know how long these individuals received their antibiotics for and if they had repeated courses over a period of years.(1)
While antibiotic stewardship programmes have been shown to be effective (18) in other settings, to ensure their successful execution, evidence must be generated to show how antibiotics in the treatment of acne are used over the course of the disease. Until this

evidence is generated and until there is evidence of resulting harm, it will be difficult to change current practice.(19) Given the global health emergency of AMR and the dominant role antibiotics play in the treatment of acne – a highly prevalent and ubiquitous skin condition, there is a clearly defined evidence gap which needs to be addressed.(20) This drug utilisation study aims to establish current practice amongst GPs in the UK with prescribing antibiotics for acne is over a time period of at least five-years.

References


1. Francis NA, Entwistle K, Santer M, Layton AM, Eady EA, Butler CC. The management of acne vulgaris in primary care: a cohort study of consulting and prescribing patterns using the Clinical Practice Research Datalink. Br J Dermatol. 2017;176(1):107-15.
2. methodology WHoccfds. https://www.whocc.no/ddd/definition_and_general_considera/.
3. Organization. WH. Global action plan on antimicrobial resistance. . 2015.
4. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The review on antimicrobial resistance May 2016.
5. Bhate K, Williams HC. Epidemiology of acne vulgaris. The British journal of dermatology. 2013;168(3):474-85.
6. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet (London, England). 2012;379(9813):361-72.
7. Whitehouse HJ FE, El- Mansori I, Layton AM. . Oral antibiotics for acne: are we adopting premium use? Presentation at the Annual Conference of the British Association of Dermatologists, Birmingham, U.K. 5–7 July 2016.
8. Barbieri JS HO, Margolis DJ. Duration of oral tetracycline-class antibiotic therapy and use of topical retinoids for the treatment of acne among general practitioners (GP): A retrospective cohort study. ournal of the American Academy of Dermatology. 2016 Dec;75:1142-50.
9. Lee YH LG, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: Investigating practice gaps and potential cost-savings. Journal of the American Academy of Dermatology. 2014;71.
10. Whitehouse H.J. et al, . Conference Presentation: Oral antibiotics for acne: are we adopting premium use? (British Association of Dermatologists Annual Conference 2016. 2016.
11. National Institute of Health and Care Excellence. Clinical Knowledge Summaries. Acne vulgaris. revised 2014.
12. Zaenglein AL PA, Schlosser BJ. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945-73 e33.
13. Nast A DB, Bettoli V. European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. Eur Acad Dermatol Venereol. 2016;30:1261-8.
14. Barbieri JS JW, Margolis DJ. Trends in prescribing behavior of systemic agents used in the treatment of acne among dermatologists and nondermatologists: A retrospective analysis, 2004-2013. J Am Acad Dermatol. 2017;77:456-63.
15. Kuet K.H. FC FE, Eady A,and Layton A.M,. Conference Presentation: A decade later, has the prevalence of skin colonization by resistant propionibacteria increased in our patients with acne? British Association of Dermatologists Annual Conference. 2015.
16. Lee SE KJ-M, Jeong SK. Protease-activated receptor-2 mediates the expression of inflammatory cytokines, antimicrobial peptides, and matrix metalloproteinases in keratinocytes in response to Propionibacterium acnes. Arch Dermatol Res. 2010;302:745-56.
17. Bienenfeld A, Nagler AR, Orlow SJ. Oral Antibacterial Therapy for Acne Vulgaris: An Evidence-Based Review. American journal of clinical dermatology. 2017;18(4):469-90.
18. Lawes T L-LJ, Nebot CA. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. Lancet Infect Dis. 2015;15:1438-49.
19. Simpson SA WF, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. The Journal of antimicrobial chemotherapy. 2007;59:292-6.
20. Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.


12a. Upload the study protocol, including data collection forms, questionnaires and topic guides. Please upload each document separately, ensuring that the date and version number of each document is correct.

[redacted]

13. State the intended value of the project, detailing why the topic is of interest or relevance. If this project or a similar one has been done before what is the value of repeating it? Give details of overviews and/or information on the Cochrane database. This area is of increasing importance – please ensure you give a full response.

To understand the extent of any AMR as a result of antibiotics for acne in the UK, it is first necessary to establish how the antibiotics are used. Acne is a chronic disease and there are no studies with follow up longer than one year in data sources representative of the UK population to establish current prescription practice of acne treatment with antibiotics over its chronic disease course in primary care. Data from the US suggests 20% of those with acne are treated with antibiotics, however, international treatment patterns are not always generalisable, especially amid inconsistent guidelines and differing health systems.(11-14) A recent study using CPRD data found that topical or oral antibiotics were prescribed in over 50% of people who visited their GP with acne, but we do not know how long these individuals received their antibiotics for and if they had repeated courses over a period of years.(1)
While antibiotic stewardship programmes have been shown to be effective (18) in other settings, to ensure their successful execution, evidence must be generated to show how antibiotics in the treatment of acne are used over the course of the disease. Until this evidence is generated and until there is evidence of resulting harm, it will be difficult to change current practice.(19) Given the global health emergency of AMR and the dominant role antibiotics play in the treatment of acne – a highly prevalent and ubiquitous skin condition, there is a clearly defined evidence gap which needs to be addressed.(20) This drug utilisation study aims to establish current practice amongst GPs in the UK with prescribing antibiotics for acne is over a time period of at least five-years.

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2. methodology WHoccfds. https://www.whocc.no/ddd/definition_and_general_considera/.
3. Organization. WH. Global action plan on antimicrobial resistance. . 2015.
4. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The review on antimicrobial resistance May 2016.
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6. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet (London, England). 2012;379(9813):361-72.
7. Whitehouse HJ FE, El- Mansori I, Layton AM. . Oral antibiotics for acne: are we adopting premium use? Presentation at the Annual Conference of the British Association of Dermatologists, Birmingham, U.K. 5–7 July 2016.
8. Barbieri JS HO, Margolis DJ. Duration of oral tetracycline-class antibiotic therapy and use of topical retinoids for the treatment of acne among general practitioners (GP): A retrospective cohort study. ournal of the American Academy of Dermatology. 2016 Dec;75:1142-50.
9. Lee YH LG, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: Investigating practice gaps and potential cost-savings. Journal of the American Academy of Dermatology. 2014;71.
10. Whitehouse H.J. et al, . Conference Presentation: Oral antibiotics for acne: are we adopting premium use? (British Association of Dermatologists Annual Conference 2016. 2016.
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13. Nast A DB, Bettoli V. European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. Eur Acad Dermatol Venereol. 2016;30:1261-8.
14. Barbieri JS JW, Margolis DJ. Trends in prescribing behavior of systemic agents used in the treatment of acne among dermatologists and nondermatologists: A retrospective analysis, 2004-2013. J Am Acad Dermatol. 2017;77:456-63.
15. Kuet K.H. FC FE, Eady A,and Layton A.M,. Conference Presentation: A decade later, has the prevalence of skin colonization by resistant propionibacteria increased in our patients with acne? British Association of Dermatologists Annual Conference. 2015.
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17. Bienenfeld A, Nagler AR, Orlow SJ. Oral Antibacterial Therapy for Acne Vulgaris: An Evidence-Based Review. American journal of clinical dermatology. 2017;18(4):469-90.
18. Lawes T L-LJ, Nebot CA. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. Lancet Infect Dis. 2015;15:1438-49.
19. Simpson SA WF, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. The Journal of antimicrobial chemotherapy. 2007;59:292-6.
20. Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.

15. Overall aim of project

To understand the use of long-term antibiotics for acne in the United Kingdom.

16. Specific objectives of project

In a population level sample of patients with acne in primary care, what are the prescribing patterns of oral and topical antibiotics used to treat acne over a five-year time period?

## Methods

Note: Please do not copy and paste directly from the protocol. Applications where large portions of text have been copied and pasted directly from the protocol, and therefore do not properly answer the question, will be invalidated

18. Specify the procedures/methodology to be conducted during the project. Please include outcome measures and plans for data management and analysis. For literature reviews, include details on search strategy, search terms, inclusion and exclusion criteria.

Study Type

Descriptive drug utilisation study.

Study Design

Drug utilisation study

Outcomes to be Measured

This is a drug utilisation study aiming to identify how topical and oral antibiotics for acne are prescribed over the course of this chronic disease.

Outcomes will therefore be defined as:
1) Initiation of an oral or topical antibiotic for acne.
2) Substituting/switching a topical or oral antibiotic for another between classes.
3) Addition of an antibiotic to existing antibiotic treatment
4) Discontinuation of a topical or oral antibiotic.
5) Duration of antibiotic treatment including median duration.
6) Re-initiation of an antibiotic – this is defined as a further prescription of an antibiotic after having previously been prescribed an antibiotic for a minimum of 4 weeks for acne, regardless of class, if there is no antibiotic prescription covering the previous 60 days.

Definitions to be used:

Treatment initiation:
A new topical or oral antibiotic prescribed for at least 28 days preceded by 365 days of no antibiotic use. As there are no Daily Defined Doses (DDDs) for topicals, 0.5g per day will be amount used to define a daily dose as has been used by other studies.(1, 2) For the purposes of analysis, people with an antibiotic prescription for acne for less than 28 days will be excluded.

Treatment switching:
Treatment switching is defined as the addition of a second antibiotic class (for acne) without the continuous use of the initial first antibiotic. The new antibiotic is used in place of the previous antibiotic treatment. Therefore, if a second drug is added, but with less than 30 overlapping days' supply, this will be defined as a treatment switch between antibiotics. Second, third and fourth antibiotic initiation will only be considered treatment switches if there are 30 or less days' supply from the prescription of the previous antibiotic.

Treatment addition:
If there are overlapping days' supply for the first and second antibiotic for 30 days or more then this is defined as a treatment addition of the second antibiotic, (and for subsequent antibiotic additions thereafter defined as the third and fourth additions etc).

Treatment discontinuation:
This is defined as no available days of antibiotic supply 30 days after the last covered day.

Treatment re-initiation:
This is defined as an antibiotic prescription in those who have previously received antibiotics for their acne with a treatment gap of at least 30 days.

We will stratify drug utilisation across age categories, geographic location (if possible) and sex to understand prescribing in separate populations.

Eligibility for inclusion:
Patients from the general population will be eligible for inclusion between the years 2004 to 2018. Patients between the ages of 8 and 50 of any sex will be eligible. People will be eligible for inclusion from the latest of their current registration date + 1 year (CRD+1), the day the practice was deemed to be up to standard (UTS), the day the study started (1st of January 2004) or the patient's 8th birthday.

Study population:
From those eligible for inclusion, people with a new acne diagnostic code between the 1st of January 2004 and the 31st of December 2018 will be defined as the study population. A new acne diagnosis is defined as any individual with an acne code (appendix A) who has not previously had an acne code in the 1 year prior to the study start. We will exclude patients with prior use of prescribed acne medication including antibiotics for acne (see appendix C) in the previous 365 days before the first diagnostic code. The Read codes identified for acne are listed in Appendix A.

Study start:
From this population of people with acne, those commencing prescriptions of topical or oral antibiotics will be identified on the day they receive their diagnostic code onwards. Study entry begins on the date of the acne diagnostic code.

Misclassification:
Our method if identifying people with acne hinges on individuals having a diagnostic code. We expect that not all treated acne is coded as such. Thus, we plan a sensitivity analysis whereby individuals can be included in the study by meeting the following criteria:
1) The prescription of a long-term antibiotic commonly given to treat acne (tetracycline, macrolide or dihydrofolate reductase inhibitor) for at least 28 days with no acne code, and no diagnostic code in the preceding or subsequent 3 months of the antibiotic prescription for urinary tract infection, sickle cell disease or splenectomy, osteomyelitis, rosacea, cellulitis or hidradenitis suppurativa (conditions which may be treated with long-term antibiotics). Follow up in this scenario will begin from the day of the antibiotic prescription.
2) No diagnostic code for acne, but a prescription of a typical acne medication (e.g. a topical retinoid or topical benzoyl peroxide) listed in the British National Formulary acne chapter (see Appendix D). Follow up for these individuals will begin on the day of acne medication prescription.

The rationale underpinning this sensitivity analysis is that it will improve our understanding of how many acne cases we may have missed using our main entry criteria.

Exposures, Outcomes and Covariates
Exposures:
This is a drug utilisation study and thus does not have exposures in the traditional sense. We will explore what drugs people are initiating for acne and their utilisation patterns thereafter inclusive of switching drugs, discontinuing drugs and adding drugs.

Outcomes:
This is a drug utilisation study so there are no traditional outcomes. The focus is on treatment trajectories; the antibiotics patients initiate, the antibiotics they are switched to, which antibiotics are added in addition to existing treatment and which are discontinued. See section D for further details.

Covariates:
We will stratify drug patterns according to the following age categories (8-11, 12-18, 19-25, 26-35, 36-45, 46-50) and sex.

Primary analyses:
The main analysis will describe, in graphical and tabular format, topical and oral antibiotic treatment trajectories over a time period of five-years.

Desired data structure:
The antibiotic medications listed in the British National Formulary (BNF) section on acne medications will be used and categorised as follows:

The antibiotics used to treat acne will be classified into the following groups (see appendix B):
1. Topical antibiotic e.g. topical clindamycin or erythromycin
2. Topical antibiotic combination e.g. clindamycin and tretinoin, or benzoyl peroxide and clindamycin
3. Oral antibiotic inclusive of tetracyclines, macrolides and dihydrofolate reductase inhibitors e.g. trimethoprim.
4. No antibiotic prescribed but presence of code indicating acne.

The utilisation of the oral antibiotics prescribed will be expressed as numbers of Daily Defined Doses (DDDs) /1000 people coded for acne. There are no DDDs for topical preparations so therefore 0.5g per day will be taken as a daily dose as has been used in other studies.

From January 2014 (when a new acne diagnosis is recorded) cohort entry will be defined and follow up will begin. We will examine changes to antibiotic drug therapy over the subsequent five-year time period. The specific antibiotic initiation, addition, switches or overlap of two antibiotics and censoring will be noted (described above). The quantity of each medication (and therefore duration) for each group will be described with medians and the interquartile ranges will be presented.

Plan for addressing confounding
This is a descriptive drug utilisation study and as such there is no confounding. We will stratify drug utilisation across age categories, geographic location (if possible) and sex to understand prescribing in separate populations.

Plans for addressing missing data
Not applicable for this study – see section L for plans of addressing misclassification.
Age and sex are well recorded in CPRD data.

CPRD access: institutional multi access used licence. I will process, access and store data at LSHTM.

23. Proposed start date of the project

16/09/2019

24. Proposed end date of the project

01/06/2020

## Experience

30. State the personal experience of the applicant and of senior collaborators in the research project in the field concerned, and their contribution to this project. Indicate any previous work done related to the project topic including student and/or professional work, or publications

Ketaki Bhate
MSC in Epidemiology with research project undertaken using the CPRD. I have written the study protocol.
Professor Sinead Langan is clinically a consultant dermatologist has extensive experience of conducting studies using the CPRD.
Supervisor to Ketaki Bhate's PhD (NIHR DRF)

Both Ketaki Bhate and Sinead Langan have been involved in this study from inception.

Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.

30a. Upload the CVs for all main investigators working on the project. For MSc students, please upload your CV only.

[redacted]

## Informed Consent - Secondary Data

34. Is consent in place for secondary use of the data?

- (•) Yes
- ( ) No

34c. Please give details of the participant consent that was obtained when the original project(s) took place. Please upload copies of the original consent form(s). If there are no original consent forms (e.g. for audit or DHS data) please explain this.

Patients were consented by GPs when data were collected for their health records. Data are anonymised.

## Confidentiality & Data

40. State how your data will be stored and what will be done with it at the end of the project.

The data will be stored on a secure data server at the London School of Hygiene and Tropical Medicine. Access will be restricted to myself and named collaborators. weekly backup tapes will be made and then overwritten once a more up-to-date monthly backup has been made; monthly backup tapes will be retained for 12 months and then overwritten, but the final monthly backup tape in each 12-month cycle will be retained. Data will remain on the secure server for the full retention period, as stipulated by the respective data owners. Since the data used for this project will be archived by the data owners, the data processing programs created for this project would enable the derived study data to be re-created after the retention period ends.

## Funding

46. Do you have external funding for this project?

- (•) Yes
- ( ) No

46a. If yes, please provide the name of the funder

NIHR

46a(i). If yes, include details of the funding available for this project.

I am funded by an NIHR Doctoral Research Fellowship DRF-2018-11-ST2-066.

Date grant accepted or funding agreed:

01/11/2019

Date end of funding:

01/11/2021

46a(ii). Are you in receipt of any funding from the United States? Or will you be collaborating with (or with individuals from) a US Institution/organisation?

- (•) Yes
- ( ) No

47. Has the project been sent out for peer/independent scientific review (please select yes if the project is being sent to the SCC)?

- (•) Yes
- ( ) No

47b. If yes, who has provided peer/independent scientific review of the project?

ISAC.

I am not funded by the US I am funded only by the NIHR. I have up to 3 months of funding via the NIHR for an overseas research visit. Here I will be working on this study for some of the time there. I plan this visit for April 2020. I will be using the remote desktop and accessing the network and my PC at my desk at LSHTM. I will not be carrying the data with me overseas.

49. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- ( ) Yes
- (•) No

50. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- ( ) Yes
- (•) No

## Local Approval

69. For projects using previously-collected human data, give details of all approvals under which the original project(s) took place. Please quote names of Ethics Committees and approval reference numbers (required even if previous approval was from LSHTM); if possible give web link to original project application. If there are no original approvals (e.g. for audit or DHS data) please explain this.

ISAC protocol 19_168 approved 12.08.19.
This is a new study and does not represent an addition or change to a previously submitted application.

Documents

| Type | Document Name | File Name | Version Date | Version | Size |
|---|---|---|---|---|---|
| Local Approval | 19_168_ISAC feedback | 19_168_ISAC feedback.docx | 28/08/2019 | 1 | 37.2 KB |

69a. Will your analyses be for purposes entirely covered by the original ethics application where the data was collected, as detailed above?

- ○ Yes, this falls within the aims and scope of the original project
- ◉ No, the analyses and aims differ from the original project

69a(ii). If no, please detail how you will amend the original ethics application to include the current analysis.

n/a

## Signature Instructions

The form should be completed and finalised prior to signing or requesting signatures. Students should ensure that the Supervisor signs prior to the Course Director/Project Module Organiser. For external supervisors, please ensure that they have registered for an account prior to requesting the signature.

## Signature - Applicant

Student signature

I declare that:

- I Have read and understood, and agree to abide by the LSHTM Good Research Practice policy as well as all applicable Standard Operating Procedures, including on informed consent
- I undertake to abide by all regulations, guidelines and standards of good practice, including but not limited to the Data Protection Act 2018 and the Declaration of Helsinki
- I undertake to abide by the UK Data Protection Act 1998 and any applicable local laws.
- I undertake to abide by all local rules for non-UK research.
- I agree to conduct my project on the basis set out in this form, and to consult staff (initially, my Supervisor) if making any subsequent changes – especially any that would affect the information given with respect to ethics approval.
- I undertake to adhere to all conditions set out by review bodies in giving approval and will not start the project until all required approvals are in place
- I agree to comply with the relevant safety requirements, and will submit a separate request for LSHTM travel insurance where relevant.
- I confirm that there are no conflicts of interest that preclude my participation in the project

[redacted]

## Signature - Supervisor

Supervisor signature

I declare that:

- I agree that the information submitted in this application is a reasonable summary of the proposed project.
- I agree that this form correctly indicates whether or not ethics approval will be required.
- I agree that this form contains adequate information for the ethics committee to form an opinion of the proposed project.
- I agree that all required supporting documentation is attached to this application.
- (For MSc projects only) I agree that responses in the Risk Assessment section address the main risks connected with a project of this nature
- I have reviewed the risk of the project, including travel, and agree that it is an acceptable risk to the student
- I confirm that there are no conflicts of interest that preclude my role as supervisor for this project
- I Have read and understood, and agree to abide by the LSHTM Good Research Practice policy

[redacted]

## Signature - Other

Note:

**The form will automatically submit upon receipt of all required signatures.**

**After submission, you will receive a confirmation email with further details.**

**If you have not received a confirmation email within 5 working days please email ethics@lshtm.ac.uk (staff) or MScethics@lshtm.ac.uk (students) to check the status of your submission.**

# A2.3 Supplementary material to published manuscript (sensitivity analyses)

APPENDIX

A sensitivity analysis **(Tables S1-S3)** altering the gap allowed between prescriptions to define continuous courses of therapy from 28 days to 14 days when constructing consecutive courses meant 95,603 people had 304,852 courses of antibiotics prescribed. Shortening the gap between prescriptions to 14 days in the sensitivity analysis from 28 days in the main analysis led to greater proportions of individuals receiving second courses of antibiotic, n=61,218 (64.0 %) (tetracycline n=53,205 (63.9% of people who received a first course tetracycline), Macrolides n=7,529 (67.1% of people who received a first course macrolide) and trimethoprim n=576 (53.8% of people who received a first course trimethoprim) using a 14 day gap versus, n=56,261 (58.2 %) (tetracycline n=47,920 (58.6% of people who received a first course of tetracycline), macrolides n=7,796 (59.2% of people who received a first course macrolide) and trimethoprim n=545 (31.1% of people who received a first course trimethoprim) using a 28 day gap (**Table 5**). Using the 14-day interval, the median duration of courses remained 56 days (IQR 28 -56 days) while the median number of courses per person was five (IQR 3-8) compared to a median duration of courses of 56 days (IQR 47-88) and the median number of courses of four (IQR 2-6) when allowing 28-day gaps between consecutive prescriptions to define continuous courses of therapy. The median duration between all courses was 132 days (IQR 61-330).

**S1: Sensitivity analysis.** Continuous courses formed with 14 or less days gap between prescriptions. Population characteristics and time spent on oral antibiotics throughout follow up. Data are person years (% of total person time in specific strata). n=95,603 people with 304,852 prescriptions)

| | | **Denominator (n=217,410 people with acne code)** | **People with at least 28 days of oral antibiotic (n-96,703** |
|---|---|---|---|
| | Total person years | 1,102,202 | 210,789 (19.1) |
| **Gender** | Female | 708,283 | 138,836 (19.6) |
| | Male | 393,919 | 71,953 (18.3) |
| **Age band*** | 8-11 | 5,708 | 2,470 (43.3) |
| | 12-18 | 356,339 | 100,181(28.1) |
| | 19-25 | 354,488 | 51,386 (14.5) |
| | 26-35 | 230,272 | 33,300 (14.5 |
| | 36-50 | 155,396 | 23,452 (15.1) |
| **Calendar period**** | 2004-2008 | 175,526 | 55,850 (31.8) |
| | 2009-2013 | 456,566 | 101,254 (22.2) |
| | 2014-2020 | 470,110 | 53,685 (11.8) |
| **Quintiles of IMD** | 1 (most deprived) | 241,285 | 49,104 (20.4) |
| | 2 | 179,364 | 35,690 (20.0) |
| | 3 | 208,237 | 39,534 (19.0) |
| | 4 | 212,805 | 39,608 (18.6) |
| | 5 (least deprived) | 260,511 | 46,853 (18.0) |
| **Ethnicity** | White | 378,553 | 73,484 (19.4) |
| | South Asian | 26,937 | 4,669(17.3) |
| | Black | 12,514 | 1,826(14.6) |
| | Other or Mixed | 12,041 | 1,967 (16.3 |
| | Missing | 672,156 | 128,833 (19.2) |

* Ageband individual was in when antibiotic prescribed

** Calendar period individual was in when antibiotic prescribed

**S2:** Number of people (N=95,603) and duration category (treatment course length) of first oral antibiotic exposure on the day of or after acne code and the proportion of people with acne prescribed an antibiotic receiving a 2nd prescription for an antibiotic. i.e., >14 days after the first prescription.

Continuous courses from individual prescriptions were formed if an antibiotic within the same class was prescribed within 14 days of the start date of the current prescription unless the antibiotic class was changed, in this case two individual courses are described.

| **Antibiotic** | **Number of people receiving an antibiotic prescription exposure length 28 -41 days (%)** | **Number of people receiving an antibiotic prescription exposure length 42 - 90 days (%)** | **Number of people receiving an antibiotic prescription exposure length 91 - 180 days n (%)** | **Number of people receiving an antibiotic prescription exposure 181-365 (%)** | **Number of people receiving an antibiotic prescription exposure length over 365 days (%)** |
|---|---|---|---|---|---|
| **All antibiotics (**n=95,603) | 37,734(39.5) | 56,243 (58.8) | 1,552 (1.6) | 52 (0.1) | 22 (0.0) |
| **Tetracyclines** (n=83,324) | 30,648 (36.8) | 51,284 (61.6) | 1,329 (1.6) | 45 (0.1 | 18 (0.0) |
| **Macrolides** (n=11,209) | 6,357 (56.7) | 4,640 (41.4) | 204 (1.8) | 6 (0.1) | <5 (0.0) |
| **Trimethoprim** (n=1,070) | 729 (68.1) | 319 (29.8) | 19 (1.8) | <5 (0.1) | <5(0.0) |

**S3:** Second antibiotic exposure relative to first with treatment gap of at least 14 days between courses. Median gap between first and second course 167 days (IQR 74-405).

| **1st Antibiotic course (n=95,603)** | **2nd Antibiotic course n=61,218 (64.5 %) Number of people receiving second course of antibiotic for a minimum continuous exposure of 28 days (% of total first course class, n (%)** | | |
|---|---|---|---|
| **Tetracycline** n=83,324 | 53,205 (63.9) | Tetracycline<br>Macrolide<br>Trimethoprim | 48,300 (90.8)<br>4,457 (8.4)<br>448 (0.8) |
| **Macrolide** n=11,209 | 7, 529 (67.1) | Tetracycline<br>Macrolide<br>Trimethoprim | 3,113 (41.4)<br>4,326 (57.5)<br>90 (1.2) |
| **Trimethoprim** n=1,070 | 576 (53.8) | Tetracycline<br>Macrolide<br>Trimethoprim | 268 (46.5)<br>40 (6.9)<br>268 (46.5) |

**S4:** Age category at acne diagnosis by first antibiotic prescribed and sex, n (%). Column percentages.

| **Antibiotic class n (%)** | **Age category n (%)** | | | | |
|---|---|---|---|---|---|
| | **8-11** | **12-18** | **19-25** | **26-35** | **36-50** |
| **Tetracycline** | | | | | |
| **Female** n=47,702 (58.4) | 2,021 (83.6) | 23,195 (46.2) | 9,370 (70.6) | 8,747 (83.6) | 4,369 (82.4) |
| **Male** n=33,970 (41.6) | 397 (16.4) | 27,017 (53.8) | 3,909 (29.4) | 1,713 (16.4) | 934 (17.6) |
| **Total** n= 81,672 | 2,418 | 50,212 | 13,279 | 10,460 | 5,303 |
| **Macrolide** | | | | | |
| **Female** n= 8,155 (61.7) | 729 (84.1) | 3,852 (48.8) | 1,389 (73.7) | 1,523 (86.1) | 662 (83.2) |
| **Male** n= 5,061 (38.3) | 138 (15.9) | 4,048 (51.2) | 495 (26.3) | 246 (13.9) | 136 (16.8) |
| **Total** n=13,216 | 867 | 7,900 | 1,884 | 1,769 | 796 |
| **Trimethoprim** | | | | | |
| **Female** n=1,372 (75.6) | 82 (88.2) | 581 (64.7) | 281 (81.9) | 262 (90.7) | 166 (86.5) |
| **Male** n= 443 (24.4) | 11 (11.8) | 317 (35.3) | 62 (18.1) | 27 (9.3) | 26(13.5) |
| **Total** n=1,815 | 93 | 898 | 343 | 289 | 192 |

## A2.4 Code list development

Since 1985, healthcare professionals across primary and secondary care enter clinical diagnoses, treatments and outcomes onto NHS IT systems using codes with easily identifiable clinical terms. The Clinical Practice Research Datalink (CPRD) comprises of data entered and stored within NHS IT systems. Patient with relevant clinical conditions and treatments can be pulled from the raw data files the CPRD holds by the creation of relevant codelists. Clinical diagnosis codes are referred to as Read codes.

**Acne codes**

There are no validated codelists for acne vulgaris however there have been published studies that have used the CPRD to investigate acne. I therefore identified a method of creating a codelist for acne in six stages.

1. An acne vulgaris codelist was obtained from another published study where the CPRD was used to investigate acne treatments.(80)
2. The existing codelist was examined and refined for the purposes of my study – codes which included causes of acne rather than acne vulgaris, or a description of acne lesions not specific for acne (e.g. 'papule') rather than a lesion pathognomic of acne vulgaris were removed.
3. A list of inclusion and exclusion terms were created. the CPRD GOLD Medical Dictionary Read term field was searched for inclusion terms which were then examined manually to create a provisional codelist.
4. This was cross checked with the codelist from the previous study using an acne codelist outlined above.
5. Codes which required further discussion were then highlighted and discussed with a second dermatologist.
6. The final codelist was then examined by supervisors including a dermatologist, and my advisory committee including a general practitioner.

**Antibiotic codes**

1. An antibiotic codelist was obtained and examined from the authors of another study which used CPRD data to investigate acne treatments.(80)
2. A list of inclusion and exclusion terms were identified – e.g., terms which indicated a route of antibiotic delivery which was not oral e.g., topical or parenteral were excluded.
3. Oral antibiotics that appeared in the acne BNF (British National Formulary) chapter were included as well as oral antibiotics that appear elsewhere in the BNF which may be prescribed by GPs for acne as second line oral antibiotics.
4. THE CPRD GOLD product dictionary was searched using predefined search terms.
5. The extracted codelist was then reviewed manually and edited. It was compared to the codelist from another study investigating antibiotics for acne as outlined above.(80) This involved removing antibiotic codes where the mode of delivery was ambiguous or not stated. Only orally administered antibiotics were included.
6. The final antibiotic codelist was reviewed by supervisors including a dermatologist and then by my advisory committee.

## A2.5 Supplementary material to methodology

**Acne BNF chapter**

Code for prescriptions of the medications in the acne BNF chapter were reviewed and oral antibiotics were removed. Any individual who had had a prescription for an acne medication in the BNF chapter (not oral antibiotics) in the prior one year to the date of acne code were removed from the study population.

**Defining the study population**

I defined people with acne by identifying a single acne diagnostic Read code entered onto the health record between 1st January 2004 and 31st July 2019. There were 995,113 people with an acne code at any time point in the CPRD. In order to capture incident acne, such that oral antibiotic treatment patterns could be captured from acne diagnosis, people who

had been given an acne diagnostic code or had been prescribed acne medication (codelist acne BNF chapter - **appendix 2**) in the prior one year before the start of follow up (1st January 2004) were excluded. Aetiological studies have shown acne generally occurs between the ages of 8 and 50. Below age eight, it is likely that acne has an alternative cause, for example, infantile acne which may be due to the influence maternal hormones in breast milk. After age 50, the prevalence of acne is low.(63) The published manuscript contains a flowchart of how the inclusion and exclusion criteria were applied and how the study population of 217,410 people was derived (**Figure 2 of manuscript in chapter 5**).

**Defining antibiotic prescription length (total exposure duration)**

The CPRD holds information on the total number of tablets prescribed (quantity) as well as the recommended number of tablets to be taken per day (numeric daily dose, NDD). From this information, the total treatment duration per prescription can be calculated by division. Some of the information was unreliable however and the following section described how this unreliable information was captured and corrected.

There were 5,747,181 antibiotic therapy records for people in the CPRD who had an acne Read code.

1. If the quantity and/or NDD were missing, they were replaced as per the following:
    a. NDD
        i. If another record existed for the same patient, the same quantity and dose was entered.
        ii. If the above was not available then the median NDD for the same dose and quantity group (quantity above or below 90) was imputed.
        iii. If a record existed for the same patient, the NDD for the same dose was entered.
        iv. If there were no other records for the patient without missing data, the median NDD was taken from the same age group, sex, dose and quantity.
        v. Lastly, the median NDD was imputed from the same age group, sex, dose and quantity group.
    b. Quantity only

i. If a record existed for the same patient, the same NDD and dose was used.
ii. If a record existed for the same patient then the same dose, NDD group (quantity above or below 90) was imputed.
iii. If a record existed for the same patient, the same dose was entered.
iv. If there were no other records for the patient without missing data, the quantity was taken from the median NDD for the same age group, sex dose and NDD.
v. Lastly, the same NDD was imputed from the same age group, sex, dose and NDD group.

Where it was not possible to ascertain quantity and NDD in order to calculate duration, the median duration was entered.

**Defining a long-term oral antibiotic for acne**

Most guidelines recommend that a course of oral antibiotics for acne is prescribed for three to four months and some guidelines recommend that oral antibiotic effectiveness can be assessed at six weeks.(45, 69, 78). The three main classes of oral antibiotic prescribed for acne in the UK, tetracyclines, macrolides and trimethoprim are also prescribed for other conditions such as urinary tract infections, or skin and soft tissue infections however courses are for less than two weeks. In view of the guideline recommendations for the use of oral antibiotic treatment for acne, 28 days was chosen as the minimum duration of a prescription as it would be rare for durations of less than 28 days to be for acne, and therefore other indications for the antibiotic could be excluded. A similar framework for minimum duration of antibiotics for acne was used by Francis et al.(80)

**Refinement of prescriptions - bridging individual prescriptions together to form complete continuous courses**

In some circumstances, it is possible GPs prescribe fewer than 28 days of an oral antibiotic for acne if a class of antibiotic were to be trialled and if found to be appropriate for the patient, another prescription provided to bridge onto the existing prescription to provide a longer course. It is also possible that patients may receive an initial 28 day course of oral

antibiotic and then be re-prescribed further antibiotics till they obtain their full treatment course as intended by their GP. Therefore, it was important to bridge individual prescriptions together to make a continuous course so that a full treatment length or course could be described.

After consideration, 28 days was chosen as the time gap between the last covered day of the previous prescription and the start date of the next prescription – if there was 28 days or fewer between the last covered day and the start date of a new prescription for the same antibiotic class then one continuous course of antibiotics was described. The duration of 28 days was chosen as it gives an appropriate amount of time for the patient to establish that their current supply is finishing, request a new prescription from their GP, for the GP to issue a new prescription, for the prescription to be sent to the pharmacy or collected from the surgery and then taken to the pharmacy, for the pharmacy to dispense medication and for the patient to collect it and continue their treatment. If there were 29 days or greater between the last covered day (prescription start date + intended number of days of treatment) of the previous prescription and the start date of the next prescription, then two distinct courses were described. The course end was therefore the last covered day with at least 28 days with no antibiotic treated days before another prescription for another antibiotic if there was one issued. The gap between individual prescriptions forming a course were presumed antibiotic covered days and contributed to the overall duration of the course. This would allow for intermittent exposure to antibiotic if for example if a patient missed days of taking the antibiotic within a course and therefore the supply lasted longer.

GP personal prescribing preference and local policy dictate the duration of prescription for acne with some GPs prescribing 28 days or one month, some 56 days or two months and some 84 days or three months. More recently in latter years, local drug and prescribing committees or pharmaceutical advisors to CCGs or PCTs have recommended shorter durations to be prescribed therefore it is more likely that shorter durations e.g. 28 days are prescribed and not the full recommended treatment duration of three months. There is no national acne prescribing policy and GPs consider their own prescribing preferences, local prescribing policy and the patient they are treating when issuing prescriptions. More recent prescribing recommendations across all drugs mean that some GPs by default prescribe no more than 28 days per prescription.

# A2.6 Final list of codes

## Acne

| medcode | readcode | readterm (Code list adapted from Francis et al 2017 doi: 10.1111/bjd.15081) |
|---|---|---|
| 20164 | M260z11 | Acne necrotica |
| 48105 | M260.00 | Acne varioliformis |
| 24184 | M261700 | Acne neonatorum |
| 31828 | M261900 | Occupational acne |
| 379 | M261000 | Acne vulgaris |
| 12672 | M261E00 | Acne excoriee des jeunes filles |
| 16612 | M25y600 | Acne keloid |
| 34937 | M261J00 | Acne necrotica |
| 32041 | M261B00 | Steroid acne |
| 1654 | M261600 | Cystic acne |
| 9008 | M261100 | Acne conglobata |
| 100167 | M261K00 | Acne keloidalis |
| 10183 | M260000 | Acne frontalis |
| 4065 | M261.00 | Other acne |
| 52909 | Myu6800 | [X]Other acne |
| 9961 | M261H00 | Acne keloid |
| 33367 | Myu6F00 | [X]Acne, unspecified |
| 53994 | M261F00 | Acne fulminans |
| 4360 | M261A00 | Pustular acne |
| 107861 | M261200 | Bromine acne |
| 25737 | N25..00 | SAPHO syndrome Synov, Acne, Pustul, Hyperost, Osteomyelitis |
| 15655 | M261z00 | Other acne NOS |
| 43811 | M261G00 | Acne agminata |
| 25590 | M261X00 | Acne, unspecified |
| 54566 | M260z00 | Acne varioliformis NOS |
| 17895 | 2FG5.00 | Acne scar |
| 10048 | M261800 | Infantile acne |
| 55983 | M261300 | Chlorine acne |
| 16324 | M261D00 | Acne urticata |
| 55003 | 2FY0.00 | O/E - closed comedones |

## Oral antibiotics

| bnfcode | productname | drugsubstancename | routeofadministration |
|---|---|---|---|
| 5010300 | Achromycin 125mg/5ml Oral solution (Wyeth Pharmaceuticals) | Tetracycline Hydrochloride | Oral |
| 5010300 | Achromycin 250mg Tablet (Wyeth Pharmaceuticals) | Tetracycline hydrochloride | Oral |
| 5010300 | Achromycin 250mg capsules (Wyeth Pharmaceuticals) | Tetracycline hydrochloride | Oral |
| 5010300 | Achromycin v 250mg Capsule (Wyeth Pharmaceuticals) | Tetracycline hydrochloride | Oral |
| 13060201 | Acnamino MR 100mg capsules (Almus Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Acnamino MR 100mg capsules (Dexcel-Pharma Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Aknemin 100mg capsules (Almirall Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Aknemin 50 capsules (Almirall Ltd) | Minocycline hydrochloride | Oral |
| 5010500 | Arpimycin 125mg/5ml Liquid (Rosemont Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Arpimycin 125mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Arpimycin 250mg/5ml Liquid (Rosemont Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Arpimycin 250mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Arpimycin 500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010300 | Aureomycin 250mg Capsule (Wyeth Pharmaceuticals) | Chlortetracycline Hydrochloride | Oral |
| 50000000 | Aureomycin Powder (Wyeth Pharmaceuticals) | Chlortetracycline Hydrochloride | |
| 5010300 | Berkmycen 250mg Tablet (Berk Pharmaceuticals Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Blemix 100mg tablets (Ashbourne Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Blemix 50mg tablets (Ashbourne Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Chlortetracycline 250mg capsules | Chlortetracycline Hydrochloride | Oral |
| 5010300 | Cyclodox 100mg Capsule (Berk Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Cyclomin 100mg Tablet (Berk Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Cyclomin 50mg Tablet (Berk Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Demix 100 capsules (Ashbourne Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Demix 50 capsules (Ashbourne Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxatet 100mg Tablet (Manufacturer unknown) | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline (as hyclate) 100mg dispersible tablets | Doxycycline Monohydrate | Oral |
| 5010300 | Doxycycline (as hyclate) 100mg tablets | Doxycycline Hyclate | Oral |
| 12030100 | Doxycycline (as hyclate) 20mg capsules | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline (as hyclate) 50mg capsules with microgranules | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline (as hyclate) 50mg capsules with microgranules | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline (as hyclate) 50mg/5ml oral solution | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline 100mg Capsule (IVAX Pharmaceuticals UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg Capsule (Neo Laboratories Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg Tablet (Neo Laboratories Ltd) | Doxycycline Hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules (A A H Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules (Actavis UK Ltd) | Doxycycline hyclate | Oral |
| 13060201 | Doxycycline 100mg capsules (Almus Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules (IVAX Pharmaceuticals UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules (Mylan) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg capsules (Teva UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 100mg dispersible tablets sugar free | Doxycycline monohydrate | Oral |
| 12030100 | Doxycycline 20mg tablets | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 40mg modified-release capsules | Doxycycline monohydrate | Oral |
| 5010300 | Doxycycline 50mg capsules | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 50mg capsules (A A H Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 50mg capsules (IVAX Pharmaceuticals UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 50mg capsules (Kent Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxycycline 50mg capsules (Mylan) | Doxycycline hyclate | Oral |

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| 5010300 | Doxycycline 50mg capsules (Teva UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxylar 100mg capsules (Sandoz Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Doxylar 50mg capsules (Sandoz Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Efracea 40mg modified-release capsules (Galderma (UK) Ltd) | Doxycycline monohydrate | Oral |
| 5010500 | Erycen 250mg Tablet (Berk Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erycen 500mg Tablet (Berk Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erymax 250mg Capsule (Elan Pharma) | Erythromycin | Oral |
| 5010500 | Erymax 250mg gastro-resistant capsules (Teva UK Ltd) | Erythromycin | Oral |
| 5010500 | Erymax sprinkle 125mg Capsule (Elan Pharma) | Erythromycin | Oral |
| 5010500 | Erymin 250mg/5ml Oral suspension (Elan Pharma) | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythoden 250mg/5ml Liquid (Stevenden Healthcare) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythrocin 250 tablets (Advanz Pharma) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 250mg Tablet (Abbott Laboratories Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 500 500mg Tablet (Abbott Laboratories Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 500 tablets (Advanz Pharma) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 500 tablets (Dowelhurst Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 500 tablets (Sigma Pharmaceuticals Plc) | Erythromycin stearate | Oral |
| 5010500 | Erythrocin 500 tablets (Stephar (U.K.) Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythrolar 250mg Tablet (Lagap) | Erythromycin stearate | Oral |
| 5010500 | Erythrolar 250mg tablets (Ennogen Pharma Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythrolar 250mg/5ml Liquid (Lagap) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythrolar 500mg Tablet (Lagap) | Erythromycin stearate | Oral |
| 5010500 | Erythrolar 500mg tablets (Ennogen Pharma Ltd) | Erythromycin stearate | Oral |
| 5010500 | Erythromid 250mg Tablet (Abbott Laboratories Ltd) | Erythromycin | Oral |
| 5010500 | Erythromid ds 500mg Tablet (Abbott Laboratories Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 125mg sprinkle capsules | Erythromycin | Oral |
| 5010500 | Erythromycin 125mg/5ml Liquid (Berk Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin 125mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin 125mg/5ml oral suspension | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin 250mg Capsule (Actavis UK Ltd) | Erythromycin Lactobionate | Oral |
| 5010500 | Erythromycin 250mg Gastro-resistant tablet (Co-Pharma Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg Tablet (Berk Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg Tablet (C P Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant capsules | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant capsules (A A H Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant capsules (Teva UK Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (A A H Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (Abbott Laboratories Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (Actavis UK Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (Almus Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (Mylan) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg gastro-resistant tablets (Teva UK Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 250mg.5ml oral suspension | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin 250mg/5ml Liquid (C P Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin 250mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin 500mg Tablet (C P Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010500 | Erythromycin 500mg Tablet (Teva UK Ltd) | Erythromycin | |
| 5010500 | Erythromycin 500mg ec gastro-resistant tablets | Erythromycin | Oral |

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| 5010500 | Erythromycin 500mg/5ml oral suspension | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin estolate 125mg/5ml suspension | Erythromycin Lactobionate | Oral |
| 5010500 | Erythromycin estolate 250mg capsules | Erythromycin Lactobionate | Oral |
| 5010500 | Erythromycin estolate 250mg/5ml suspension | Erythromycin Lactobionate | Oral |
| 5010500 | Erythromycin estolate 500mg tablets | Erythromycin Lactobionate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Mylan) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Teva UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Teva UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 500mg tablets | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 500mg/5ml oral suspension | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Teva UK Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin ethylsuccinate 125mg sachets | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin ethylsuccinate 1g sachets | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin ethylsuccinate 250mg sachets | Erythromycin Ethyl Succinate | Oral |
| 0 | Erythromycin ethylsuccinate 500mg sachets | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythromycin stearate 250mg tablets | Erythromycin stearate | Oral |
| 5010500 | Erythromycin stearate 500mg tablets | Erythromycin stearate | Oral |
| 5010500 | Erythroped 250mg Powder (Abbott Laboratories Ltd) | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythroped 250mg Sachets (Abbott Laboratories Ltd) | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythroped 250mg/5ml Liquid (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped 250mg/5ml Oral suspension (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped A 500mg tablets (Advanz Pharma) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped A 500mg tablets (Lexon (UK) Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped A 500mg tablets (Sigma Pharmaceuticals Plc) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped Forte SF 500mg/5ml oral suspension (Advanz Pharma) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped PI SF 125mg/5ml oral suspension (Advanz Pharma) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped SF 250mg/5ml oral suspension (Advanz Pharma) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped a 1g Sachets (Abbott Laboratories Ltd) | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythroped a 500mg Tablet (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped forte 500mg Sachets (Abbott Laboratories Ltd) | Erythromycin Ethyl Succinate | Oral |
| 5010500 | Erythroped forte 500mg/5ml Liquid (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped forte 500mg/5ml Oral suspension (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped pi 125mg Sachets (Abbott Laboratories Ltd) | Erythromycin Ethyl Succinate | Oral |

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| 5010500 | Erythroped pi 125mg/5ml Liquid (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Erythroped pi 125mg/5ml Oral suspension (Abbott Laboratories Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Ilosone 125mg/5ml Liquid (Dista Products Ltd) | Erythromycin Lactobionate | Oral |
| 5010500 | Ilosone 250mg Capsule (Dista Products Ltd) | Erythromycin Lactobionate | Oral |
| 5010500 | Ilosone 250mg/5ml Liquid (Dista Products Ltd) | Erythromycin Lactobionate | Oral |
| 5010500 | Ilosone 500mg Tablet (Dista Products Ltd) | Erythromycin | Oral |
| 5010500 | Ilotycin 250mg Tablet (Eli Lilly and Company Ltd) | Erythromycin | Oral |
| 5010300 | Imperacin 250mg Tablet (AstraZeneca UK Ltd) | Oxytetracycline dihydrate | Oral |
| 5010800 | Ipral 100mg Tablet (E R Squibb and Sons Ltd) | Trimethoprim | Oral |
| 5010800 | Ipral 200mg Tablet (E R Squibb and Sons Ltd) | Trimethoprim | Oral |
| 5010800 | Ipral 50mg/5ml Liquid (E R Squibb and Sons Ltd) | Trimethoprim | Oral |
| 5010500 | Kerymax 250mg gastro-resistant capsules (Kent Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010300 | Lymecycline 408mg capsules | Lymecycline | Oral |
| 5010300 | Lymecycline 408mg capsules (A A H Pharmaceuticals Ltd) | Lymecycline | Oral |
| 5010300 | Lymecycline 408mg capsules (Teva UK Ltd) | Lymecycline | Oral |
| 5010300 | Minocin 100mg tablets (Wyeth Pharmaceuticals) | Minocycline hydrochloride | Oral |
| 5010300 | Minocin 50mg tablets (Wyeth Pharmaceuticals) | Minocycline hydrochloride | Oral |
| 5010300 | Minocin MR 100mg capsules (Mylan) | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg capsules | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg modified-release capsules | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg modified-release capsules (A A H Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg tablets | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg tablets (A A H Pharmaceuticals Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 100mg tablets (Actavis UK Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 50mg Tablet (Lagap) | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 50mg capsules | Minocycline hydrochloride | Oral |
| 5010300 | Minocycline 50mg tablets | Minocycline hydrochloride | Oral |
| 5010800 | Monotrim 100mg tablets (Abbott Healthcare Products Ltd) | Trimethoprim | Oral |
| 5010800 | Monotrim 200mg tablets (Abbott Healthcare Products Ltd) | Trimethoprim | Oral |
| 5010800 | Monotrim 50mg/5ml Liquid (Solvay Healthcare) | Trimethoprim | Oral |
| 5010800 | Monotrim 50mg/5ml oral suspension (Chemidex Pharma Ltd) | Trimethoprim | Oral |
| 5010300 | Nordox 100mg Capsule (Sankyo Pharma UK Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Oxymycin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 125mg/5ml syrup | Oxytetracycline Dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg Tablet (C P Pharmaceuticals Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg capsules | Oxytetracycline Dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (A A H Pharmaceuticals Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (Actavis UK Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (Almus Pharmaceuticals Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (IVAX Pharmaceuticals UK Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (Sandoz Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg tablets (Teva UK Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetracycline 250mg/5ml oral suspension | Oxytetracycline dihydrate | Oral |
| 5010300 | Oxytetramix 250 tablets (Ashbourne Pharmaceuticals Ltd) | Oxytetracycline dihydrate | Oral |
| 12030100 | Periostat 20mg tablets (Alliance Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |
| 5010500 | Primacine 125mg/5ml Liquid (Pinewood Healthcare) | Erythromycin ethyl succinate | Oral |
| 5010500 | Primacine 500mg/5ml Liquid (Pinewood Healthcare) | Erythromycin ethyl succinate | Oral |
| 5010500 | Rommix 125mg/5ml Oral suspension sugar free (Ashbourne Pharmaceuticals Ltd) | Erythromycin ethyl succinate | Oral |
| 5010500 | Rommix 250 EC tablets (Ashbourne Pharmaceuticals Ltd) | Erythromycin | Oral |

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| 5010500 | Rommix 500mg Tablet (Ashbourne Pharmaceuticals Ltd) | Erythromycin | Oral |
| 5010300 | Sebomin MR 100mg capsules (Actavis UK Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Sebren MR 100mg capsules (Teva UK Ltd) | Minocycline hydrochloride | Oral |
| 5010300 | Sustamycin 250mg Capsule (Boehringer Mannheim UK Ltd) | Tetracycline Hydrochloride | Oral |
| 5010800 | Syraprim 100mg Tablet (Wellcome Medical Division) | Trimethoprim | Oral |
| 5010800 | Syraprim 300mg Tablet (Wellcome Medical Division) | Trimethoprim | Oral |
| 5010300 | Terramycin 250mg Capsule (Pfizer Ltd) | Oxytetracycline Dihydrate | Oral |
| 5010300 | Terramycin 250mg tablets (Pfizer Ltd) | Oxytetracycline dihydrate | Oral |
| 5010300 | Tetrabid-organon 250mg Capsule (Organon Laboratories Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetrachel 250mg Capsule (Berk Pharmaceuticals Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetrachel 250mg Tablet (Berk Pharmaceuticals Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 125mg/5ml oral solution | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 125mg/5ml syrup | Tetracycline Hydrochloride | Oral |
| 5010300 | Tetracycline 250mg Capsule (Berk Pharmaceuticals Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 250mg capsules | Tetracycline Hydrochloride | Oral |
| 5010300 | Tetracycline 250mg capsules | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 250mg tablets | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 250mg tablets (A A H Pharmaceuticals Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 250mg tablets (Actavis UK Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetracycline 250mg tablets (Teva UK Ltd) | Tetracycline hydrochloride | Oral |
| 5010300 | Tetralysal 300 capsules (DE Pharmaceuticals) | Lymecycline | Oral |
| 5010300 | Tetralysal 300 capsules (Galderma (UK) Ltd) | Lymecycline | Oral |
| 5010300 | Tetralysal 408mg Capsule (Pharmacia Ltd) | Lymecycline | Oral |
| 5010500 | Tiloryth 250mg gastro-resistant capsules (Tillomed Laboratories Ltd) | Erythromycin | Oral |
| 5010800 | Trimethoprim 100mg tablets | Trimethoprim | Oral |
| 5010800 | Trimethoprim 100mg tablets (A A H Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 100mg tablets (Kent Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 100mg tablets (Teva UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (A A H Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (Actavis UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (Almus Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (IVAX Pharmaceuticals UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (Ranbaxy (UK) Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (Sandoz Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 200mg tablets (Teva UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 300mg Tablet | Trimethoprim | Oral |
| 5010800 | Trimethoprim 50mg/5ml oral suspension sugar free | Trimethoprim | Oral |
| 5010800 | Trimethoprim 50mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 0 | Trimethoprim 50mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Trimethoprim 50mg/5ml oral suspension sugar free (Teva UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimopan 100mg tablets (Teva UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimopan 200mg tablets (Teva UK Ltd) | Trimethoprim | Oral |
| 5010800 | Trimopan 50mg/5ml Liquid (Berk Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010800 | Triprimix 200 Tablet (Ashbourne Pharmaceuticals Ltd) | Trimethoprim | Oral |
| 5010300 | Vibramycin 100mg Dispersible tablet (Pfizer Ltd) | Doxycycline monohydrate | Oral |
| 5010300 | Vibramycin 100mg capsules (Pfizer Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Vibramycin 50 capsules (Pfizer Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Vibramycin 50mg/5ml Oral solution (Pfizer Ltd) | Doxycycline Hyclate | Oral |
| 5010300 | Vibramycin Acne Pack 50mg capsules (Pfizer Ltd) | Doxycycline hyclate | Oral |
| 5010300 | Vibramycin-D 100mg dispersible tablets (Pfizer Ltd) | Doxycycline monohydrate | Oral |
| 5010300 | Vibrox 100mg capsules (Kent Pharmaceuticals Ltd) | Doxycycline hyclate | Oral |

**Acne BNF chapter codes**

Available on the LSHTM Data Compass pages https://doi.org/10.17037/DATA.00002845.

# Appendix 3 - supplementary materials to Chapter 6 – cohort study

Bhate K, Sinnott SJ, Margolis DJ, Mansfield KE, Francis N, Leyrat C, Hopkins S, Stabler R, Shallcross L, Mathur R, Langan SM. Long-term oral antibiotic for acne and antibiotic treatment failure: three population-based cohort studies in the United Kingdom.

## CONTENTS



## Supplementary tables and figures

# A3.1 ISAC study protocol

Medicines & Healthcare products Regulatory Agency

CPRD

1

General information

**Protocol reference Id**

20_000229

**Study title**

Do long-term oral antibiotics for acne contribute to antibiotic treatment failure?

**Research Area**

Disease Epidemiology

**Does this protocol describe an observational study using purely CPRD data?**

Yes

**Does this protocol involve requesting any additional information from GPs, or contact with patients?**

No

## 2 Research team

| | |
|---|---|
| **Role** | Chief Investigator |
| **Title** | Professor of Clinical Epidemiology |
| **Full name** | Sinead Langan |
| **Affiliation/organisation** | London School of Hygiene & Tropical Medicine ( LSHTM ) |
| **Email** | sinead.langan@lshtm.ac.uk |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Corresponding Applicant |
| **Title** | Clinical research fellow |
| **Full name** | Ketaki Bhate |
| **Affiliation/organisation** | London School of Hygiene & Tropical Medicine ( LSHTM ) |
| **Email** | ketaki.bhate@lshtm.ac.uk |
| **Will this person be analysing the data?** | Yes |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Collaborator |
| **Title** | Professor of Primary Care Research |
| **Full name** | Nick Francis |
| **Affiliation/organisation** | University of Southampton |
| **Email** | nick.francis@soton.ac.uk |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

| | |
|---|---|
| **Role** | Collaborator |
| **Title** | Consultant |
| **Full name** | Susan Hopkins |
| **Affiliation/organisation** | Royal Free London NHS Foundation Trust |
| **Email** | susanhopkins@nhs.net |
| **Will this person be analysing the data?** | No |
| **Status** | Confirmed |

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3

## Access to data

**Sponsor**

London School of Hygiene & Tropical Medicine ( LSHTM )

**Funding source for the study**

**Is the funding source for the study the same as Chief Investigator's affiliation?**

No

**Funding source for the study**

National Institute for Health Research ( NIHR )

**Institution conducting the research**

**Is the institution conducting the research the same as Chief Investigator's affiliation?**

Yes

**Institution conducting the research**

London School of Hygiene & Tropical Medicine ( LSHTM )

**Method to access the data**

**Indicate the method that will be used to access the data**

Institutional multi-study licence

**Is the institution the same as Chief Investigator's affiliation?**

Yes

**Institution name**

London School of Hygiene & Tropical Medicine ( LSHTM )

**Extraction by CPRD**

**Will the dataset be extracted by CPRD**

No

**Multiple data delivery**

**This study requires multiple data extractions over its lifespan**

No

**Data processors**

| | |
|---|---|
| **Data processor is** | Same as the chief investigator's affiliation |
| **Processing** | Yes |
| **Accessing** | Yes |
| **Storing** | Yes |
| **Processing area** | UK |

## 4 Information on data

**Primary care data**

CPRD GOLD

**Do you require data linkages**

Yes

**Patient level data**

HES Admitted Patient Care

**NCRAS data**

**Covid 19 linkages**

**Area level data**

**Do you require area level data?**

Yes

**Practice level (UK)**

Practice Level Index of Multiple Deprivation

**Patient level (England only)**

Patient Level Index of Multiple Deprivation

| |
|---|
| |
| |
| |

5

Protocol information

**Lay Summary**

Acne, or 'spots', affect almost everyone. Doctors sometimes prescribe antibiotics to treat acne. Most people find antibiotics improve their acne, not because acne is an infection, but because antibiotics lessen the redness of spots. Using antibiotics does not stop spots coming back. Acne treatment guidelines recommend repeated courses of antibiotics, each lasting 3-6 months. Antibiotic courses can be given intermittently over many years.

Unfortunately, some bugs (bacteria) become resistant to antibiotics. If we use antibiotics too often or for too long, bacteria develop ways to avoid antibiotics. This is important because it means that antibiotics used to treat infections stop working; this is called antimicrobial resistance. Scientists have predicted by 2050, 10 million people per year will die because some antibiotics no longer work.

It is possible that repeated antibiotic courses, potentially given over many years, to treat acne may contribute to antimicrobial resistance. Our study will use large amounts of information that is collected when people visit their doctor to explore how antibiotics for acne might contribute to antimicrobial resistance. We will look at how well people respond to antibiotics for common infections after they have had antibiotic tablets for acne compared to people who did not get antibiotic tablets for their acne (e.g., did they need to switch to an alternative antibiotic after the first antibiotic was prescribed?). Our study will compare whether antibiotics are less effective in treating infections in people with acne who have had long-term antibiotics to those with acne who haven't had long-term antibiotics.

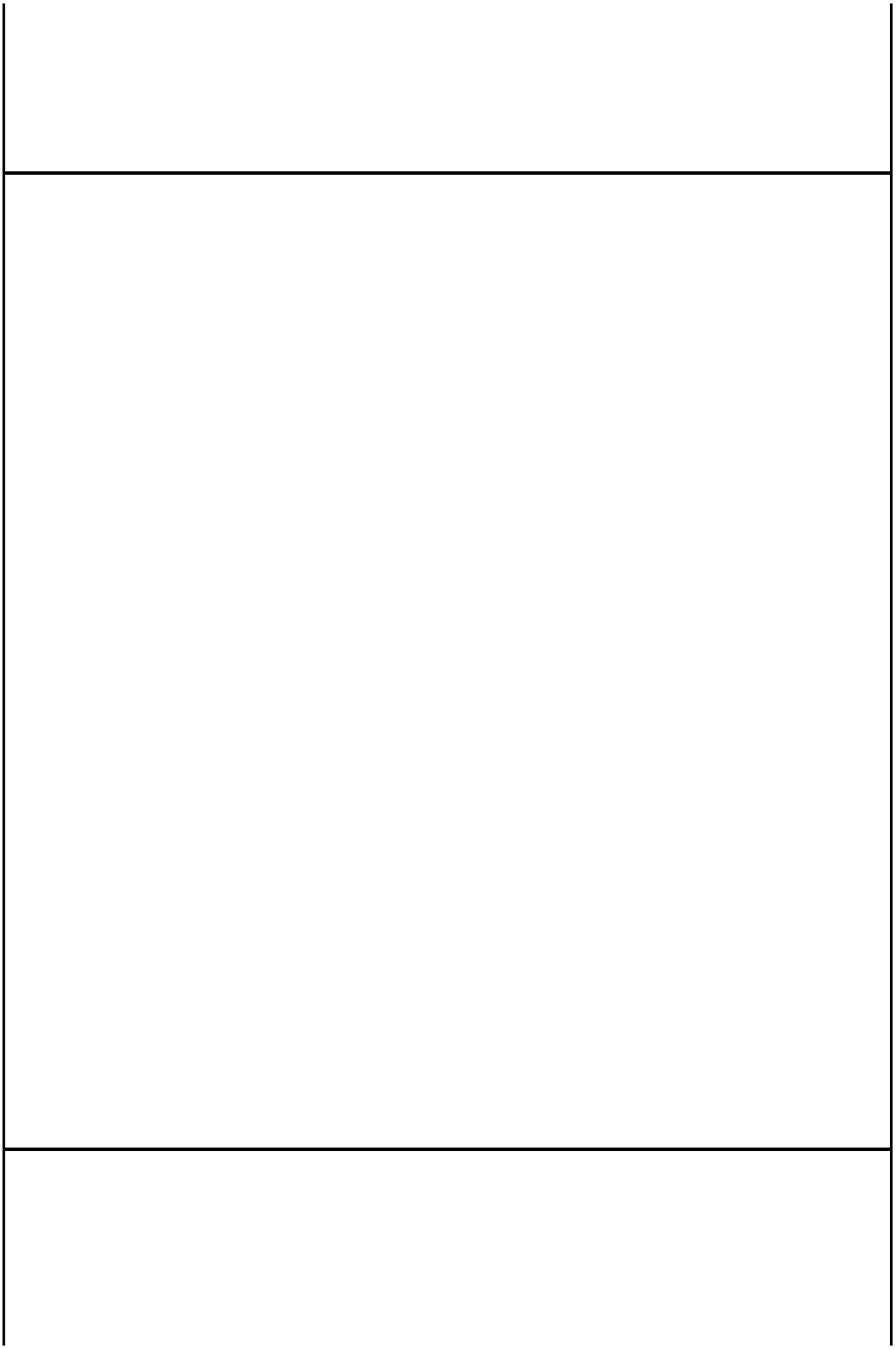
**Technical Summary**

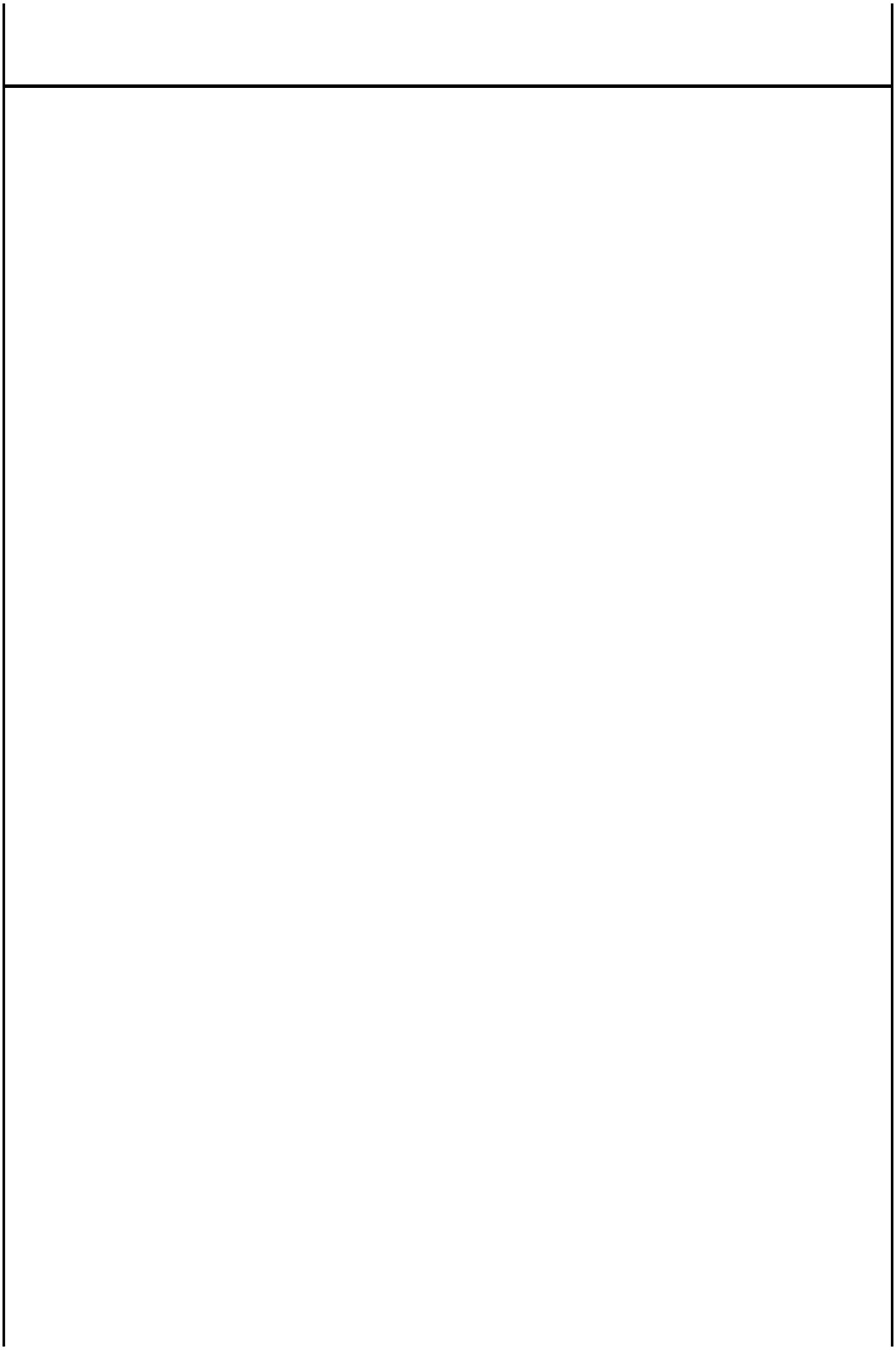
Long-term antibiotics for acne may contribute to antimicrobial resistance potentially leading to antibiotic treatment failure (i.e., when an antibiotic fails to effectively treat an infection due to antimicrobial resistance). Our aim is to establish if oral antibiotics for acne contribute to antibiotic treatment failure when antibiotics are prescribed for common infections (i.e., lower respiratory tract, skin/soft tissues, urinary tract). As we cannot directly capture antimicrobial resistance in electronic health records, we will use antibiotic treatment failure as a proxy.

We will undertake a cohort study to compare antibiotic treatment failure (i.e., prescription of an alternative antibiotic, or infection-related hospital admission, for common infections [lower respiratory tract, skin/soft tissue, urinary tract]) in people with acne who have been treated with long-term oral antibiotics (prescription of 28 days or more for antibiotic classes used to treat acne: tetracyclines, macrolides, trimethoprim, recorded on or after first acne diagnosis) to people with acne who have not been treated with long-term oral antibiotics.
Our study population will include individuals (aged 8-50) who have received an acne diagnostic code between the 1st of January 2004 and the 31st of December 2019.

We will follow individuals from date of first non-acne antibiotic within one week following a specific infection after initial acne diagnosis.

We will use Cox regression to estimate hazard ratios (95% confidence intervals), comparing antibiotic failure in those with acne who have been treated with long-term oral antibiotics compared to those with acne not treated with long term oral antibiotics, adjusted for confounders including age, sex, recent hospitalisation, and other medical conditions.





Richard J. Silverwood, Sinéad M. Langan. Association Between Atopic Eczema and Cancer in England and Denmark. JAMA Dermatol. 2020.
25. Mathur R BK, Chaturvedi N, Leon DA, vanStaa T, Grundy E et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. . J Public Health (Oxf). 2014;36:684-92.
26. Dréno B BV, Ochsendorf F, Layton A, Mobacken H, Degreef H; 2004. European Expert Group on Oral Antibiotics in Acne. European recommendations on the use of oral antibiotics for acne. Eur J Dermatol 14( Nov-Dec;):391-9.

**Appendices**

appendix-a---codelist-isac-cohort-study_acne-codes_1.txt

appendix-a---codelist-isac-cohort-study_alcohol_7.txt

appendix-a---codelist-isac-cohort-study_antibiotic-codes_2.txt

appendix-a---codelist-isac-cohort-study_bnf-codes_3.txt

appendix-a---codelist-isac-cohort-study_lrti_4.txt

appendix-a---codelist-isac-cohort-study_ssti_5.txt

appendix-a---codelist-isac-cohort-study_uti_6.txt

**Grant ID**
DRF-2018-011-ST2-066

# A3.2 LSHTM ethics approval

## LSHTM Ethics Application & CARE Form

### Project Information

Staff members/students based at:

- (•) LSHTM
- ( ) MRCG@LSHTM

1. Full project title

Understanding the use of long-term antibiotics for acne in the United Kingdom

2. Is this Project in fulfillment of a degree?

(•) Yes ( ) No

2a. Degree registered for

PhD

2b. Have you completed upgrading?

- ( ) Yes
- (•) No

2b (ii). If you have not yet completed upgrading, please state when upgrading is likely to take place, as well, detail why you are submitting to the ethics committee at this stage.

Upgrading 13th September 2019. This study has been approved by ISAC.

2f(deg). Is this an original submission, or are you responding to a request for clarification from the LSHTM ethics committee?

- ( ) Original submission
- (•) Responding to request for clarification

2f(i-deg) Please upload a covering letter responding to the committee's request for clarification (please use the same format as that shown in the template cover letter available under Help-Templates). Please upload all amended documents in the relevant section of the form.

Documents

| Type | Document Name | File Name | Version Date | Version | Size |
|---|---|---|---|---|---|
| Covering Letter | LEO Cover letter 18.10.19 | LEO Cover letter 18.10.19.docx | 18/10/2019 | 1 | 14.9 KB |
| Covering Letter | LEO Cover letter 31.10.19 | LEO Cover letter 31.10.19.docx | 31/10/2019 | 1 | 15.1 KB |

## Student Details

3a. Student details

Title First Name Surname

[redacted]

Address [redacted]

[redacted]

City [redacted]

Postcode [redacted]

Telephone [redacted]

Email [redacted]

3c. Supervisor's name.

[redacted]

3c (i). Supervisor's email address (if more than one, please only provide the email address of your main supervisor)

Email [redacted]

3 c(ii). Supervisor's institution

- (•) LSHTM
- ( ) MRC Gambia or Uganda
- ( ) Other

3e. Supervisor status

Confirmed

## Project Type

Note: Completing the filter will enable and disable sections of the form so you may not see all questions.

4. Does the research involve primary data collection, analysis of data/samples that have already been collected, or a mix of both?

- ○ Primary
- ◉ Previously collected data/samples
- ○ Mixed

4a(iii). Select type of project:

Project using data from secondary sources

6. Is this project being undertaken by Chariot Innovations or by the Rapid Support Team?

- ○ Yes
- ◉ No

## Samples

6a. Does this research project involve the collection, or use of previously collected, human tissue samples e.g urine, stool, blood etc? (Please select yes even if the samples are not considered relevant material under the Human Tissue Act)

- ○ Yes
- ◉ No

6b. Will this project involve living animals (either laboratory, livestock or wild animals) AND/OR biological material that has been obtained from animals in the experiments planned?

- ○ Yes
- ◉ No

## Fast-Track

7. Does this project use anonymised and unlinkable secondary datasets only?

- (•) Yes
- ( ) No

7a. Will this project be conducted within the NHS?

- ( ) Yes
- (•) No

7b. Is this application for fast-track? Note: MSc applications are not currently available for fast-track

- (•) Yes
- ( ) No

7c. Select reason for fast-track

Using anonymised and unlinkable secondary datasets only

## Vulnerable Groups

8c. Does this research project involve vulnerable groups? Vulnerable groups include: children, individuals with mental disability or learning difficulties, pregnant women, prisoners etc (see information icon for full description).

- ( ) Yes
- (•) No

## Security Sensitive Research Material

9. Does this research involve access to and/or storage of security sensitive research material? (please see information icon for what is considered security sensitive material)

- ( ) Yes
- (•) No

## Geography

10. List the countries where the research project is to be conducted (For example: if you are conducting a secondary data analysis for your project and you will be based in the UK, select UK regardless of where the original data has come from):

United Kingdom

10. List the countries where the research project is to be conducted (For example: if you are conducting a secondary data analysis for your project and you will be based in the UK, select UK regardless of where the original data has come from):

United States of America

Please be aware that all primary health research conducted in the UK requires a sponsor. Please contact the RGIO at RGIO@lshtm.ac.uk for more information on sponsorship.

## Outline

Note: Please do not copy and paste directly from the protocol. Applications where large portions of text have been copied and pasted directly from the protocol, and therefore do not properly answer the question, will be invalidated

12. Give an outline of the proposed project, including background to the proposal. Include information from any systematic reviews that have been conducted. Sufficient detail must be given to allow the Committee to make an informed decision without reference to other documents.

A. Study Background

The future effectiveness of antibiotics is in jeopardy with the World Health Organisation declaring the threat of Antimicrobial Resistance (AMR) a most urgent crisis. (3) Without intervention, future deaths from infections as a result of AMR is estimated at 10 million per year and by 2050, the cost of AMR could reach 100 trillion USD.(4)

The overuse of antibiotics is a known cause of AMR as repeated and sustained exposure allows microbes to develop mechanisms to avoid the effects of the drugs designed to defeat them.

Topical and oral antibiotics are commonly prescribed for the treatment of acne vulgaris, a chronic skin disorder with onset predominantly in adolescence. Given the psychosocial consequences and potential for permanent disfigurement with scarring, it is imperative that people with acne receive effective treatment.(5, 6) Prevalence studies show that 80-100% of teenagers have acne and that 20% are moderately to severely affected. The high prevalence of acne means that both topical and oral antibiotics are used in a large proportion of the adolescent population and for variable durations ranging from 6 weeks to many months, and in some cases, several years.(7, 8) Differences between international guidelines regarding duration of treatment is one of the reasons that antibiotics for acne are used for significantly longer than recommended .(8-13) Tetracyclines and macrolides are the two most common oral antibiotic classes prescribed for acne with varying durations of average use depending on treatment setting and between different countries.(8, 14)

Although acne is not an infectious disease and aetiologically is multifactorial, we already know that some strains of Cutibacterium acnes (formally Propionibacterium acnes or P. acnes), the bacteria pathophysiologically associated with acne, are now resistant to commonly used antibiotics in acne, making their initial use as anti-microbial agents futile.(15, 16) However, we do not know how these long-term antibiotics for acne may attenuate microbiota elsewhere, and the ability of other bacteria at other infective sites to withstand the effect of antibiotics. Despite this, the anti-inflammatory effect of antibiotics ensures their continued use as their clinical effectiveness is demonstrated (17), albeit their effects may not be sustained. Considering the relationship between long term exposure to antibiotics and AMR, and the burden of acne vulgaris at the population level, this practice may not be optimal.

To understand the extent of any AMR as a result of antibiotics for acne in the UK, it is first necessary to establish how the antibiotics are used. Acne is a chronic disease and there are no studies with follow up longer than one year in data sources representative of the UK population to establish current prescription practice of acne treatment with antibiotics over its chronic disease course in primary care. Data from the US suggests 20% of those with acne are treated with antibiotics, however, international treatment patterns are not always generalisable, especially amid inconsistent guidelines and differing health systems.(11-14) A recent study using CPRD data found that topical or oral antibiotics were prescribed in over 50% of people who visited their GP with acne, but we do not know how long these individuals received their antibiotics for and if they had repeated courses over a period of years.(1)
While antibiotic stewardship programmes have been shown to be effective (18) in other settings, to ensure their successful execution, evidence must be generated to show how antibiotics in the treatment of acne are used over the course of the disease. Until this

evidence is generated and until there is evidence of resulting harm, it will be difficult to change current practice.(19) Given the global health emergency of AMR and the dominant role antibiotics play in the treatment of acne – a highly prevalent and ubiquitous skin condition, there is a clearly defined evidence gap which needs to be addressed.(20) This drug utilisation study aims to establish current practice amongst GPs in the UK with prescribing antibiotics for acne is over a time period of at least five-years.

References


1. Francis NA, Entwistle K, Santer M, Layton AM, Eady EA, Butler CC. The management of acne vulgaris in primary care: a cohort study of consulting and prescribing patterns using the Clinical Practice Research Datalink. Br J Dermatol. 2017;176(1):107-15.
2. methodology WHoccfds. https://www.whocc.no/ddd/definition_and_general_considera/.
3. Organization. WH. Global action plan on antimicrobial resistance. . 2015.
4. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The review on antimicrobial resistance May 2016.
5. Bhate K, Williams HC. Epidemiology of acne vulgaris. The British journal of dermatology. 2013;168(3):474-85.
6. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet (London, England). 2012;379(9813):361-72.
7. Whitehouse HJ FE, El- Mansori I, Layton AM. . Oral antibiotics for acne: are we adopting premium use? Presentation at the Annual Conference of the British Association of Dermatologists, Birmingham, U.K. 5–7 July 2016.
8. Barbieri JS HO, Margolis DJ. Duration of oral tetracycline-class antibiotic therapy and use of topical retinoids for the treatment of acne among general practitioners (GP): A retrospective cohort study. ournal of the American Academy of Dermatology. 2016 Dec;75:1142-50.
9. Lee YH LG, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: Investigating practice gaps and potential cost-savings. Journal of the American Academy of Dermatology. 2014;71.
10. Whitehouse H.J. et al, . Conference Presentation: Oral antibiotics for acne: are we adopting premium use? (British Association of Dermatologists Annual Conference 2016. 2016.
11. National Institute of Health and Care Excellence. Clinical Knowledge Summaries. Acne vulgaris. revised 2014.
12. Zaenglein AL PA, Schlosser BJ. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945-73 e33.
13. Nast A DB, Bettoli V. European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. Eur Acad Dermatol Venereol. 2016;30:1261-8.
14. Barbieri JS JW, Margolis DJ. Trends in prescribing behavior of systemic agents used in the treatment of acne among dermatologists and nondermatologists: A retrospective analysis, 2004-2013. J Am Acad Dermatol. 2017;77:456-63.
15. Kuet K.H. FC FE, Eady A,and Layton A.M,. Conference Presentation: A decade later, has the prevalence of skin colonization by resistant propionibacteria increased in our patients with acne? British Association of Dermatologists Annual Conference. 2015.
16. Lee SE KJ-M, Jeong SK. Protease-activated receptor-2 mediates the expression of inflammatory cytokines, antimicrobial peptides, and matrix metalloproteinases in keratinocytes in response to Propionibacterium acnes. Arch Dermatol Res. 2010;302:745-56.
17. Bienenfeld A, Nagler AR, Orlow SJ. Oral Antibacterial Therapy for Acne Vulgaris: An Evidence-Based Review. American journal of clinical dermatology. 2017;18(4):469-90.
18. Lawes T L-LJ, Nebot CA. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. Lancet Infect Dis. 2015;15:1438-49.
19. Simpson SA WF, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. The Journal of antimicrobial chemotherapy. 2007;59:292-6.
20. Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.


12a. Upload the study protocol, including data collection forms, questionnaires and topic guides. Please upload each document separately, ensuring that the date and version number of each document is correct.

13. State the intended value of the project, detailing why the topic is of interest or relevance. If this project or a similar one has been done before what is the value of repeating it? Give details of overviews and/or information on the Cochrane database. This area is of increasing importance – please ensure you give a full response.

To understand the extent of any AMR as a result of antibiotics for acne in the UK, it is first necessary to establish how the antibiotics are used. Acne is a chronic disease and there are no studies with follow up longer than one year in data sources representative of the UK population to establish current prescription practice of acne treatment with antibiotics over its chronic disease course in primary care. Data from the US suggests 20% of those with acne are treated with antibiotics, however, international treatment patterns are not always generalisable, especially amid inconsistent guidelines and differing health systems.(11-14) A recent study using CPRD data found that topical or oral antibiotics were prescribed in over 50% of people who visited their GP with acne, but we do not know how long these individuals received their antibiotics for and if they had repeated courses over a period of years.(1)
While antibiotic stewardship programmes have been shown to be effective (18) in other settings, to ensure their successful execution, evidence must be generated to show how antibiotics in the treatment of acne are used over the course of the disease. Until this evidence is generated and until there is evidence of resulting harm, it will be difficult to change current practice.(19) Given the global health emergency of AMR and the dominant role antibiotics play in the treatment of acne – a highly prevalent and ubiquitous skin condition, there is a clearly defined evidence gap which needs to be addressed.(20) This drug utilisation study aims to establish current practice amongst GPs in the UK with prescribing antibiotics for acne is over a time period of at least five-years.

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9. Lee YH LG, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: Investigating practice gaps and potential cost-savings. Journal of the American Academy of Dermatology. 2014;71.
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11. National Institute of Health and Care Excellence. Clinical Knowledge Summaries. Acne vulgaris. revised 2014.
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20. Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.

15. Overall aim of project

To understand the use of long-term antibiotics for acne in the United Kingdom.

16. Specific objectives of project

In a population level sample of patients with acne in primary care, what are the prescribing patterns of oral and topical antibiotics used to treat acne over a five-year time period?

## Methods

Note: Please do not copy and paste directly from the protocol. Applications where large portions of text have been copied and pasted directly from the protocol, and therefore do not properly answer the question, will be invalidated

18. Specify the procedures/methodology to be conducted during the project. Please include outcome measures and plans for data management and analysis. For literature reviews, include details on search strategy, search terms, inclusion and exclusion criteria.

Study Type

Descriptive drug utilisation study.

Study Design

Drug utilisation study

Outcomes to be Measured

This is a drug utilisation study aiming to identify how topical and oral antibiotics for acne are prescribed over the course of this chronic disease.

Outcomes will therefore be defined as:
1) Initiation of an oral or topical antibiotic for acne.
2) Substituting/switching a topical or oral antibiotic for another between classes.
3) Addition of an antibiotic to existing antibiotic treatment
4) Discontinuation of a topical or oral antibiotic.
5) Duration of antibiotic treatment including median duration.
6) Re-initiation of an antibiotic – this is defined as a further prescription of an antibiotic after having previously been prescribed an antibiotic for a minimum of 4 weeks for acne, regardless of class, if there is no antibiotic prescription covering the previous 60 days.

Definitions to be used:

Treatment initiation:
A new topical or oral antibiotic prescribed for at least 28 days preceded by 365 days of no antibiotic use. As there are no Daily Defined Doses (DDDs) for topicals, 0.5g per day will be amount used to define a daily dose as has been used by other studies.(1, 2) For the purposes of analysis, people with an antibiotic prescription for acne for less than 28 days will be excluded.

Treatment switching:
Treatment switching is defined as the addition of a second antibiotic class (for acne) without the continuous use of the initial first antibiotic. The new antibiotic is used in place of the previous antibiotic treatment. Therefore, if a second drug is added, but with less than 30 overlapping days' supply, this will be defined as a treatment switch between antibiotics. Second, third and fourth antibiotic initiation will only be considered treatment switches if there are 30 or less days' supply from the prescription of the previous antibiotic.

Treatment addition:
If there are overlapping days' supply for the first and second antibiotic for 30 days or more then this is defined as a treatment addition of the second antibiotic, (and for subsequent antibiotic additions thereafter defined as the third and fourth additions etc).

Treatment discontinuation:
This is defined as no available days of antibiotic supply 30 days after the last covered day.

Treatment re-initiation:
This is defined as an antibiotic prescription in those who have previously received antibiotics for their acne with a treatment gap of at least 30 days.

We will stratify drug utilisation across age categories, geographic location (if possible) and sex to understand prescribing in separate populations.

Eligibility for inclusion:
Patients from the general population will be eligible for inclusion between the years 2004 to 2018. Patients between the ages of 8 and 50 of any sex will be eligible. People will be eligible for inclusion from the latest of their current registration date + 1 year (CRD+1), the day the practice was deemed to be up to standard (UTS), the day the study started (1st of January 2004) or the patient's 8th birthday.

Study population:
From those eligible for inclusion, people with a new acne diagnostic code between the 1st of January 2004 and the 31st of December 2018 will be defined as the study population. A new acne diagnosis is defined as any individual with an acne code (appendix A) who has not previously had an acne code in the 1 year prior to the study start. We will exclude patients with prior use of prescribed acne medication including antibiotics for acne (see appendix C) in the previous 365 days before the first diagnostic code. The Read codes identified for acne are listed in Appendix A.

Study start:
From this population of people with acne, those commencing prescriptions of topical or oral antibiotics will be identified on the day they receive their diagnostic code onwards. Study entry begins on the date of the acne diagnostic code.

Misclassification:
Our method if identifying people with acne hinges on individuals having a diagnostic code. We expect that not all treated acne is coded as such. Thus, we plan a sensitivity analysis whereby individuals can be included in the study by meeting the following criteria:
1) The prescription of a long-term antibiotic commonly given to treat acne (tetracycline, macrolide or dihydrofolate reductase inhibitor) for at least 28 days with no acne code, and no diagnostic code in the preceding or subsequent 3 months of the antibiotic prescription for urinary tract infection, sickle cell disease or splenectomy, osteomyelitis, rosacea, cellulitis or hidradenitis suppurativa (conditions which may be treated with long-term antibiotics). Follow up in this scenario will begin from the day of the antibiotic prescription.
2) No diagnostic code for acne, but a prescription of a typical acne medication (e.g. a topical retinoid or topical benzoyl peroxide) listed in the British National Formulary acne chapter (see Appendix D). Follow up for these individuals will begin on the day of acne medication prescription.

The rationale underpinning this sensitivity analysis is that it will improve our understanding of how many acne cases we may have missed using our main entry criteria.

Exposures, Outcomes and Covariates
Exposures:
This is a drug utilisation study and thus does not have exposures in the traditional sense. We will explore what drugs people are initiating for acne and their utilisation patterns thereafter inclusive of switching drugs, discontinuing drugs and adding drugs.

Outcomes:
This is a drug utilisation study so there are no traditional outcomes. The focus is on treatment trajectories; the antibiotics patients initiate, the antibiotics they are switched to, which antibiotics are added in addition to existing treatment and which are discontinued. See section D for further details.

Covariates:
We will stratify drug patterns according to the following age categories (8-11, 12-18, 19-25, 26-35, 36-45, 46-50) and sex.

Primary analyses:
The main analysis will describe, in graphical and tabular format, topical and oral antibiotic treatment trajectories over a time period of five-years.

Desired data structure:
The antibiotic medications listed in the British National Formulary (BNF) section on acne medications will be used and categorised as follows:

The antibiotics used to treat acne will be classified into the following groups (see appendix B):
1. Topical antibiotic e.g. topical clindamycin or erythromycin
2. Topical antibiotic combination e.g. clindamycin and tretinoin, or benzoyl peroxide and clindamycin
3. Oral antibiotic inclusive of tetracyclines, macrolides and dihydrofolate reductase inhibitors e.g. trimethoprim.
4. No antibiotic prescribed but presence of code indicating acne.

The utilisation of the oral antibiotics prescribed will be expressed as numbers of Daily Defined Doses (DDDs) /1000 people coded for acne. There are no DDDs for topical preparations so therefore 0.5g per day will be taken as a daily dose as has been used in other studies.

From January 2014 (when a new acne diagnosis is recorded) cohort entry will be defined and follow up will begin. We will examine changes to antibiotic drug therapy over the subsequent five-year time period. The specific antibiotic initiation, addition, switches or overlap of two antibiotics and censoring will be noted (described above). The quantity of each medication (and therefore duration) for each group will be described with medians and the interquartile ranges will be presented.

Plan for addressing confounding
This is a descriptive drug utilisation study and as such there is no confounding. We will stratify drug utilisation across age categories, geographic location (if possible) and sex to understand prescribing in separate populations.

Plans for addressing missing data
Not applicable for this study – see section L for plans of addressing misclassification.
Age and sex are well recorded in CPRD data.

CPRD access: institutional multi access used licence. I will process, access and store data at LSHTM.

23. Proposed start date of the project

16/09/2019

24. Proposed end date of the project

01/06/2020

## Experience

30. State the personal experience of the applicant and of senior collaborators in the research project in the field concerned, and their contribution to this project. Indicate any previous work done related to the project topic including student and/or professional work, or publications

Ketaki Bhate
MSC in Epidemiology with research project undertaken using the CPRD. I have written the study protocol.
Professor Sinead Langan is clinically a consultant dermatologist has extensive experience of conducting studies using the CPRD.
Supervisor to Ketaki Bhate's PhD (NIHR DRF)

Both Ketaki Bhate and Sinead Langan have been involved in this study from inception.

Sinnott SB, K; Margolis, DJ; Langan, SM. Antibiotics and acne: an emerging iceberg of antibiotic resistance? . British Journal of Dermatology 2016;175(6):1127-8.

30a. Upload the CVs for all main investigators working on the project. For MSc students, please upload your CV only.

[redacted]

## Informed Consent - Secondary Data

34. Is consent in place for secondary use of the data?

- (•) Yes
- ( ) No

34c. Please give details of the participant consent that was obtained when the original project(s) took place. Please upload copies of the original consent form(s). If there are no original consent forms (e.g. for audit or DHS data) please explain this.

Patients were consented by GPs when data were collected for their health records. Data are anonymised.

## Confidentiality & Data

40. State how your data will be stored and what will be done with it at the end of the project.

The data will be stored on a secure data server at the London School of Hygiene and Tropical Medicine. Access will be restricted to myself and named collaborators. weekly backup tapes will be made and then overwritten once a more up-to-date monthly backup has been made; monthly backup tapes will be retained for 12 months and then overwritten, but the final monthly backup tape in each 12-month cycle will be retained. Data will remain on the secure server for the full retention period, as stipulated by the respective data owners. Since the data used for this project will be archived by the data owners, the data processing programs created for this project would enable the derived study data to be re-created after the retention period ends.

## Funding

46. Do you have external funding for this project?

- (•) Yes
- ( ) No

46a. If yes, please provide the name of the funder

NIHR

46a(i). If yes, include details of the funding available for this project.

I am funded by an NIHR Doctoral Research Fellowship DRF-2018-11-ST2-066.

Date grant accepted or funding agreed:

01/11/2019

Date end of funding:

01/11/2021

46a(ii). Are you in receipt of any funding from the United States? Or will you be collaborating with (or with individuals from) a US Institution/organisation?

- (•) Yes
- ( ) No

47. Has the project been sent out for peer/independent scientific review (please select yes if the project is being sent to the SCC)?

- (•) Yes
- ( ) No

47b. If yes, who has provided peer/independent scientific review of the project?

ISAC.

I am not funded by the US I am funded only by the NIHR. I have up to 3 months of funding via the NIHR for an overseas research visit. Here I will be working on this study for some of the time there. I plan this visit for April 2020. I will be using the remote desktop and accessing the network and my PC at my desk at LSHTM. I will not be carrying the data with me overseas.

49. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- ( ) Yes
- (•) No

50. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- ( ) Yes
- (•) No

## Local Approval

69. For projects using previously-collected human data, give details of all approvals under which the original project(s) took place. Please quote names of Ethics Committees and approval reference numbers (required even if previous approval was from LSHTM); if possible give web link to original project application. If there are no original approvals (e.g. for audit or DHS data) please explain this.

ISAC protocol 19_168 approved 12.08.19.
This is a new study and does not represent an addition or change to a previously submitted application.

Documents

| Type | Document Name | File Name | Version Date | Version | Size |
|---|---|---|---|---|---|
| Local Approval | 19_168_ISAC feedback | 19_168_ISAC feedback.docx | 28/08/2019 | 1 | 37.2 KB |

69a. Will your analyses be for purposes entirely covered by the original ethics application where the data was collected, as detailed above?

- ○ Yes, this falls within the aims and scope of the original project
- ◉ No, the analyses and aims differ from the original project

69a(ii). If no, please detail how you will amend the original ethics application to include the current analysis.

n/a

## Signature Instructions

The form should be completed and finalised prior to signing or requesting signatures. Students should ensure that the Supervisor signs prior to the Course Director/Project Module Organiser. For external supervisors, please ensure that they have registered for an account prior to requesting the signature.

## Signature - Applicant

Student signature

I declare that:

- I Have read and understood, and agree to abide by the LSHTM Good Research Practice policy as well as all applicable Standard Operating Procedures, including on informed consent
- I undertake to abide by all regulations, guidelines and standards of good practice, including but not limited to the Data Protection Act 2018 and the Declaration of Helsinki
- I undertake to abide by the UK Data Protection Act 1998 and any applicable local laws.
- I undertake to abide by all local rules for non-UK research.
- I agree to conduct my project on the basis set out in this form, and to consult staff (initially, my Supervisor) if making any subsequent changes – especially any that would affect the information given with respect to ethics approval.
- I undertake to adhere to all conditions set out by review bodies in giving approval and will not start the project until all required approvals are in place
- I agree to comply with the relevant safety requirements, and will submit a separate request for LSHTM travel insurance where relevant.
- I confirm that there are no conflicts of interest that preclude my participation in the project

[redacted]

## Signature - Supervisor

Supervisor signature

I declare that:

- I agree that the information submitted in this application is a reasonable summary of the proposed project.
- I agree that this form correctly indicates whether or not ethics approval will be required.
- I agree that this form contains adequate information for the ethics committee to form an opinion of the proposed project.
- I agree that all required supporting documentation is attached to this application.
- (For MSc projects only) I agree that responses in the Risk Assessment section address the main risks connected with a project of this nature
- I have reviewed the risk of the project, including travel, and agree that it is an acceptable risk to the student
- I confirm that there are no conflicts of interest that preclude my role as supervisor for this project
- I Have read and understood, and agree to abide by the LSHTM Good Research Practice policy

[redacted]

## Signature - Other

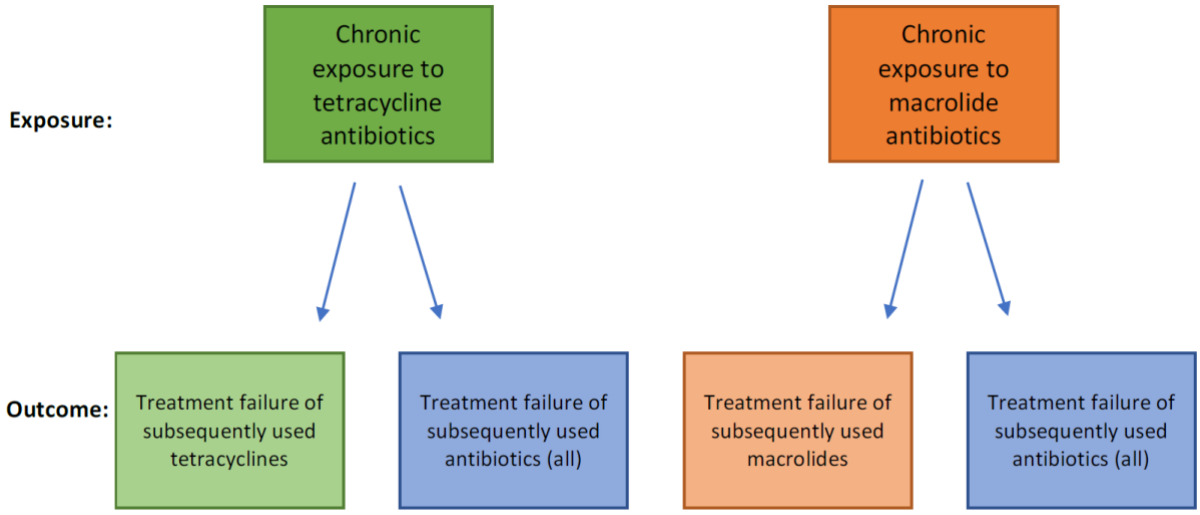
Note:

**The form will automatically submit upon receipt of all required signatures.**

**After submission, you will receive a confirmation email with further details.**

**If you have not received a confirmation email within 5 working days please email ethics@lshtm.ac.uk (staff) or MScethics@lshtm.ac.uk (students) to check the status of your submission.**

## A3.3 Supplementary material for cohort study




**Supplementary figure 1:** Outcome of treatment failure will be investigated for all antibiotics in order to capture cross resistance in addition to class of antibiotic prescribed for acne

**Background of the selected infections in cohort study**

Lower Respiratory Tract Infections (LRTI), Urinary Tract Infections (UTI) and Skin and Soft Tissue Infections (SSTI) are the three most common infections for which oral antibiotics are prescribed in UK primary care.(184) **Figure 1.5** below depicts the percentage of prescribed antibiotics by age and sex for diagnoses of infections.

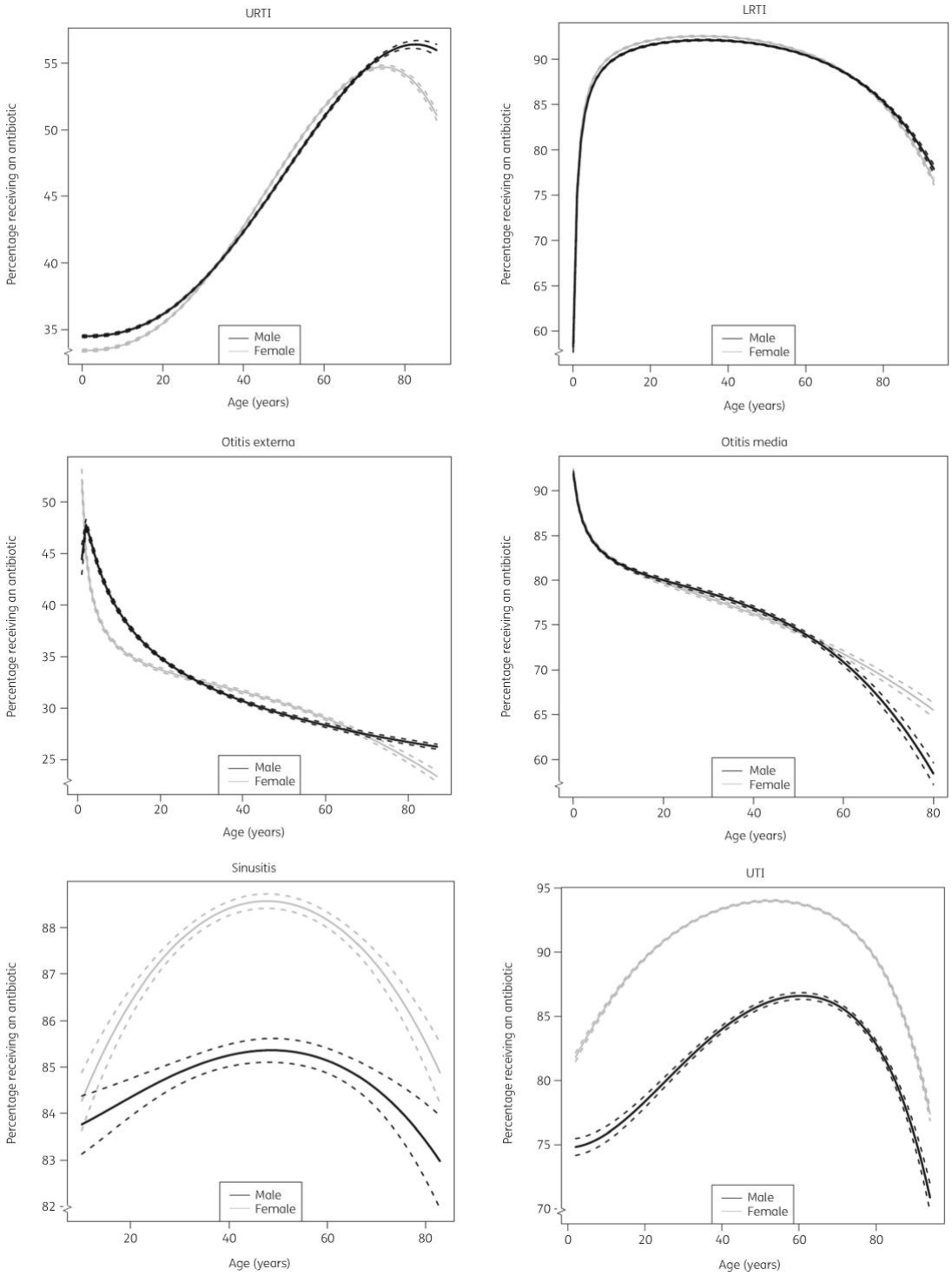



**Figure 1.5.** Percentage of patients receiving an antibiotic for each common infection stratified by age and sex. Dashed lines are 95% confidence intervals. Reproduced with permission from Journal of Antimicrobial Chemotherapy under CC-BY-NC license, Palin et al, Antibiotic prescribing for common infections in UK general practice: variability and drivers Copyright (2019), Oxford University Press

Lower respiratory tract infection (LRTI)

LRTIs comprise bronchitis (infection and inflammation of the airways) and pneumonia (infection and inflammation of the lung parenchymal tissue).(185, 186) LRTIs can be caused by bacteria, fungi or viruses. Bacteria are the most common organisms associated with LRTI. Streptococcus pneumoniae is the most common pathogen associated with community acquired pneumonia worldwide and in the UK, other common pathogens include Haemophilus influenzae, *Chlamydia pneumoniae and Mycoplasma pneumoniae*.(187, 188) LRTI is the fourth most common cause of Disability Associated Life Years according to the Global Burden of Diseases Study.(189)

Urinary tract infection (UTI)

UTIs comprise infections of the bladder, kidneys, ureters and or the urethra, and women are predominantly affected.(190) The most common pathogen associated with UTIs is *Escherichia coli* accounting for up to 80% of all UTIs.(191) Other pathogens that are less frequently associated with UTIs include *Staphyloccocus saprophyticus* (5-10% of cases), *Klebsiella* species and *Proteus mirabilis*.(190)

Skin and soft tissue infection (SSTI)

SSTIs encompass a variety of infections that involve the skin and underlying subcutaneous tissue including the fat, fascia and muscle. SSTIs range from superficial infections requiring no antibiotics, to more severe infections requiring topical or oral antibiotics.(192) While there are several definitions of SSTIs, erysipelas, cellulitis, fasciitis, and more serious necrotising infections are included.(193) *Staphyloccocus aureus* and *Streptococcus pyogenes* are common bacteria involved in the pathogenesis of SSTIs.(194)

**Variable definitions**

Acne

I defined acne by identifying a single acne diagnostic Read code at any time point in the health record (methodology of diagnostic code list formulation outlined in **Appendix 2**). No exclusions were applied based on previous acne treatments.

Acne antibiotic

The same definition for long-term antibiotic for acne (an oral antibiotic classically prescribed for acne for a minimum duration of 28 days) in the drug utilisation study was used for the cohort study– Research question 2, chapter 5 (**Appendix 2**).

Infections

Lower Respiratory Tract Infection (LRTI), Skin and Soft Tissue Infection (SSTI) and Urinary Tract Infection (UTI) were identified in the CPRD by the single entry of a diagnostic Read code. For an individual to be eligible for our infection cohorts, an oral antibiotic classically prescribed for the infection had to be prescribed within seven days of the diagnostic Read code. Using a prescription of an oral antibiotic for an infection was necessary to investigate our outcome of antibiotic treatment failure within 30 days. Additionally, a prescription of an oral antibiotic for LRTI within the subsequent seven days as well as a diagnostic Read code for LRTI ensured that mild or suspected infections, not requiring an oral antibiotic were not included and only more serious infections, requiring an oral antibiotic were captured. Individuals with a diagnostic Read code and no oral antibiotic were not eligible for inclusion into the cohort.

Antibiotic for infection

Where there were two antibiotics for an infection prescribed within the subsequent seven days of an infection, the start date of the latest of the two prescriptions was used as the index date as the second prescription is more likely to be the antibiotic that was taken for the intended duration prescribed. It is possible that antibiotic treatment failure could occur as a result of a few days of the first antibiotic, however a switch in antibiotic within seven days could also be due to an intolerance or allergy to the first prescribed antibiotic, or a

supply issue where the first antibiotic was not available. Analyses were repeated in a sensitivity analysis whereby the oral antibiotic for the infection was required to be prescribed on the same day as the diagnostic Read code for the infection thereby testing my definition.

**Covariates**

Deprivation

The study population was linked to the patient level Index of multiple deprivation 2015 (IMD 2015). IMD 2015 is a proxy measure for deprivation. IMD is comprised of seven domains (income, employment, health, education, crime, barriers to housing and services and living and environment), that are combined, weighted and divided into quintiles ranking from 1, the least deprived to 5, most deprived.(195) Patient level IMD (linked to the patients postcode of residence) was used as a proxy where available and where missing, the practice level IMD was used (using the postcode of the General Practice the patient is registered at). IMD at the patient level only includes people registered at a General Practice in England therefore where IMD at the patient level was not available, the practice level IMD was used.

Ethnicity

I categorised ethnicity into the follow five categories: White, South Asian, Black, Other and Mixed. Ethnicity was identified using a validated algorithm.(128) Where there was more than one ethnicity recorded for an individual, I used the most frequently recorded ethnicity and in the case of several ethnicities being recorded, the most recent was used.

Harmful alcohol use

Harmful alcohol use was identified using Read codes suggesting harmful or heavy alcohol use, or a prescription of a medication used to maintain alcohol abstinence.

Diabetes

Diabetes was identified using diagnostic Read codes for diabetes type 1 and 2, unspecified diabetes and complications of diabetes. Diabetes insipidus, secondary diabetes (e.g. diabetes secondary to oral steroid use) and gestational diabetes were excluded. Any record of diabetes prior to index date was used to indicate the presence of diabetes.

Asthma

To define asthma, I used any diagnostic Read code in the CPRD for asthma prior to index date. Any record of asthma prior to index date was used to indicate the presence of asthma.

**Justification of covariates**

Harmful alcohol use: An association has previously been reported between harmful alcohol use and susceptibility to infections. A systematic review found an 83% increased risk of developing a community acquired pneumonia with harmful alcohol use.(196) Harmful alcohol use may be related to the exposure of receiving an oral antibiotic for acne, either if people do not present to their GP or present frequently due to their comorbidity. I do not believe harmful alcohol use to be on the causal pathway.

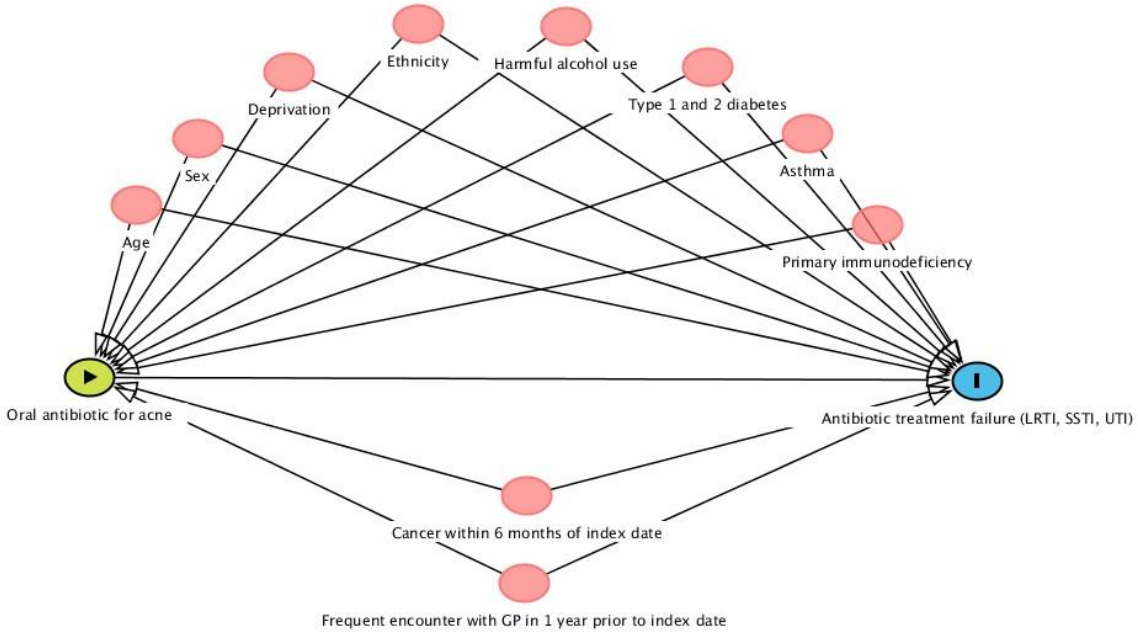
Deprivation: Deprivation is a key health determinant indicator and an important factor to adjust for when considering health outcomes.(197) Deprivation is associated with my exposure of receiving oral antibiotics for acne from primary care services and also is an independent risk factor for my outcome of antibiotic treatment failure. Deprivation is not on the causal pathway.

Ethnicity: there may be variation in exposure to oral antibiotics for acne and the outcome of antibiotic treatment failure by ethnicity.

Asthma: People with asthma may a) visit their GP more frequently and therefore acne may also be diagnosed and treated. People with asthma also may be treated with oral corticosteroids which may affect acne severity or onset. Additionally, asthma is a risk factor for my outcome of antibiotic treatment failure if people are treated with immunosuppressants (e.g., oral steroids) and is not on the causal pathway.

Diabetes: People with asthma may a) visit their GP more frequently and similarly to asthma, may also be diagnosed with and be treated for acne and b) diabetes if poorly controlled may lead to an increased likelihood of infections. Diabetes is not on the causal pathway.

**Directed Acyclic Graph (DAG) diagram**




DAG diagram depicting the confounders and effects modifiers between oral antibiotics for acne and subsequent antibiotic treatment failures to infections (LRTI, SSTI and UTI).

## Final list of codes

LRTI

| Medcode | Readcode | Readterm |
|---|---|---|
| 99214 | Hyu1100 | [x]acute bronchiolitis due to other specified organisms |
| 73100 | Hyu1000 | [x]acute bronchitis due to other specified organisms |
| 66397 | Hyu1.00 | [x]other acute lower respiratory infections |
| 63763 | Hyu0A00 | [x]other bacterial pneumonia |
| 53753 | Hyu0H00 | [x]other pneumonia, organism unspecified |
| 114636 | Hyu0900 | [x]pneumonia due to other aerobic gram-negative bacteria |
| 98381 | Hyu0B00 | [x]pneumonia due to other specified infectious organisms |
| 111027 | Hyu0C00 | [x]pneumonia in bacterial diseases classified elsewhere |
| 54669 | Hyu6.00 | [x]suppurative & necrotic conditions of lower respir tract |
| 100943 | Ayu3A00 | [x]whooping cough, unspecified |
| 29005 | H530.00 | abscess of lung |
| 21185 | H53..00 | abscess of lung and mediastinum |
| 34659 | H53z.00 | abscess of lung and mediastinum nos |
| 11202 | H530z00 | abscess of lung nos |
| 35189 | H530300 | abscess of lung with pneumonia |
| 24800 | H060x00 | acute bacterial bronchitis unspecified |
| 1019 | H061.00 | acute bronchiolitis |
| 105895 | H061700 | acute bronchiolitis due to human metapneumovirus |
| 66228 | H061600 | acute bronchiolitis due to other specified organisms |
| 17917 | H061z00 | acute bronchiolitis nos |
| 17185 | H061200 | acute bronchiolitis with bronchospasm |
| 312 | H060.00 | acute bronchitis |
| 29669 | H06..00 | acute bronchitis and bronchiolitis |
| 31886 | H060A00 | acute bronchitis due to mycoplasma pneumoniae |
| 20198 | H060z00 | acute bronchitis nos |
| 41137 | H06z.00 | acute bronchitis or bronchiolitis nos |
| 21145 | H060400 | acute croupous bronchitis |
| 69192 | H061300 | acute exudative bronchiolitis |
| 37447 | H06z112 | acute lower respiratory tract infection |
| 6124 | H062.00 | acute lower respiratory tract infection |
| 101775 | H060100 | acute membranous bronchitis |
| 49794 | H060900 | acute neisseria catarrhalis bronchitis |
| 9043 | H060600 | acute pneumococcal bronchitis |
| 71370 | H060200 | acute pseudomembranous bronchitis |
| 11072 | H060300 | acute purulent bronchitis |
| 43362 | H060700 | acute streptococcal bronchitis |
| 11101 | H060500 | acute tracheobronchitis |
| 5978 | H060.11 | acute wheezy bronchitis |
| 34732 | A054.00 | amoebic lung abscess |
| 100650 | AB63600 | aspergillus bronchitis |
| 101204 | H470.11 | aspiration pneumonia |
| 25054 | H470312 | aspiration pneumonia due to vomit |
| 10992 | H47..11 | aspiration pneumonitis |
| 5324 | H28..00 | atypical pneumonia |
| 31689 | H511.00 | bacterial pleurisy with effusion |
| 44842 | H511z00 | bacterial pleurisy with effusion nos |
| 23095 | H22z.00 | bacterial pneumonia nos |
| 3683 | H261.00 | basal pneumonia due to unspecified organism |
| 3842 | A330.00 | bordetella pertussis |

| | | |
|---|---|---|
| 110596 | 43wE.00 | bordetella pertussis deoxyribonucleic acid detection |
| 3480 | H30z.00 | bronchitis nos |
| 148 | H30..00 | bronchitis unspecified |
| 886 | H25..00 | bronchopneumonia due to unspecified organism |
| 2476 | H07..00 | chest cold |
| 68 | H06z011 | chest infection |
| 22795 | H22..11 | chest infection - other bacterial pneumonia |
| 19400 | H26..11 | chest infection - pnemonia due to unspecified organism |
| 29166 | H21..11 | chest infection - pneumococcal pneumonia |
| 30653 | H23..11 | chest infection - pneumonia organism os |
| 17359 | H30..11 | chest infection - unspecified bronchitis |
| 16287 | H25..11 | chest infection - unspecified bronchopneumonia |
| 2581 | H06z000 | chest infection nos |
| 24316 | H24..11 | chest infection with infectious disease ec |
| 17025 | H233.00 | chlamydial pneumonia |
| 3243 | H31..00 | chronic bronchitis |
| 15157 | H31z.00 | chronic bronchitis nos |
| 15626 | H310000 | chronic catarrhal bronchitis |
| 21061 | H3y0.00 | chronic obstruct pulmonary dis with acute lower resp infectn |
| 45089 | H31y100 | chronic tracheobronchitis |
| 5909 | H312011 | chronic wheezy bronchitis |
| 104121 | H2B..00 | community acquired pneumonia |
| 103475 | H564.11 | cryptogenic organising pneumonia |
| 60299 | H22y011 | e.coli pneumonia |
| 14798 | H312100 | emphysematous bronchitis |
| 2375 | H50..00 | empyema |
| 34282 | H50z.00 | empyema nos |
| 66856 | H500000 | empyema with bronchocutaneous fistula |
| 34651 | H500100 | empyema with bronchopleural fistula |
| 59340 | H500.00 | empyema with fistula |
| 111451 | H500z00 | empyema with fistula nos |
| 113005 | H500300 | empyema with mediastinal fistula |
| 53494 | H501.00 | empyema with no fistula |
| 99547 | H500400 | empyema with pleural fistula nos |
| 57667 | H530200 | gangrenous pneumonia |
| 104264 | H2C..00 | hospital acquired pneumonia |
| 24356 | H540100 | hypostatic bronchopneumonia |
| 23333 | H540000 | hypostatic pneumonia |
| 1934 | H301.00 | laryngotracheobronchitis |
| 1849 | H21..00 | lobar (pneumococcal) pneumonia |
| 9639 | H260.00 | lobar pneumonia due to unspecified organism |
| 3358 | H06z100 | lower resp tract infection |
| 8318 | H260000 | lung consolidation |
| 38052 | H501300 | lung empyema nos |
| 24248 | H313.00 | mixed simple and mucopurulent chronic bronchitis |
| 11150 | H311.00 | mucopurulent chronic bronchitis |
| 61513 | H311z00 | mucopurulent chronic bronchitis nos |
| 37711 | H530100 | multiple lung abscess |
| 96059 | 4JUK.00 | mycoplasma pneumoniae detected |
| 7267 | 65VA.00 | notification of whooping cough |
| 27819 | H312.00 | obstructive chronic bronchitis |
| 44525 | H312z00 | obstructive chronic bronchitis nos |
| 50408 | A730.00 | ornithosis with pneumonia |
| 13563 | SP13100 | other aspiration pneumonia as a complication of care |
| 28634 | H22..00 | other bacterial pneumonia |
| 66043 | H31y.00 | other chronic bronchitis |
| 68066 | H31yz00 | other chronic bronchitis nos |
| 11849 | H2y..00 | other specified pneumonia or influenza |
| 64286 | A33yz00 | other whooping cough nos |
| 44425 | H501200 | pleural empyema |

| | | |
|---|---|---|
| 51398 | A3By400 | pleuropneumonia-like organism (pplo) infection |
| 43345 | H511000 | pneumococcal pleurisy with effusion |
| 12061 | H22y200 | pneumonia - legionella |
| 43884 | H22yz00 | pneumonia due to bacteria nos |
| 60119 | H230.00 | pneumonia due to eaton's agent |
| 65419 | H22y000 | pneumonia due to escherichia coli |
| 23546 | H220.00 | pneumonia due to klebsiella pneumoniae |
| 1576 | H231.00 | pneumonia due to mycoplasma pneumoniae |
| 52384 | H22yX00 | pneumonia due to other aerobic gram-negative bacteria |
| 50867 | H22y.00 | pneumonia due to other specified bacteria |
| 25694 | H23..00 | pneumonia due to other specified organisms |
| 73735 | H232.00 | pneumonia due to pleuropneumonia like organisms |
| 45425 | H22y100 | pneumonia due to proteus |
| 30591 | H221.00 | pneumonia due to pseudomonas |
| 34251 | H23z.00 | pneumonia due to specified organism nos |
| 5612 | H224.00 | pneumonia due to staphylococcus |
| 12423 | H223.00 | pneumonia due to streptococcus |
| 63858 | H223000 | pneumonia due to streptococcus, group b |
| 572 | H26..00 | pneumonia due to unspecified organism |
| 40498 | H24..00 | pneumonia with infectious diseases ec |
| 66362 | H24z.00 | pneumonia with infectious diseases ec nos |
| 67901 | H24y100 | pneumonia with nocardiasis |
| 62623 | H242.00 | pneumonia with ornithosis |
| 69782 | H24y.00 | pneumonia with other infectious diseases ec |
| 70559 | H24yz00 | pneumonia with other infectious diseases ec nos |
| 35082 | H243.11 | pneumonia with pertussis |
| 60482 | H24y300 | pneumonia with q-fever |
| 72182 | H24y400 | pneumonia with salmonellosis |
| 106908 | H244.00 | pneumonia with tularaemia |
| 49398 | H24y600 | pneumonia with typhoid fever |
| 30437 | H243.00 | pneumonia with whooping cough |
| 47295 | A205.00 | pneumonic plague, unspecified |
| 38065 | H263.00 | pneumonitis, unspecified |
| 30509 | SP13200 | post operative chest infection |
| 32172 | A551.00 | postmeasles pneumonia |
| 34300 | H262.00 | postoperative pneumonia |
| 70710 | A203.00 | primary pneumonic plague |
| 40159 | H311000 | purulent chronic bronchitis |
| 4899 | H06z200 | recurrent chest infection |
| 7092 | H30..12 | recurrent wheezy bronchitis |
| 293 | H06z111 | respiratory tract infection |
| 64799 | H571.00 | rheumatic pneumonia |
| 58896 | A022200 | salmonella pneumonia |
| 109448 | A204.00 | secondary pneumonic plague |
| 25603 | H310.00 | simple chronic bronchitis |
| 61118 | H310z00 | simple chronic bronchitis nos |
| 33730 | H530000 | single lung abscess |
| 93010 | H511100 | staphylococcal pleurisy with effusion |
| 108784 | H511200 | streptococcal pleurisy with effusion |
| 55391 | H060v00 | subacute bronchitis unspecified |
| 3163 | H300.00 | tracheobronchitis nos |
| 152 | H302.00 | wheezy bronchitis |
| 763 | A33..00 | whooping cough |
| 53897 | A33y.00 | whooping cough - other specified organism |
| 42548 | A33z.00 | whooping cough nos |

SSTI

| Medcode | Readcode | Readterm |
|---|---|---|
| 18067 | M092100 | [x]abdominal wall abscess |
| 44243 | M094000 | [x]abscess of axilla |
| 31606 | M092000 | [x]abscess of buttock |
| 30161 | M093.00 | [x]abscess of buttock |
| 30172 | M090.00 | [x]abscess of face |
| 30078 | M094.00 | [x]abscess of limb |
| 37379 | M091.00 | [x]abscess of neck |
| 42481 | M09y.00 | [x]abscess of other site |
| 45211 | M092.00 | [x]abscess of trunk |
| 29345 | M084.00 | [x]cellulitis of breast |
| 5605 | M080.00 | [x]cellulitis of finger and toe |
| 1315 | M081.00 | [x]cellulitis of other parts of limb |
| 30260 | M08y.00 | [x]cellulitis of other sites |
| 9233 | M080.13 | [x]cellulitis of thumb |
| 6193 | M092200 | [x]perineal abscess |
| 72625 | SyuJ000 | [x]post-traumatic wound infection, not elsewhere classified |
| 5965 | M03z100 | abscess nos |
| 4336 | J54..00 | abscess of anal and rectal regions |
| 49211 | N22y300 | abscess of bursa |
| 113185 | N22yK00 | abscess of bursa-ankle |
| 57123 | N22yF00 | abscess of bursa-elbow |
| 71294 | N22yL00 | abscess of bursa-foot |
| 70207 | N22yH00 | abscess of bursa-hip |
| 55390 | N22yJ00 | abscess of bursa-knee |
| 103301 | N22yE00 | abscess of bursa-shoulder |
| 96402 | N22yG00 | abscess of bursa-wrist |
| 28041 | M034011 | abscess of dorsum of hand |
| 16969 | F506.00 | abscess of external ear |
| 16835 | F4D1200 | abscess of eyelid |
| 5950 | K424011 | abscess of labia |
| 16362 | J085000 | abscess of lip |
| 37435 | L450.11 | abscess of nipple - obstetric |
| 40291 | M034012 | abscess of palm of hand |
| 21296 | M03y011 | abscess of scalp |
| 8713 | K284000 | abscess of scrotum |
| 23848 | M03..11 | abscess of skin area excluding digits of hand or foot |
| 33332 | N22y200 | abscess of tendon |
| 99358 | N22y600 | abscess of tendon-arm |
| 73104 | N22yB00 | abscess of tendon-foot |
| 100895 | N22y700 | abscess of tendon-forearm |
| 71687 | N22y800 | abscess of tendon-hand |
| 70219 | N22yA00 | abscess of tendon-leg |
| 73551 | N22y900 | abscess of tendon-thigh |
| 29296 | C050200 | abscess of thyroid |
| 19970 | J090000 | abscess of tongue |
| 4187 | K424000 | abscess of vulva |
| 9556 | K310.11 | abscess, breast, non puerperal |
| 37630 | N22y.11 | abscess, contracture or calcification of bursa or tendon |
| 20144 | F501111 | abscess, external ear |

| | | |
|---|---|---|
| 14730 | K310400 | acute nonpuerperal breast abscess |
| 31823 | K410400 | acute pyometra or uterine abscess |
| 16000 | J54z.00 | ano-rectal abscess nos |
| 1064 | K318.00 | breast abscess |
| 641 | M00..00 | carbuncle |
| 44596 | M00z.00 | carbuncle nos |
| 46419 | M002300 | carbuncle of abdominal wall |
| 103521 | M006400 | carbuncle of ankle |
| 47671 | M005000 | carbuncle of anus |
| 27809 | M003100 | carbuncle of axilla |
| 57078 | M002200 | carbuncle of back |
| 32096 | M002100 | carbuncle of breast |
| 35986 | M005.00 | carbuncle of buttock |
| 36153 | M005z00 | carbuncle of buttock nos |
| 62989 | M002000 | carbuncle of chest wall |
| 27814 | M000000 | carbuncle of ear |
| 17179 | M003300 | carbuncle of elbow |
| 34818 | M000.00 | carbuncle of face |
| 94897 | M000100 | carbuncle of face (excluding eye) |
| 19320 | M000z00 | carbuncle of face nos |
| 44036 | M004200 | carbuncle of finger |
| 100306 | M002500 | carbuncle of flank |
| 50123 | M007.00 | carbuncle of foot |
| 62948 | M007z00 | carbuncle of foot nos |
| 114185 | M007000 | carbuncle of foot unspecified |
| 27754 | M003400 | carbuncle of forearm |
| 55852 | M005100 | carbuncle of gluteal region |
| 33629 | M002600 | carbuncle of groin |
| 54931 | M004.00 | carbuncle of hand |
| 44565 | M004z00 | carbuncle of hand nos |
| 97114 | M00y000 | carbuncle of head (excluding face) |
| 21393 | M007100 | carbuncle of heel |
| 51251 | M006000 | carbuncle of hip |
| 73789 | M006200 | carbuncle of knee |
| 35899 | K42y100 | carbuncle of labium |
| 45747 | M006.00 | carbuncle of leg (excluding foot) |
| 92964 | M006z00 | carbuncle of leg (excluding foot) nos |
| 70382 | M006300 | carbuncle of lower leg |
| 28339 | M000200 | carbuncle of nasal septum |
| 54003 | M001.00 | carbuncle of neck |
| 67068 | M00y.00 | carbuncle of other specified site |
| 54142 | M00yz00 | carbuncle of other specified site nos |
| 47895 | M002700 | carbuncle of perineum |
| 39521 | K284200 | carbuncle of scrotum |
| 65836 | M003000 | carbuncle of shoulder |
| 66950 | M000300 | carbuncle of temple region |
| 35728 | M006100 | carbuncle of thigh |
| 15698 | M004100 | carbuncle of thumb |
| 27861 | M007200 | carbuncle of toe |
| 60174 | M002.00 | carbuncle of trunk |
| 96369 | M002z00 | carbuncle of trunk nos |
| 30967 | M002400 | carbuncle of umbilicus |
| 66105 | M003200 | carbuncle of upper arm |
| 67139 | M003.00 | carbuncle of upper arm and forearm |
| 72102 | M003z00 | carbuncle of upper arm and forearm nos |
| 17009 | K42y000 | carbuncle of vagina |
| 37309 | K424100 | carbuncle of vulva |
| 60748 | M004000 | carbuncle of wrist |
| 27933 | J54..11 | cellulitis - anus or rectum |
| 12167 | M03zz00 | cellulitis and abscess nos |
| 309 | M03z.00 | cellulitis and abscess nos |
| 4973 | M032300 | cellulitis and abscess of abdominal wall |
| 10974 | M036400 | cellulitis and abscess of ankle |
| 3461 | M033.00 | cellulitis and abscess of arm |
| 48630 | M033z00 | cellulitis and abscess of arm nos |
| 1772 | M033100 | cellulitis and abscess of axilla |
| 1874 | M032200 | cellulitis and abscess of back |
| 16176 | M032100 | cellulitis and abscess of breast |
| 2897 | M035.00 | cellulitis and abscess of buttock |
| 2658 | M030011 | cellulitis and abscess of cheek |

| | | |
|---|---|---|
| 24401 | M030000 | cellulitis and abscess of cheek (external) |
| 4394 | M032000 | cellulitis and abscess of chest wall |
| 15549 | M030200 | cellulitis and abscess of chin |
| 25081 | M02z.00 | cellulitis and abscess of digit nos |
| 3223 | M033300 | cellulitis and abscess of elbow |
| 3998 | M030.00 | cellulitis and abscess of face |
| 20389 | M030z00 | cellulitis and abscess of face nos |
| 4779 | M020.00 | cellulitis and abscess of finger |
| 5697 | M02..00 | cellulitis and abscess of finger and toe |
| 26071 | M020z00 | cellulitis and abscess of finger nos |
| 3527 | M020000 | cellulitis and abscess of finger unspecified |
| 23585 | M032500 | cellulitis and abscess of flank |
| 27757 | M037.11 | cellulitis and abscess of foot |
| 31148 | M037.00 | cellulitis and abscess of foot excluding toe |
| 29113 | M037z00 | cellulitis and abscess of foot nos |
| 2089 | M037000 | cellulitis and abscess of foot unspecified |
| 27903 | M033400 | cellulitis and abscess of forearm |
| 15475 | M030400 | cellulitis and abscess of forehead |
| 1923 | M032600 | cellulitis and abscess of groin |
| 1415 | M034.11 | cellulitis and abscess of hand |
| 27908 | M034.00 | cellulitis and abscess of hand excluding digits |
| 23604 | M034z00 | cellulitis and abscess of hand nos |
| 2914 | M034000 | cellulitis and abscess of hand unspecified |
| 24960 | M03y000 | cellulitis and abscess of head unspecified |
| 15642 | M037100 | cellulitis and abscess of heel |
| 3597 | M036000 | cellulitis and abscess of hip |
| 2216 | M036200 | cellulitis and abscess of knee |
| 10326 | M036.11 | cellulitis and abscess of leg |
| 7865 | M036.00 | cellulitis and abscess of leg excluding foot |
| 680 | M036z00 | cellulitis and abscess of leg nos |
| 25890 | M036300 | cellulitis and abscess of lower leg |
| 2711 | M031.00 | cellulitis and abscess of neck |
| 10485 | M030111 | cellulitis and abscess of nose |
| 21580 | M030100 | cellulitis and abscess of nose (external) |
| 4400 | M032700 | cellulitis and abscess of perineum |
| 5089 | M033000 | cellulitis and abscess of shoulder |
| 16032 | M030500 | cellulitis and abscess of temple region |
| 2847 | M036100 | cellulitis and abscess of thigh |
| 3960 | M021.00 | cellulitis and abscess of toe |
| 20384 | M021z00 | cellulitis and abscess of toe nos |
| 3363 | M021000 | cellulitis and abscess of toe unspecified |
| 27717 | M032.00 | cellulitis and abscess of trunk |
| 36349 | M032z00 | cellulitis and abscess of trunk nos |
| 14937 | M032400 | cellulitis and abscess of umbilicus |
| 44034 | M033200 | cellulitis and abscess of upper arm |
| 3465 | M034100 | cellulitis and abscess of wrist |
| 7328 | M037200 | cellulitis in diabetic foot |
| 4207 | M03z000 | cellulitis nos |
| 31534 | M086.00 | cellulitis of ankle |
| 9648 | M088.00 | cellulitis of arm |
| 17226 | M08A.00 | cellulitis of axilla |
| 21208 | M034013 | cellulitis of dorsum of hand |
| 205 | M038.00 | cellulitis of external ear |
| 7821 | F4D1400 | cellulitis of eyelid |
| 16011 | F4D0.11 | cellulitis of eyelids |
| 7972 | M082.00 | cellulitis of face |
| 27681 | M030600 | cellulitis of face |
| 5228 | J083000 | cellulitis of floor of mouth |
| 7684 | M08B.00 | cellulitis of foot |
| 6368 | M085.00 | cellulitis of leg |

| | | |
|---|---|---|
| 17562 | J085100 | cellulitis of lip |
| 28181 | M089.00 | cellulitis of neck |
| 27619 | M034014 | cellulitis of palm of hand |
| 16304 | K272300 | cellulitis of penis |
| 4456 | K284300 | cellulitis of scrotum |
| 16606 | M03..13 | cellulitis of skin area excluding digits of hand or foot |
| 94868 | M08C.00 | cellulitis of toe |
| 25039 | M083.00 | cellulitis of trunk |
| 52366 | M032800 | cellulitis of trunk |
| 8852 | F501112 | cellulitis, external ear |
| 71884 | K404100 | chronic abscess of the broad ligament |
| 71263 | K404200 | chronic abscess of the parametrium |
| 24899 | K404400 | chronic abscess of the pouch of douglas |
| 48280 | K310500 | chronic nonpuerperal breast abscess |
| 72237 | K310600 | chronic subareolar nonpuerperal abscess |
| 59750 | M057.00 | chronic symmetrical impetigo |
| 6152 | M09..00 | cutaneous abscess |
| 6833 | M08..00 | cutaneous cellulitis |
| 2488 | 7G25111 | drainage of abscess nec |
| 6233 | 7303100 | drainage of abscess of external ear |
| 8960 | 7G25011 | drainage of abscess of head or neck |
| 10893 | 7G25112 | drainage of boil of skin nec |
| 16668 | 7G25012 | drainage of boil of skin of head or neck |
| 25403 | M2y7.00 | eosinophilic cellulitis [wells] |
| 112747 | 2Fd2.11 | eron class 3 skin and soft tissue infection |
| 111080 | 2Fd0.00 | eron class i skin and soft tissue infection |
| 1156 | A35..00 | erysipelas |
| 27616 | F501411 | erysipelas - otitis externa |
| 1367 | M244.00 | folliculitis |
| 3209 | M244100 | folliculitis (sycosis) barbae |
| 24408 | M244200 | folliculitis depilans |
| 15683 | M244z00 | folliculitis nos |
| 4126 | A98yy14 | gonococcal cellulitis |
| 943 | M05..00 | impetigo |
| 17353 | F501711 | impetigo - otitis externa |
| 8458 | M053.00 | impetigo circinata |
| 10017 | M051.00 | impetigo contagiosa bullosa |
| 73731 | M052.00 | impetigo contagiosa gyrata |
| 20278 | M050.00 | impetigo contagiosa unspecified |
| 16999 | M056.00 | impetigo follicularis |
| 25686 | M143.00 | impetigo herpetiformis |
| 14934 | M05z.00 | impetigo nos |
| 50721 | M055.00 | impetigo simplex |
| 95904 | 7G25700 | incision and drainage of abscess |
| 68242 | F501400 | infective otitis externa due to erysipelas |
| 16249 | F501700 | infective otitis externa due to impetigo |
| 73103 | N230A00 | muscle abscess |
| 70192 | N230E00 | muscle abscess-arm |
| 100876 | N230C00 | muscle abscess-back |
| 94601 | N230L00 | muscle abscess-foot |
| 70208 | N230F00 | muscle abscess-forearm |
| 98866 | N230G00 | muscle abscess-hand |
| 94568 | N230K00 | muscle abscess-leg |
| 73806 | N230B00 | muscle abscess-neck |
| 70190 | N230D00 | muscle abscess-shoulder |

| | | |
|---|---|---|
| 94730 | N230J00 | muscle abscess-thigh |
| 15228 | H1y1000 | nasal septum abscess |
| 20371 | L451.00 | obstetric breast abscess |
| 44482 | L451z00 | obstetric breast abscess nos |
| 63755 | L451000 | obstetric breast abscess unspecified |
| 35656 | J552200 | omental abscess |
| 17651 | 7H21200 | open drainage of abdominal abscess nec |
| 24824 | F4G0200 | orbital abscess |
| 4328 | F4G0100 | orbital cellulitis |
| 17032 | K424.00 | other abscess of vulva |
| 23905 | K424z00 | other abscess of vulva nos |
| 16536 | M03..00 | other cellulitis and abscess |
| 14972 | M03y.00 | other specified cellulitis and abscess |
| 29591 | K272000 | penile abscess |
| 21194 | K272200 | penile carbuncle |
| 37424 | J540.11 | perianal cellulitis |
| 30042 | M244400 | perifolliculitis |
| 16448 | M244700 | perifolliculitis of scalp |
| 6956 | SK03.00 | post-traumatic wound infection nec |
| 2364 | SP25500 | postoperative wound infection, unspecified |
| 51854 | SP25600 | postoperative wound infection-deep |
| 16222 | SP25700 | postoperative wound infection-superficial |
| 6613 | M24y000 | pseudofolliculitis barbae |
| 9531 | M244300 | pustular folliculitis |
| 9056 | J546.00 | rectal abscess |
| 24204 | J54..12 | rectal abscess |
| 9006 | M095.00 | skin abscess |
| 44021 | AB62200 | subcutaneous phaeomycotic abscess and cyst |
| 33359 | J542.00 | submucous ano-rectal abscess |

UTI

| Medcode | Readcode | Readterm |
|---|---|---|
| 150 | K190z00 | urinary tract infection, site not specified nos |
| 389 | K15..00 | cystitis |
| 1106 | K10y100 | pyelitis unspecified |
| 1289 | K190.00 | urinary tract infection, site not specified |
| 1353 | K155.00 | recurrent cystitis |
| 1572 | K190.11 | recurrent urinary tract infection |
| 1899 | K10y000 | pyelonephritis unspecified |
| 2546 | K101.00 | acute pyelonephritis |
| 2650 | K190400 | chronic urinary tract infection |
| 2939 | K100600 | calculous pyelonephritis |
| 2985 | K190311 | recurrent uti |
| 3469 | K152y00 | chronic cystitis unspecified |
| 3610 | K102100 | perinephric abscess |
| 4453 | K190100 | pyuria, site not specified |
| 4654 | K100.00 | chronic pyelonephritis |
| 4993 | K190000 | bacteriuria, site not specified |
| 9378 | 1AG..00 | recurrent urinary tract infections |
| 9534 | 46U3.00 | urine culture - e. coli |
| 10295 | A981100 | acute gonococcal cystitis |
| 10515 | K190300 | recurrent urinary tract infection |
| 10857 | K15y.00 | other specified cystitis |
| 11315 | K152z00 | other chronic cystitis nos |
| 11447 | K153.11 | follicular cystitis |
| 11585 | K151.00 | chronic interstitial cystitis |
| 12484 | K15z.00 | cystitis nos |
| 12570 | K190200 | post operative urinary tract infection |
| 13911 | 46U3.11 | urine culture - escherich.coli |
| 13918 | 46U7.00 | urine culture - pseudomonas |
| 13921 | 46U2.00 | urine culture - mixed growth |
| 13922 | 46U4.00 | urine culture - proteus |
| 14711 | K10y200 | pyonephrosis unspecified |
| 14828 | K101200 | acute pyelitis |
| 15074 | K150.00 | acute cystitis |
| 15357 | K102000 | renal abscess |
| 16511 | 46U8.00 | urine culture - bacteria os |
| 21158 | K100200 | chronic pyelitis |
| 22682 | K15y000 | cystitis cystica |
| 23772 | K102.00 | renal and perinephric abscess |
| 23776 | K151200 | submucous cystitis |

| | | |
|---|---|---|
| 25055 | K100300 | chronic pyonephrosis |
| 29460 | K151z00 | chronic interstitial cystitis nos |
| 29497 | K213.00 | prostatocystitis |
| 30068 | K152000 | subacute cystitis |
| 30964 | K154z00 | cystitis in diseases ec nos |
| 32787 | K152.00 | other chronic cystitis |
| 32909 | K154200 | cystitis in bilharziasis |
| 34630 | K15yz00 | other cystitis nos |
| 34645 | K15y200 | abscess of bladder |
| 35360 | K100400 | nonobstructive reflux-associated chronic pyelonephritis |
| 38572 | K104.00 | xanthogranulomatous pyelonephritis |
| 38698 | K101z00 | acute pyelonephritis nos |
| 40903 | 46U6.00 | urine culture - staph. albus |
| 42184 | 46U5.00 | urine culture - str. faecalis |
| 44897 | K154700 | cystitis in trichomoniasis |
| 47790 | K101300 | acute pyonephrosis |
| 48111 | K100z00 | chronic pyelonephritis nos |
| 48855 | K100500 | chronic obstructive pyelonephritis |
| 48908 | A983100 | chronic gonococcal cystitis |
| 49212 | K102200 | renal carbuncle |
| 49235 | A160200 | tuberculous pyelonephritis |
| 49842 | K154000 | cystitis in actinomycosis |
| 50837 | A160100 | tuberculous pyelitis |
| 53944 | K10y.00 | pyelonephritis and pyonephrosis unspecified |
| 55168 | K154600 | cystitis in moniliasis |
| 56771 | K154800 | cystitis in tuberculosis |
| 57568 | K100100 | chronic pyelonephritis with medullary necrosis |
| 59121 | K10yz00 | unspecified pyelonephritis nos |
| 64482 | K101000 | acute pyelonephritis without medullary necrosis |
| 68954 | K154500 | cystitis in gonorrhoea |
| 69151 | A32y300 | diphtheritic cystitis |
| 70189 | Kyu5100 | [x]other cystitis |
| 71787 | K10y400 | pyelitis in diseases ec |
| 72686 | Kyu5000 | [x]other chronic cystitis |
| 73412 | K102z00 | renal and perinephric abscess nos |
| 93839 | K154.00 | cystitis in diseases ec |
| 95710 | K10y300 | pyelonephritis in diseases ec |
| 97002 | K190500 | urinary tract infection |
| 97040 | K154100 | cystitis in amoebiasis |
| 99631 | K100000 | chronic pyelonephritis without medullary necrosis |
| 105634 | K106.00 | candida pyelonephritis |
| 107568 | SP07Q00 | catheter-associated urinary tract infection |
| 107843 | SP07Q11 | cauti - catheter-associated urinary tract infection |
| 110092 | K101400 | emphysematous pyelonephritis |
| 114581 | K154300 | cystitis in echinococcus infestation |

**Antibiotics for LRTI, SSTI and UTI**

Available on the LSHTM Data Compass pages

# A3.4 Manuscript appendix 3 – sensitivity analyses LRTI cohort

**Sensitivity analysis 1.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status (with acne date, antibiotic for acne date and LRTI and LRTI antibiotic date after 2004).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=48,858 | **With oral antibiotic for acne** n=23,631 | **Without oral antibiotic for acne** n=25,227 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 417,501 | 201,012 | 216,489 |
| Median (IQR) duration of follow-up (years) | 8.6 (5.5-11.5) | 8.4 (5.5-11.4) | 8.7 (5.5-11.6) |
| **Sex** | | | |
| Female (%) | 33,227 (68.0%) | 15,438 (65.3%) | 17,789 (70.5%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 615 (1.3%) | 245 (1.0%) | 370 (1.5%) |
| 12-18 | 19,720 (40.4%) | 9,507 (40.2%) | 10,213 (40.5%) |
| 19-25 | 10,723 (21.9%) | 4,928 (20.9%) | 5,795 (23.0%) |
| 26-35 | 10,951 (22.4%) | 5,155 (21.8%) | 5,796 (23.0%) |
| 36+ | 6,849 (14.0%) | 3,796 (16.1%) | 3,053 (12.1%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 10,127 20.7 | 5046 (21.4%) | 5,081 (20.1%) |
| 2 | 8133 16.7 | 4,084 (17.3%) | 4,049 (16.1%) |
| 3 | 9,237 18.9 | 4,420 (18.7%) | 4,817 (19.1%) |
| 4 | 9,327 19.1 | 4,494 (19.0%) | 4,833 (19.2%) |
| 5(most deprived) | 12,034 24.6 | 5,587 (23.6%) | 6,447 (25.6%) |
| **Harmful alcohol use (%)***** | 1,501 (6.4%) | 724 (3.1%) | 777 (3.1%) |
| **Asthma (%)***** | 15,419 (65.2%) | 7,652 (32.4%) | 7,767 (30.8%) |
| **Diabetes (%)***** | 674 (1.4%) | 367 (1.6%) | 307 (1.2%) |
| **Ethnicity** | | | |
| White | 21,558 (44.1%) | 10,337 (43.7%) | 11,221 (44.5%) |
| South Asian | 1,630 (3.3%) | 705 (3.0%) | 925 (3.7%) |
| Black | 579 (1.2%) | 226 (1.0%) | 353 (1.4%) |
| Other | 361 (0.7%) | 140 (0.6%) | 221 (0.9%) |
| Mixed | 307 (0.6%) | 135 (0.6%) | 172 (0.7%) |
| Not stated or missing | 24,423 (50.0%) | 12,088 (51.2%) | 12,335 (48.9%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 1.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and LRTI and LRTI antibiotic date after 2004).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 25,102 | 108,584 | 2,273 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 23,499 | 106,509 | 2,565 | **1.22 (1.15, 1.29)** | **1.25 (1.18, 1.33)** | **1.25 (1.18, 1.33)** | **1.22 (1.15, 1.29)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 2.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status (using 14 days intervals to make continuous courses)**.**

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=114,770 | **With oral antibiotic for acne** n=39,392 | **Without oral antibiotic for acne** n=75,378 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,704,070 | 523,906 | 1,180,164 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.4) | 12.1 (7.5-18.0) | 14.5 (8.9-21.5) |
| **Sex** | | | |
| Female (%) | 72,186 (62.9%) | 23,024 (58.4%) | 49,162 (65.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,646 (1.4%) | 510 (1.3%) | 1,136 (1.5%) |
| 12-18 | 54,060 (47.1%) | 19,221 (48.8%) | 34,839 (46.2%) |
| 19-25 | 24,501 (21.3%) | 7,476 (19.0%) | 17,025 (22.6%) |
| 26-35 | 23,465 (20.4%) | 7,846 (19.9%) | 15,619 (20.7%) |
| 36+ | 11,098 (9.7%) | 4,339 (11.0%) | 6,759 (9.0%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 24,113 (21.0%) | 8,548 (21.7%) | 15,565 (20.7%) |
| 2 | 20,005 (17.4%) | 7,174 (18.2%) | 12,831 (17.0%) |
| 3 | 21,711 (18.9%) | 7,353 (18.7%) | 14,358 (19.1%) |
| 4 | 21,042 (18.3%) | 7,166 (18.2%) | 13,876 (18.4%) |
| 5(most deprived) | 27,899 (24.3%) | 9,151 (23.2%) | 18,748 (24.9%) |
| **Harmful alcohol use (%)***** | 3,189 (8.1%) | 907 (2.3%) | 2,282 (3.0%) |
| **Asthma (%)***** | 30,375 (77.1%) | 10,773 (27.3%) | 19,602 (26.0%) |
| **Diabetes (%)***** | 1,566 (1.4%) | 465 (1.2%) | 1,101 (1.5%) |
| **Ethnicity** | | | |
| White | 43,585 (38.0%) | 13,931 (35.4%) | 29,654 (39.3%) |
| South Asian | 2,531 (2.2%) | 812 (2.1%) | 1,719 (2.3%) |
| Black | 927 (0.8%) | 270 (0.7%) | 657 (0.9%) |
| Other | 523 (0.5%) | 152 (0.4%) | 371 (0.5%) |
| Mixed | 470 (0.4%) | 144 (0.4%) | 326 (0.4%) |
| Not stated or missing | 66,734 (58.1%) | 24,083 (61.1%) | 42,651 (56.6%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 2.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (using 14 days to define courses of antibiotic for acne).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 75,136 | 531,572 | 6,884 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 39,202 | 310,931 | 3,864 | **0.96 (0.92, 0.99)** | **0.98 (0.94, 1.02)** | **0.98 (0.94, 1.02)** | **0.96 (0.92, 1.00)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 3.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status, excluding people with primary immunodeficiency.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=114,761 | **With oral antibiotic for acne** n=49,768 | **Without oral antibiotic for acne** n=64,993 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,703,948 | 678,528 | 1,025,420 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.4) | 12.4 (7.6-18.5) | 14.7 (9.0-21.6) |
| **Sex** | | | |
| Female (%) | 72,181 (62.9%) | 30,960 (62.2%) | 41,221 (63.4%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,646 (1.4%) | 673 (1.4%) | 973 (1.5%) |
| 12-18 | 54,055 (47.1%) | 23,253 (46.7%) | 30,802 (47.4%) |
| 19-25 | 24,498 (21.3%) | 9,776 (19.6%) | 14,722 (22.7%) |
| 26-35 | 23,464 (20.4%) | 10,336 (20.8%) | 13,128 (20.2%) |
| 36+ | 11,098 (9.7%) | 5,730 (11.5%) | 5,368 (8.3%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 24,111 (21.0%) | 10,506 (21.1%) | 13,605 (20.9%) |
| 2 | 20,004 (17.4%) | 8,922 (17.9%) | 11,082 (17.1%) |
| 3 | 21,710 (18.9%) | 9,368 (18.8%) | 12,342 (19.0%) |
| 4 | 21,039 (18.3%) | 9,147 (18.4%) | 11,892 (18.3%) |
| 5(most deprived) | 27,897 (24.3%) | 11,825 (23.8%) | 16,072 (24.7%) |
| **Harmful alcohol use (%)***** | 3,189 (6.4%) | 1,235 (2.5%) | 1,954 (3.0%) |
| **Asthma (%)***** | 30,370 (61.0%) | 13,954 (28.0%) | 16,416 (25.3%) |
| **Diabetes (%)***** | 1,573 (1.4%) | 666 (1.3%) | 907 (1.4%) |
| **Ethnicity** | | | |
| White | 43,581 (38.0%) | 18,066 (36.3%) | 25,515 (39.3%) |
| South Asian | 2,529 (2.2%) | 1,016 (2.0%) | 1,513 (2.3%) |
| Black | 931 (0.8%) | 352 (0.7%) | 579 (0.9%) |
| Other | 524 (0.5%) | 190 (0.4%) | 334 (0.5%) |
| Mixed | 469 (0.4%) | 178 (0.4%) | 291 (0.4%) |
| Not stated or missing | 66,727 (58.1%) | 29,966 (60.2%) | 36,761 (56.6%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 3.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding primary immunodeficiency)

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 64,761 | 458,266 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 49,568 | 384,200 | 5,094 | **1.08 (1.04, 1.12)** | **1.09 (1.05, 1.13)** | **1.09 (1.05, 1.13)** | **1.08 (1.04, 1.13)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 4.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status excluding cancer diagnosis in six months prior to start of follow up (excluding skin cancer).

| | **Study population** n=114,621 | **With oral antibiotic for acne** n=49,703 | **Without oral antibiotic for acne** n=64,918 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,701,489 | 677,650 | 1,023,839 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.3) | 12.4 (7.6-18.5) | 14.6 (9.0-21.6) |
| **Sex** | | | |
| Female (%) | 72,080 (62.9%) | 30,910 (62.2%) | 41,170 (63.4%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,646 (1.4%) | 673 (1.4%) | 973 (1.5%) |
| 12-18 | 54,030 (47.1%) | 23,246 (46.8%) | 30,784 (47.4%) |
| 19-25 | 24,475 (21.4%) | 9,763 (19.6%) | 14,712 (22.7%) |
| 26-35 | 23,413 (20.4%) | 10,313 (20.7%) | 13,100 (20.2%) |
| 36+ | 11,057 (9.6%) | 5,708 (11.5%) | 5,349 (8.2%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 24,080 (21.0%) | 10,495 (21.1%) | 13,585 (20.9%) |
| 2 | 19,985 (17.4%) | 8,913 (17.9%) | 11,072 (17.1%) |
| 3 | 21,692 (18.9%) | 9,358 (18.8%) | 12,334 (19.0%) |
| 4 | 21,001 (18.3%) | 9,129 (18.4%) | 11,872 (18.3%) |
| 5(most deprived) | 27,863 (24.3%) | 11,808 (23.8%) | 16,055 (24.7%) |
| **Harmful alcohol use (%)***** | 3,183 (6.4%) | 1,230 (2.5%) | 1,953 (3.0%) |
| **Asthma (%)***** | 30,347 (61.1%) | 13,945 (28.1%) | 16,402 (25.3%) |
| **Diabetes (%)***** | 1,563 (1.4%) | 659 (1.3%) | 904 (1.4%) |
| **Ethnicity** | | | |
| White | 43,531 (38.0%) | 18,041 (36.3%) | 25,490 (39.3%) |
| South Asian | 2,530 (2.2%) | 1,017 (2.0%) | 1,513 (2.3%) |
| Black | 927 (0.8%) | 349 (0.7%) | 578 (0.9%) |
| Other | 523 (0.5%) | 189 (0.4%) | 334 (0.5%) |
| Mixed | 468 (0.4%) | 178 (0.4%) | 290 (0.4%) |
| Not stated or missing | 66,642 (58.1%) | 29,929 (60.2%) | 36,713 (56.6%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 4.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding diagnosis of cancer within six months of start of follow up (excluding skin cancer)).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 64,686 | 457,847 | 5,637 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 49,503 | 383,944 | 5,078 | **1.08 (1.04, 1.12)** | **1.09 (1.05, 1.13)** | **1.09 (1.05, 1.13)** | **1.08 (1.04, 1.13)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 5.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status (including individuals with complete ethnicity data).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=24,435 | **With oral antibiotic for acne** n=11,543 | **Without oral antibiotic for acne** n=12,892 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 209,232 | 97,951 | 111,281 |
| Median (IQR) duration of follow-up (years) | 8.6 (5.7-11.4) | 8.4 (5.6-11.2) | 8.7 (5.7-11.5) |
| **Sex** | | | |
| Female (%) | 17,383 (71.1%) | 7,905 (68.5%) | 9,478 (73.5%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 239 (1.0%) | 79 (0.7%) | 160 (1.2%) |
| 12-18 | 8,700 (35.6%) | 4,072 (35.3%) | 4,628 (35.9%) |
| 19-25 | 5,636 (23.1%) | 2,491 (21.6%) | 3,145 (24.4%) |
| 26-35 | 6,076 (24.9%) | 2,809 (24.3%) | 3,267 (25.3%) |
| 36+ | 3,784 (15.5%) | 2,092 (18.1%) | 1,692 (13.1%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 4,855 (19.9%) | 2,335 (20.2%) | 2,520 (19.6%) |
| 2 | 4,267 (17.5%) | 2,108 (18.3%) | 2,159 (16.8%) |
| 3 | 4,894 (20.0%) | 2,280 (19.8%) | 2,614 (20.3%) |
| 4 | 4,338 (17.6%) | 2,000 (17.3%) | 2,338 (18.1%) |
| 5(most deprived) | 6,081 (24.9%) | 2,820 (24.4%) | 3,261 (25.3%) |
| **Harmful alcohol use (%)***** | 869 (7.5%) | 405 (3.5%) | 464 (3.6%) |
| **Asthma (%)***** | 7,526 (65.2%) | 3,678 (31.9%) | 3,848 (29.8%) |
| **Diabetes (%)***** | 382 (1.6%) | 214 (1.9%) | 168 (1.3%) |
| **Ethnicity** | | | |
| White | 21,558 (88.2%) | 10,337 (89.6%) | 11,221 (87.0%) |
| South Asian | 1,630 (6.7%) | 705 (6.1%) | 925 (7.2%) |
| Black | 579 (2.4%) | 226 (2.0%) | 353 (2.7%) |
| Other | 361 (1.5%) | 140 (1.2%) | 221 (1.7%) |
| Mixed | 307 (1.3%) | 135 (1.2%) | 172 (1.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 5**. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and LRTI and LRTI anotbiotic date after 2004, and complete data for ethnicity included).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 12,856 | 54,359 | 1,156 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 11,509 | 51,112 | 1,260 | **1.22 (1.13, 1.32)** | **1.24 (1.15, 1.35)** | **1.25 (1.15, 1.35)** | **1.22 (1.13, 1.32)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 6.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status only including patients with GP contact in one year prior to index date.

Values are numbers (percentages) unless stated otherwise

| | Study population n=111,951 | With oral antibiotic for acne n=48,642 | Without oral antibiotic for acne n=63,309 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,657,703 | 661,147 | 996,557 |
| Median (IQR) duration of follow-up (years) | 13.5 (8.3-20.3) | 12.3 (7.6-18.5) | 14.6 (9.0-21.6) |
| **Sex** | | | |
| Female (%) | 70,620 (63.1%) | 30,338 (62.4%) | 40,282 (63.6%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,595 (1.4%) | 657 (1.4%) | 938 (1.5%) |
| 12-18 | 52,534 (46.9%) | 22,621 (46.5%) | 29,913 (47.2%) |
| 19-25 | 23,948 (21.4%) | 9,585 (19.7%) | 14,363 (22.7%) |
| 26-35 | 22,973 (20.5%) | 10,135 (20.8%) | 12,838 (20.3%) |
| 36+ | 10,901 (9.7%) | 5,644 (11.6%) | 5,257 (8.3%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 23,820 (21.3%) | 10,404 (21.4%) | 13,416 (21.2%) |
| 2 | 19,789 (17.7%) | 8,831 (18.2%) | 10,958 (17.3%) |
| 3 | 21,292 (19.0%) | 9,212 (18.9%) | 12,080 (19.1%) |
| 4 | 20,304 (18.1%) | 8,840 (18.2%) | 11,464 (18.1%) |
| 5(most deprived) | 26,746 (23.9%) | 11,355 (23.3%) | 15,391 (24.3%) |
| **Harmful alcohol use (%)***** | 3,126 (6.4%) | 1,215 (2.5%) | 1,911 (3.0%) |
| **Asthma (%)***** | 29,639 (60.9%) | 13,647 (28.1%) | 15,992 (25.3%) |
| **Diabetes (%)***** | 1,530 (1.4%) | 648 (1.3%) | 882 (1.4%) |
| **Ethnicity** | | | |
| White | 42,657 (38.1%) | 17,707 (36.4%) | 24,950 (39.4%) |
| South Asian | 2,498 (2.2%) | 1,007 (2.1%) | 1,491 (2.4%) |
| Black | 920 (0.8%) | 347 (0.7%) | 573 (0.9%) |
| Other | 517 (0.5%) | 187 (0.4%) | 330 (0.5%) |
| Mixed | 458 (0.4%) | 172 (0.4%) | 286 (0.5%) |
| Not stated or missing | 64,901 (58.0%) | 29,222 (60.1%) | 35,679 (56.4%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 6.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not including individuals who have had GP contact in the one year prior to index date.

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 63,084 | 443,265 | 5,516 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 48,447 | 373,469 | 4,987 | **1.08 (1.04, 1.12)** | **1.09 (1.05, 1.13)** | **1.09 (1.05, 1.13)** | **1.08 (1.04, 1.12)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 7.** Characteristics of the LRTI study population at cohort entry where the oral antibiotic prescription for LRTI is on the same day as the LRTI diagnosis date.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=114,770 | **With oral antibiotic for acne** n=39,392 | **Without oral antibiotic for acne** n=75,378 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,704,070 | 523,906 | 1,180,164 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.4) | 12.1 (7.5-18.0) | 14.5 (8.9-21.5) |
| **Sex** | | | |
| Female (%) | 72,186 (62.9%) | 23,024 (58.4%) | 49,162 (65.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,646 (1.4%) | 510 (1.3%) | 1,136 (1.5%) |
| 12-18 | 54,060 (47.1%) | 19,221 (48.8%) | 34,839 (46.2%) |
| 19-25 | 24,501 (21.3%) | 7,476 (19.0%) | 17,025 (22.6%) |
| 26-35 | 23,465 (20.4%) | 7,846 (19.9%) | 15,619 (20.7%) |
| 36+ | 11,098 (9.7%) | 4,339 (11.0%) | 6,759 (9.0%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 24,113 (21.0%) | 8,548 (21.7%) | 15,565 (20.7%) |
| 2 | 20,005 (17.4%) | 7,174 (18.2%) | 12,831 (17.0%) |
| 3 | 21,711 (18.9%) | 7,353 (18.7%) | 14,358 (19.1%) |
| 4 | 21,042 (18.3%) | 7,166 (18.2%) | 13,876 (18.4%) |
| 5(most deprived) | 27,899 (24.3%) | 9,151 23.2%) | 18,748 (24.9%) |
| **Harmful alcohol use (%)***** | 3,189 (8.1%) | 907 (2.3%) | 2,282 (3.0%) |
| **Asthma (%)***** | 30,375 (77.1%) | 10,773 (27.3%) | 19,602 (26.0%) |
| **Diabetes (%)***** | 1,566 (1.4%) | 465 (1.2%) | 1,101 (1.5%) |
| **Ethnicity** | | | |
| White | 43,585 (38.0%) | 13,931 (35.4%) | 29,654 (39.3%) |
| South Asian | 2,529 (2.2%) | 812 (2.1%) | 1,717 (2.3%) |
| Black | 930 (0.8%) | 272 (0.7%) | 658 (0.9%) |
| Other | 525 (0.5%) | 153 (0.4%) | 372 (0.5%) |
| Mixed | 468 (0.4%) | 142 (0.4%) | 326 (0.4%) |
| Not stated or missing | 66,733 (58.1%) | 24,082 (61.1%) | 42,651 (56.6%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 7.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (including individuals where oral antibiotic for infection is given on the same day as infection diagnosed).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 75,136 | 531,572 | 6,884 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 39,202 | 310,931 | 3,864 | **0.96 (0.92, 0.99)** | **0.98 (0.94, 1.02)** | **0.98 (0.94, 1.02)** | **0.96 (0.92, 1.00)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

# A3.5 Manuscript appendix 4 – sensitivity analyses SSTI cohort

**Sensitivity analysis 1**. Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status (with acne date, antibiotic for acne date and SSTI and SSTI antibiotic date after 2004).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=35,127 | **With oral antibiotic for acne** n=17,711 | **Without oral antibiotic for acne** n=17,416 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 298,204 | 149,764 | 148,440 |
| Median (IQR) duration of follow-up (years) | 8.5 (5.4-11.5) | 8.4 (5.4-11.4) | 8.6 (5.4-11.6) |
| **Sex** | | | |
| Female (%) | 22,176 (63.1%) | 10,650 (60.1%) | 11,526 (66.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 414 (1.2%) | 183 (1.0%) | 231 (1.3%) |
| 12-18 | 14,803 (42.1%) | 7,260 (41.0%) | 7,543 (43.3%) |
| 19-25 | 8,290 (23.6%) | 3,965 (22.4%) | 4,325 (24.8%) |
| 26-35 | 7,442 (21.2%) | 3,825 (21.6%) | 3,617 (20.8%) |
| 36+ | 4,178 (11.9%) | 2,478 (14.0%) | 1,700 (9.8%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 7,352 (20.9%) | 3,725 (21.0%) | 3,627 (20.8%) |
| 2 | 5,843 (16.6%) | 2,976 (16.8%) | 2,867 (16.5%) |
| 3 | 6,670 (19.0%) | 3,439 (19.4%) | 3,231 (18.6%) |
| 4 | 6,728 (19.2%) | 3,371 (19.0%) | 3,357 (19.3%) |
| 5(most deprived) | 8,534 (24.3%) | 4,200 (23.7%) | 4,334 (24.9%) |
| **Harmful alcohol use (%)***** | 1,182 (6.7%) | 619 (3.5%) | 563 (3.2%) |
| **Asthma (%)***** | 8,446 (47.7%) | 4,393 (24.8%) | 4,053 (23.3%) |
| **Diabetes (%)***** | 627 (1.8%) | 371 (2.1%) | 256 (1.5%) |
| **Ethnicity** | | | |
| White | 15,337 (43.7%) | 7,617 (43.0%) | 7,720 (44.3%) |
| South Asian | 1,348 (3.8%) | 636 (3.6%) | 712 (4.1%) |
| Black | 584 (1.7%) | 241 (1.4%) | 343 (2.0%) |
| Other | 269 (0.8%) | 123 (0.7%) | 146 (0.8%) |
| Mixed | 216 (0.6%) | 93 (0.5%) | 123 (0.7%) |
| Not stated or missing | 17,373 (49.5%) | 9,001 (50.8%) | 8,372 (48.1%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 1.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and SSTI and SSTI antibiotic date after 2004).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 17,331 | 70,930 | 2,210 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 17,604 | 73,109 | 2,682 | **1.28 (1.21, 1.35)** | **1.28 (1.21, 1.36)** | **1.28 (1.21, 1.36)** | **1.27 (1.20, 1.34)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 2.** Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status (using 14 days intervals to make continuous courses).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=73,648 | **With oral antibiotic for acne** n=26,693 | **Without oral antibiotic for acne** n=46,955 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,054,645 | 339,522 | 715,122 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.1-19.5) | 11.6 (7.1-17.1) | 14.2 (8.8-20.8) |
| **Sex** | | | |
| Female (%) | 43,418 (59.0%) | 14,441 (54.1%) | 28,977 (61.7%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,164 (1.6%) | 382 (1.4%) | 782 (1.7%) |
| 12-18 | 36,346 (49.4%) | 13,317 (49.9%) | 23,029 (49.0%) |
| 19-25 | 15,932 (21.6%) | 5,336 (20.0%) | 10,596 (22.6%) |
| 26-35 | 13,902 (18.9%) | 4,986 (18.7%) | 8,916 (19.0%) |
| 36+ | 6,304 (8.6%) | 2,672 (10.0%) | 3,632 (7.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,499 (21.0%) | 5,711 (21.4%) | 9,788 (20.9%) |
| 2 | 12,929 (17.6%) | 4,854 (18.2%) | 8,075 (17.2%) |
| 3 | 14,038 (19.1%) | 5,187 (19.4%) | 8,851 (18.9%) |
| 4 | 13,403 (18.2%) | 4,818 (18.1%) | 8,585 (18.3%) |
| 5(most deprived) | 17,779 (24.1%) | 6,123 (22.9%) | 11,656 (24.8%) |
| **Harmful alcohol use (%)***** | 2,242 (8.4%) | 707 (2.6%) | 1,535 (3.3%) |
| **Asthma (%)***** | 15,322 (57.4%) | 5,541 (20.8%) | 9,781 (20.8%) |
| **Diabetes (%)***** | 1,266 (1.7%) | 417 (1.6%) | 849 (1.8%) |
| **Ethnicity** | | | |
| White | 28,547 (38.8%) | 9,765 (36.6%) | 18,782 (40.0%) |
| South Asian | 1,944 (2.6%) | 685 (2.6%) | 1,259 (2.7%) |
| Black | 813 (1.1%) | 251 (0.9%) | 562 (1.2%) |
| Other | 363 (0.5%) | 121 (0.5%) | 242 (0.5%) |
| Mixed | 306 (0.4%) | 101 (0.4%) | 205 (0.4%) |
| Not stated or missing | 41,675 (56.6%) | 15,770 (59.1%) | 25,905 (55.2%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 2.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (using 14 days to define courses of antibiotic for acne).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 46,797 | 291,116 | 5,924 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 26,558 | 178,862 | 3,940 | **1.07 (1.03, 1.12)** | **1.08 (1.04, 1.13)** | **1.08 (1.04, 1.13)** | **1.07 (1.03, 1.12)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 3.** Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status, excluding people with primary immunodeficiency.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=73,634 | **With oral antibiotic for acne** n=33,090 | **Without oral antibiotic for acne** n=40,544 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,054,473 | 437,054 | 617,419 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.1-19.5) | 12.1 (7.4-17.8) | 14.1 (8.7-20.8) |
| **Sex** | | | |
| Female (%) | 43,411 (59.0%) | 19,281 (58.3%) | 24,130 (59.5%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,164 (1.6%) | 501 (1.5%) | 663 (1.6%) |
| 12-18 | 36,342 (49.4%) | 15,952 (48.2%) | 20,390 (50.3%) |
| 19-25 | 15,928 (21.6%) | 6,784 (20.5%) | 9,144 (22.6%) |
| 26-35 | 13,897 (18.9%) | 6,459 (19.5%) | 7,438 (18.3%) |
| 36+ | 6,303 (8.6%) | 3,394 (10.3%) | 2,909 (7.2%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,497 (21.1%) | 6,883 (20.8%) | 8,614 (21.3%) |
| 2 | 12,927 (17.6%) | 5,930 (17.9%) | 6,997 (17.3%) |
| 3 | 14,035 (19.1%) | 6,367 (19.2%) | 7,668 (18.9%) |
| 4 | 13,400 (18.2%) | 6,034 (18.2%) | 7,366 (18.2%) |
| 5(most deprived) | 17,775 (24.1%) | 7,876 (23.8%) | 9,899 (24.4%) |
| **Harmful alcohol use (%)***** | 2,241 (6.8%) | 937 (2.8%) | 1,304 (3.2%) |
| **Asthma (%)***** | 15,316 (46.3%) | 7,325 (22.1%) | 7,991 (19.7%) |
| **Diabetes (%)***** | 1,266 (1.7%) | 604 (1.8%) | 662 (1.6%) |
| **Ethnicity** | | | |
| White | 28,534 (38.8%) | 12,309 (37.2%) | 16,225 (40.0%) |
| South Asian | 1,942 (2.6%) | 859 (2.6%) | 1,083 (2.7%) |
| Black | 815 (1.1%) | 302 (0.9%) | 513 (1.3%) |
| Other | 363 (0.5%) | 147 (0.4%) | 216 (0.5%) |
| Mixed | 310 (0.4%) | 121 (0.4%) | 189 (0.5%) |
| Not stated or missing | 41,670 (56.6%) | 19,352 (58.5%) | 22,318 (55.0%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 3.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding primary immunodeficiency).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 40,403 | 251,154 | 5,022 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,938 | 218,761 | 4,839 | **1.12 (1.07, 1.16)** | **1.12 (1.07, 1.16)** | **1.12 (1.08, 1.16)** | **1.11 (1.07, 1.16)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 4.** Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status excluding cancer diagnosis in six months prior to start of follow up (excluding skin cancer).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=73,461 | **With oral antibiotic for acne** n=33,028 | **Without oral antibiotic for acne** n=40,433 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,051,334 | 436,089 | 615,245 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.0-19.5) | 12.1 (7.4-17.8) | 14.1 (8.7-20.8) |
| **Sex** | | | |
| Female (%) | 43,281 (58.9%) | 19,230 (58.2%) | 24,051 (59.5%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,162 (1.6%) | 499 (1.5%) | 663 (1.6%) |
| 12-18 | 36,311 (49.4%) | 15,944 (48.3%) | 20,367 (50.4%) |
| 19-25 | 15,906 (21.7%) | 6,777 (20.5%) | 9,129 (22.6%) |
| 26-35 | 13,840 (18.8%) | 6,443 (19.5%) | 7,397 (18.3%) |
| 36+ | 6,242 (8.5%) | 3,365 (10.2%) | 2,877 (7.1%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,450 (21.0%) | 6,866 (20.8%) | 8,584 (21.2%) |
| 2 | 12,893 (17.6%) | 5,920 (17.9%) | 6,973 (17.3%) |
| 3 | 14,001 (19.1%) | 6,355 (19.2%) | 7,646 (18.9%) |
| 4 | 13,368 (18.2%) | 6,023 (18.2%) | 7,345 (18.2%) |
| 5(most deprived) | 17,749 (24.2%) | 7,864 (23.8%) | 9,885 (24.5%) |
| **Harmful alcohol use (%)***** | 2,235 (6.8%) | 936 (2.8%) | 1,299 (3.2%) |
| **Asthma (%)***** | 15,287 (46.3%) | 7,312 (22.1%) | 7,975 (19.7%) |
| **Diabetes (%)***** | 1,261 (1.7%) | 603 (1.8%) | 658 (1.6%) |
| **Ethnicity** | | | |
| White | 28,480 (38.8%) | 12,291 (37.2%) | 16,189 (40.0%) |
| South Asian | 1,937 (2.6%) | 855 (2.6%) | 1,082 (2.7%) |
| Black | 812 (1.1%) | 301 (0.9%) | 511 (1.3%) |
| Other | 362 (0.5%) | 146 (0.4%) | 216 (0.5%) |
| Mixed | 310 (0.4%) | 121 (0.4%) | 189 (0.5%) |
| Not stated or missing | 41,560 (56.6%) | 19,314 (58.5%) | 22,246 (55.0%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 4.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding diagnosis of cancer within six months of start of follow up (excluding skin cancer)).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 40,292 | 250,745 | 4,993 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,876 | 218,475 | 4,826 | **1.12 (1.07, 1.16)** | **1.12 (1.08, 1.17)** | **1.12 (1.08, 1.17)** | **1.11 (1.07, 1.16)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 5.** Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status (including individuals with complete ethnicity data).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=17,754 | **With oral antibiotic for acne** n=8,710 | **Without oral antibiotic for acne** n=9,044 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 150,012 | 73,089 | 76,923 |
| Median (IQR) duration of follow-up (years) | 8.5 (5.4-11.3) | 8.4 (5.4-11.2) | 8.6 (5.5-11.5) |
| **Sex** | | | |
| Female (%) | 11,673 (65.7%) | 5,465 (62.7%) | 6,208 (68.6%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 175 (1.0%) | 68 (0.8%) | 107 (1.2%) |
| 12-18 | 6,646 (37.4%) | 3,199 (36.7%) | 3,447 (38.1%) |
| 19-25 | 4,366 (24.6%) | 2,013 (23.1%) | 2,353 (26.0%) |
| 26-35 | 4,260 (24.0%) | 2,095 (24.1%) | 2,165 (23.9%) |
| 36+ | 2,307 (13.0%) | 1,335 (15.3%) | 972 (10.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 3,562 (20.1%) | 1,714 (19.7%) | 1,848 (20.4%) |
| 2 | 3,016 (17.0%) | 1,471 (16.9%) | 1,545 (17.1%) |
| 3 | 3,472 (19.6%) | 1,756 (20.2%) | 1,716 (19.0%) |
| 4 | 3,281 (18.5%) | 1,603 (18.4%) | 1,678 (18.6%) |
| 5(most deprived) | 4,423 (24.9%) | 2,166 (24.9%) | 2,257 (25.0%) |
| **Harmful alcohol use (%)***** | 687 (7.9%) | 347 (4.0%) | 340 (3.8%) |
| **Asthma (%)***** | 4,116 (47.3%) | 2,109 (24.2%) | 2,007 (22.2%) |
| **Diabetes (%)***** | 350 (2.0%) | 209 (2.4%) | 141 (1.6%) |
| **Ethnicity** | | | |
| White | 15,337 (86.4%) | 7,617 (87.5%) | 7,720 (85.4%) |
| South Asian | 1,348 (7.6%) | 636 (7.3%) | 712 (7.9%) |
| Black | 584 (3.3%) | 241 (2.8%) | 343 (3.8%) |
| Other | 269 (1.5%) | 123 (1.4%) | 146 (1.6%) |
| Mixed | 216 (1.2%) | 93 (1.1%) | 123 (1.4%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 5.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and SSTI and SSTI antibiotic date after 2004, and complete data for ethnicity included).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 9,031 | 36,085 | 1,143 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 8,679 | 35,205 | 1,355 | **1.30 (1.20, 1.41)** | **1.31 (1.21, 1.42)** | **1.31 (1.21, 1.41)** | **1.29 (1.19, 1.39)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 6.** Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status only including patients with GP contact in one year prior to index date.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=71,843 | **With oral antibiotic for acne** n=32,347 | **Without oral antibiotic for acne** n=39,496 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,025,465 | 425,635 | 599,830 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.0-19.5) | 12.0 (7.3-17.8) | 14.1 (8.7-20.7) |
| **Sex** | | | |
| Female (%) | 42,529 (59.2%) | 18,910 (58.5%) | 23,619 (59.8%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,127 (1.6%) | 490 (1.5%) | 637 (1.6%) |
| 12-18 | 35,309 (49.1%) | 15,520 (48.0%) | 19,789 (50.1%) |
| 19-25 | 15,576 (21.7%) | 6,653 (20.6%) | 8,923 (22.6%) |
| 26-35 | 13,631 (19.0%) | 6,340 (19.6%) | 7,291 (18.5%) |
| 36+ | 6,200 (8.6%) | 3,344 (10.3%) | 2,856 (7.2%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,247 (21.2%) | 6,791 (21.0%) | 8,456 (21.4%) |
| 2 | 12,817 (17.8%) | 5,881 (18.2%) | 6,936 (17.6%) |
| 3 | 13,752 (19.1%) | 6,263 (19.4%) | 7,489 19.0%) |
| 4 | 12,949 (18.0%) | 5,850 (18.1%) | 7,099 (18.0%) |
| 5(most deprived) | 17,078 (23.8%) | 7,562 (23.4%) | 9,516 (24.1%) |
| **Harmful alcohol use (%)***** | 2,194 (6.8%) | 922 (2.9%) | 1,272 (3.2%) |
| **Asthma (%)***** | 14,935 (46.2%) | 7,158 (22.1%) | 7,777 (19.7%) |
| **Diabetes (%)***** | 1,246 (1.7%) | 596 (1.8%) | 650 (1.7%) |
| **Ethnicity** | | | |
| White | 27,963 (38.9%) | 12,084 (37.4%) | 15,879 (40.2%) |
| South Asian | 1,904 (2.7%) | 844 (2.6%) | 1,060 (2.7%) |
| Black | 805 (1.1%) | 300 (0.9%) | 505 (1.3%) |
| Other | 356 (0.5%) | 143 (0.4%) | 213 (0.5%) |
| Mixed | 298 (0.4%) | 115 (0.4%) | 183 (0.5%) |
| Not stated or missing | 40,517 (56.4%) | 18,861 (58.3%) | 21,656 (54.8%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 6.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not including individuals who have had GP contact in the one year prior to index date.

Fitted to patients with complete data for all variables included in each model*

| | **Unadjusted model*** | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 39,362 | 242,465 | 4,915 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,199 | 212,264 | 4,729 | **1.11 (1.06, 1.15)** | **1.11 (1.07, 1.16)** | **1.11 (1.07, 1.16)** | **1.10 (1.06, 1.15)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 7.** Characteristics of the SSTI study population at cohort entry where the oral antibiotic prescription for LRTI is on the same day as the SSTI diagnosis date.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=73,648 | **With oral antibiotic for acne** n=26,693 | **Without oral antibiotic for acne** n=46,955 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,054,645 | 339,522 | 715,122 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.1-19.5) | 11.6 (7.1-17.1) | 14.2 (8.8-20.8) |
| **Sex** | | | |
| Female (%) | 43,418 (59.0%) | 14,441 (54.1%) | 28,977 (61.7%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,164 (1.6%) | 382 (1.4%) | 782 (1.7%) |
| 12-18 | 36,346 (49.4%) | 13,317 (49.9%) | 23,029 (49.0%) |
| 19-25 | 15,932 (21.6%) | 5,336 (20.0%) | 10,596 (22.6%) |
| 26-35 | 13,902 (18.9%) | 4,986 (18.7%) | 8,916 (19.0%) |
| 36+ | 6,304 (8.6%) | 2,672 (10.0%) | 3,632 (7.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,499 (21.0%) | 5,711 (21.4%) | 9,788 (20.9%) |
| 2 | 12,929 (17.6%) | 4,854 (18.2%) | 8,075 (17.2%) |
| 3 | 14,038 (19.1%) | 5,187 (19.4%) | 8,851 (18.9%) |
| 4 | 13,403 (18.2%) | 4,818 (18.1%) | 8,585 (18.3%) |
| 5(most deprived) | 17,779 (24.1%) | 6,123 (22.9%) | 11,656 (24.8%) |
| **Harmful alcohol use (%)***** | 2,242 (8.4%) | 707 (2.6%) | 1,535 (3.3%) |
| **Asthma (%)***** | 15,322 (57.4%) | 5,541 (20.8%) | 9,781 (20.8%) |
| **Diabetes (%)***** | 1,266 (1.7%) | 417 (1.6%) | 849 (1.8%) |
| **Ethnicity** | | | |
| White | 28,545 (38.8%) | 9,765 (36.6%) | 18,780 (40.0%) |
| South Asian | 1,942 (2.6%) | 683 (2.6%) | 1,259 (2.7%) |
| Black | 813 (1.1%) | 251 (0.9%) | 562 (1.2%) |
| Other | 364 (0.5%) | 122 (0.5%) | 242 (0.5%) |
| Mixed | 309 (0.4%) | 102 (0.4%) | 207 (0.4%) |
| Not stated or missing | 41,675 (56.6%) | 15,770 (59.1%) | 25,905 (55.2%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 7.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (including individuals where oral antibiotic for infection is given on the same day as infection diagnosed).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 46,797 | 291,116 | 5,924 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 26,558 | 178,862 | 3,940 | **1.07 (1.03, 1.12)** | **1.08 (1.04, 1.13)** | **1.08 (1.04, 1.13)** | **1.07 (1.03, 1.12)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

# A3.6 Manuscript appendix 5 – sensitivity analyses UTI cohort

**Sensitivity analysis 1.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status (with acne date, antibiotic for acne date and UTI and UTI antibiotic date after 2004).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=47,730 | **With oral antibiotic for acne** n=22,601 | **Without oral antibiotic for acne** n=25,129 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 387,016 | 184,630 | 202,386 |
| Median (IQR) duration of follow-up (years) | 8.0 (5.0-11.1) | 8.0 (5.2-11.1) | 8.0 (4.9-11.1) |
| **Sex** | | | |
| Female (%) | 46,049 (96.5%) | 21,695 (96.0%) | 24,354 (96.9%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 500 (1.0%) | 250 (1.1%) | 250 (1.0%) |
| 12-18 | 19,085 (40.0%) | 9,112 (40.3%) | 9,973 (39.7%) |
| 19-25 | 12,219 (25.6%) | 5,350 (23.7%) | 6,869 (27.3%) |
| 26-35 | 10,637 (22.3%) | 5,014 (22.2%) | 5,623 (22.4%) |
| 36+ | 5,289 (11.1%) | 2,875 (12.7%) | 2,414 (9.6%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 10,770 (22.6%) | 5,178 (22.9%) | 5,592 (22.3%) |
| 2 | 8,576 (18.0%) | 4,092 (18.1%) | 4,484 (17.8%) |
| 3 | 9,266 (19.4%) | 4,380 (19.4%) | 4,886 (19.4%) |
| 4 | 9,056 (19.0%) | 4,308 (19.1%) | 4,748 (19.0%) |
| 5(most deprived) | 10,062 (21.1%) | 4,643 (20.5%) | 5,419 (21.6%) |
| **Harmful alcohol use (%)***** | 894 (4.0%) | 418 (1.8%) | 476 (1.9%) |
| **Asthma (%)***** | 9,891 (43.8%) | 4,880 (21.6%) | 5,011 (19.9%) |
| **Diabetes (%)***** | 529 (1.1%) | 286(1.3%) | 243 (1.0%) |
| **Ethnicity** | | | |
| White | 22,383 (46.9%) | 10,378 (45.9%) | 12,005 (47.8%) |
| South Asian | 1,478 (3.1%) | 652 (2.9%) | 826 (3.3%) |
| Black | 493 (1.0%) | 211 (0.9%) | 282 (1.1%) |
| Other | 353 (0.7%) | 129 (0.6%) | 224 (0.9%) |
| Mixed | 335 (0.7%) | 142 (0.6%) | 193 (0.8%) |
| Not stated or missing | 22,688 (47.5%) | 11,089 (49.1%) | 11,599 (46.2%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 1.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and UTI and UTI antibiotic date after 2004).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 24,983 | 103,935 | 2,535 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 22,439 | 94,543 | 2,670 | **1.19 (1.13, 1.26)** | **1.19 (1.13, 1.26)** | **1.19 (1.13, 1.26)** | **1.19 (1.13, 1.26)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 2.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status (using 14 days intervals to make continuous courses)**.**

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=94,017 | **With oral antibiotic for acne** n=32,489 | **Without oral antibiotic for acne** n=61,528 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,250,025 | 400,863 | 849,162 |
| Median (IQR) duration of follow-up (years) | 11.9 (7.1-18.2) | 11.0 (6.7-16.7) | 12.4 (7.3-19.0) |
| **Sex** | | | |
| Female (%) | 88,567 (94.2%) | 30,516 (93.9%) | 58,051 (94.3%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,472 (1.6%) | 578 (1.8%) | 894 (1.5%) |
| 12-18 | 42,063 (44.7%) | 15,219 (46.8%) | 26,844 (43.6%) |
| 19-25 | 21,979 (23.4%) | 6,700 (20.6%) | 15,279 (24.8%) |
| 26-35 | 20,270 (21.6%) | 6,887 (21.2%) | 13,383 (21.8%) |
| 36+ | 8,233 (8.8%) | 3,105 (9.6%) | 5,128 (8.3%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,840 (22.2%) | 7,471 (23.0%) | 13,369 (21.7%) |
| 2 | 17,239 (18.3%) | 6,100 (18.8%) | 11,139 (18.1%) |
| 3 | 18,253 (19.4%) | 6,339 (19.5%) | 11,914 (19.4%) |
| 4 | 17,170 (18.3%) | 5,867 (18.1%) | 11,303 (18.4%) |
| 5(most deprived) | 20,515 (21.8%) | 6,712 (20.7%) | 13,803 (22.4%) |
| **Harmful alcohol use (%)***** | 1,529 (4.7%) | 429 (1.3%) | 1,100 (1.8%) |
| **Asthma (%)***** | 16,904 (52.0%) | 5,697 (17.5%) | 11,207 (18.2%) |
| **Diabetes (%)***** | 1,029 (1.1%) | 293 (0.9%) | 735 (1.2%) |
| **Ethnicity** | | | |
| White | 37,726 (40.1%) | 12,278 (37.8%) | 25,448 (41.4%) |
| South Asian | 2,125 (2.3%) | 677 (2.1%) | 1,448 (2.4%) |
| Black | 755 (0.8%) | 232 (0.7%) | 523 (0.9%) |
| Other | 469 (0.5%) | 124 (0.4%) | 345 (0.6%) |
| Mixed | 472 (0.5%) | 139 (0.4%) | 333 (0.5%) |
| Not stated or missing | 52,470 (55.8%) | 19,039 (58.6%) | 33,431 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 2.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (using 14 days to define courses of antibiotic for acne).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 61,262 | 398,266 | 6,228 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,272 | 226,031 | 3,647 | **0.97 (0.93, 1.01)** | **0.96 (0.92, 1.00)** | **0.96 (0.92, 1.00)** | **0.97 (0.93, 1.01)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 3.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status, exlcuding people with primary immunodeficiency.

| | **Study population** n=94,012 | **With oral antibiotic for acne** n=41,897 | **Without oral antibiotic for acne** n=52,115 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,249,961 | 530,429 | 719,532 |
| Median (IQR) duration of follow-up (years) | 11.9 (7.1-18.2) | 11.3 (6.8-17.2) | 12.3 (7.2-19.0) |
| **Sex** | | | |
| Female (%) | 88,564 (94.2%) | 39,488 (94.3%) | 49,076 (94.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,472 (1.6%) | 682 (1.6%) | 790 (1.5%) |
| 12-18 | 42,060 (44.7%) | 18,767 (44.8%) | 23,293 (44.7%) |
| 19-25 | 21,977 (23.4%) | 9,016 (21.5%) | 12,961 (24.9%) |
| 26-35 | 20,270 (21.6%) | 9,213 (22.0%) | 11,057 (21.2%) |
| 36+ | 8,233 (8.8%) | 4,219 (10.1%) | 4,014 (7.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,839 (22.2%) | 9,333 (22.3%) | 11,506 (22.1%) |
| 2 | 17,237 (18.3%) | 7,734 (18.5%) | 9,503 (18.2%) |
| 3 | 18,253 (19.4%) | 8,190 (19.6%) | 10,063 (19.3%) |
| 4 | 17,169 (18.3%) | 7,648 18.3%) | 9,521 (18.3%) |
| 5(most deprived) | 20,514 (21.8%) | 8,992 (21.5%) | 11,522 (22.1%) |
| **Harmful alcohol use (%)***** | 1,529 (3.6%) | 641 (1.5%) | 888 (1.7%) |
| **Asthma (%)***** | 16,902 (40.3%) | 7,898 (18.9%) | 9,004 (17.3%) |
| **Diabetes (%)***** | 1,029 (1.1%) | 486 (1.2%) | 543 (1.0%) |
| **Ethnicity** | | | |
| White | 37,728 (40.1%) | 16,187 (38.6%) | 21,541 (41.3%) |
| South Asian | 2,126 (2.3%) | 888 (2.1%) | 1,238 (2.4%) |
| Black | 754 (0.8%) | 286 (0.7%) | 468 (0.9%) |
| Other | 469 (0.5%) | 171 (0.4%) | 298 (0.6%) |
| Mixed | 470 (0.5%) | 188 (0.4%) | 282 (0.5%) |
| Not stated or missing | 52,465 (55.8%) | 24,177 (57.7%) | 28,288 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 3.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding primary immunodeficiency).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 51,875 | 335,700 | 5,084 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 41,654 | 288,587 | 4,790 | **1.06 (1.02, 1.11)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 4.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status excluding cancer diagnosis in six months prior to start of follow up (excluding skin cancer).

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=93,905 | **With oral antibiotic for acne** n=41,857 | **Without oral antibiotic for acne** n=52,048 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,248,005 | 529,818 | 718,188 |
| Median (IQR) duration of follow-up (years) | 11.9 (7.1-18.2) | 11.3 (6.8-17.2) | 12.3 (7.2-19.0) |
| **Sex** | | | |
| Female (%) | 88,473 (94.2%) | 39,451 (94.3%) | 49,022 (94.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,471 (1.6%) | 681 (1.6%) | 790 (1.5%) |
| 12-18 | 42,050 (44.8%) | 18,765 (44.8%) | 23,285 (44.7%) |
| 19-25 | 21,959 (23.4%) | 9,012 (21.5%) | 12,947 (24.9%) |
| 26-35 | 20,232 (21.5%) | 9,196 (22.0%) | 11,036 (21.2%) |
| 36+ | 8,193 (8.7%) | 4,203 (10.0%) | 3,990 (7.7%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,813 (22.2%) | 9,326 (22.3%) | 11,487 (22.1%) |
| 2 | 17,216 (18.3%) | 7,724 (18.5%) | 9,492 (18.2%) |
| 3 | 18,232 (19.4%) | 8,185 (19.6%) | 10,047 (19.3%) |
| 4 | 17,154 (18.3%) | 7,641 (18.3%) | 9,513 (18.3%) |
| 5(most deprived) | 20,490 (21.8%) | 8,891 (21.5%) | 11,509 (22.1%) |
| **Harmful alcohol use (%)***** | 1,527 (3.6%) | 641 (1.5%) | 886 (1.7%) |
| **Asthma (%)***** | 16,888 (40.3%) | 7,888 (18.8%) | 9,000 (17.3%) |
| **Diabetes (%)***** | 1,025 (1.1%) | 483 (1.2%) | 542 (1.0%) |
| **Ethnicity** | | | |
| White | 37,682 (40.1%) | 16,169 (38.6%) | 21,513 (41.3%) |
| South Asian | 2,126 (2.3%) | 888 (2.1%) | 1,238 (2.4%) |
| Black | 754 (0.8%) | 286 (0.7%) | 468 (0.9%) |
| Other | 470 (0.5%) | 170 (0.4%) | 300 (0.6%) |
| Mixed | 471 (0.5%) | 189 (0.5%) | 282 (0.5%) |
| Not stated or missing | 52,402 (55.8%) | 24,155 (57.7%) | 28,247 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 4.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (excluding diagnosis of cancer within six months of start of follow up (excluding skin cancer)).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 51,809 | 335,379 | 5,069 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 41,614 | 288,398 | 4,784 | **1.06 (1.02, 1.11)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** | **1.06 (1.02, 1.10)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 5.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status (including individuals with complete ethnicity data).

| | **Study population** n=25,042 | **With oral antibiotic for acne** n=11,512 | **Without oral antibiotic for acne** n=13,530 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 205,135 | 94,818 | 110,317 |
| Median (IQR) duration of follow-up (years) | 8.1 (5.3-11.0) | 8.1 (5.4-11.0) | 8.1 (5.1-11.0) |
| **Sex** | | | |
| Female (%) | 24,234 (96.8%) | 11,097 (96.4%) | 13,137 (97.1%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 201 (0.8%) | 103 (0.9%) | 98 (0.7%) |
| 12-18 | 9,111 (36.4%) | 4,252 (36.9%) | 4,859 (35.9%) |
| 19-25 | 6,704 (26.8%) | 2,822 (24.5%) | 3,882 (28.7%) |
| 26-35 | 6,103 (24.4%) | 2,797 (24.3%) | 3,306 (24.4%) |
| 36+ | 2,923 (11.7%) | 1,538 (13.4%) | 1,385 (10.2%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 5,642 (22.5%) | 2,608 (22.7%) | 3,034 (22.4%) |
| 2 | 4,641 (18.5%) | 2,143 (18.6%) | 2,498 (18.5%) |
| 3 | 4,874 (19.5%) | 2,209 (19.2%) | 2,665 (19.7%) |
| 4 | 4,572 (18.3%) | 2,078 (18.1%) | 2,494 (18.4%) |
| 5(most deprived) | 5,313 (21.2%) | 2,474 (21.5%) | 2,839 (21.0%) |
| **Harmful alcohol use (%)***** | 558 (4.8%) | 262 (2.3%) | 296 (2.2%) |
| **Asthma (%)***** | 5,067 (44.0%) | 2,473 (21.5%) | 2,594 (19.2%) |
| **Diabetes (%)***** | 306 (1.2%) | 163 (1.4%) | 143 (1.1%) |
| **Ethnicity** | | | |
| White | 22,383 (89.4%) | 10,378 (90.1%) | 12,005 (88.7%) |
| South Asian | 1,478 (5.9%) | 652 (5.7%) | 826 (6.1%) |
| Black | 493 (2.0%) | 211 (1.8%) | 282 (2.1%) |
| Other | 353 (1.4%) | 129 (1.1%) | 224 (1.7%) |
| Mixed | 335 (1.3%) | 142 (1.2%) | 193 (1.4%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 5**. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (with acne date, antibiotic for acne date and UTI and UTI anotbiotic date after 2004, and complete data for ethnicity included).

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 13,493 | 55,784 | 1,341 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 11,466 | 48,218 | 1,336 | **1.18 (1.09, 1.27)** | **1.18 (1.09, 1.27)** | **1.18 (1.09, 1.27)** | **1.17 (1.09, 1.27)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 6.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status only including patients with GP contact in one year prior to index date.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=92,251 | **With oral antibiotic for acne** n=41,153 | **Without oral antibiotic for acne** n=51,098 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,222,468 | 519,077 | 703,391 |
| Median (IQR) duration of follow-up (years) | 11.8 (7.0-18.2) | 11.3 (6.8-17.2) | 12.3 (7.2-19.0) |
| **Sex** | | | |
| Female (%) | 86,945 (94.2%) | 38,800 (94.3%) | 48,145 (94.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,437 (1.6%) | 664 (1.6%) | 773 (1.5%) |
| 12-18 | 41,181 (44.6%) | 18,389 (44.7%) | 22,792 (44.6%) |
| 19-25 | 21,581 (23.4%) | 8,867 (21.5%) | 12,714 (24.9%) |
| 26-35 | 19,916 (21.6%) | 9,058 (22.0%) | 10,858 (21.2%) |
| 36+ | 8,136 (8.8%) | 4,175 (10.1%) | 3,961 (7.8%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,582 (22.3%) | 9,205 (22.4%) | 11,377 (22.3%) |
| 2 | 17,109 (18.6%) | 7,692 (18.7%) | 9,417 (18.4%) |
| 3 | 17,925 (19.4%) | 8,052 (19.6%) | 9,873 (19.3%) |
| 4 | 16,761 (18.2%) | 7,487 (18.2%) | 9,274 (18.2%) |
| 5(most deprived) | 19,874 (21.5%) | 8,717 (21.2) | 11,157 (21.8%) |
| **Harmful alcohol use (%)***** | 1,497 (3.6%) | 632 (1.5%) | 865 (1.7%) |
| **Asthma (%)***** | 16,591 (40.3%) | 7,742 (18.8%) | 8,849 (17.3%) |
| **Diabetes (%)***** | 1,011 (1.1%) | 476 (1.2%) | 535 (1.1%) |
| **Ethnicity** | | | |
| White | 37,053 (40.2%) | 15,921 (38.7%) | 21,132 (41.4%) |
| South Asian | 2,099 (2.3%) | 877 (2.1%) | 1,222 (2.4%) |
| Black | 748 (0.8%) | 285 (0.7%) | 463 (0.9%) |
| Other | 464 (0.5%) | 168 (0.4%) | 296 (0.6%) |
| Mixed | 466 (0.5%) | 186 (0.5%) | 280 (0.5%) |
| Not stated or missing | 51,421 (55.7%) | 23,716 (57.6%) | 27,705 (54.2%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 6.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not including individuals who have had GP contact in the one year prior to index date.

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 50,864 | 327,090 | 4,992 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 40,917 | 281,839 | 4,699 | **1.06 (1.02, 1.10)** | **1.05 (1.01, 1.10)** | **1.05 (1.01, 1.10)** | **1.06 (1.01, 1.10)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 7.** Characteristics of the UTI study population at cohort entry where the oral antibiotic prescription for LRTI is on the same day as the UTI diagnosis date.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=94,017 | **With oral antibiotic for acne** n=32,489 | **Without oral antibiotic for acne** n=61,528 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,250,025 | 400,863 | 849,162 |
| Median (IQR) duration of follow-up (years) | 11.9 (7.1-18.2) | 11.0 (6.7-16.7) | 12.4 (7.3-19.0) |
| **Sex** | | | |
| Female (%) | 88,567 (94.2%) | 30,516 (93.9%) | 58,051 (94.3%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,472 (1.6%) | 578 (1.8%) | 894 (1.5%) |
| 12-18 | 42,063 (44.7%) | 15,219 (46.8%) | 26,844 (43.6%) |
| 19-25 | 21,979 (23.4%) | 6,700 (20.6%) | 15,279 (24.8%) |
| 26-35 | 20,270 (21.6%) | 6,887 (21.2%) | 13,383 (21.8%) |
| 36+ | 8,233 (8.8%) | 3,105 (9.6%) | 5,128 (8.3%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,840 (22.2%) | 7,471 (23.0%) | 13,369 (21.7%) |
| 2 | 17,239 (18.3%) | 6,100 (18.8%) | 11,139 (18.1%) |
| 3 | 18,253 (19.4%) | 6,339 (19.5%) | 11,914 (19.4%) |
| 4 | 17,170 (18.3%) | 5,867 (18.1%) | 11,303 (18.4%) |
| 5(most deprived) | 20,515 (21.8%) | 6,712 (20.7%) | 13,803 (22.4%) |
| **Harmful alcohol use (%)***** | 1,529 (4.7%) | 429 (1.3%) | 1,100 (1.8%) |
| **Asthma (%)***** | 16,904 (52.0%) | 5,697 (17.5%) | 11,207 (18.2%) |
| **Diabetes (%)***** | 1,029 (1.1%) | 294 (0.9%) | 735 (1.2%) |
| **Ethnicity** | | | |
| White | 37,724 (40.1%) | 12,277 (37.8%) | 25,447 (41.4%) |
| South Asian | 2,126 (2.3%) | 677 (2.1%) | 1,449 (2.4%) |
| Black | 753 (0.8%) | 230 (0.7%) | 523 (0.9%) |
| Other | 470 (0.5%) | 125 (0.4%) | 345 (0.6%) |
| Mixed | 473 (0.5%) | 141 (0.4%) | 332 (0.5%) |
| Not stated or missing | 52,471 (55.8%) | 19,039 (58.6%) | 33,432 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 7.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not (including individuals where oral antibiotic for infection is given on the same day as infection diagnosed).

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 61,262 | 398,266 | 6,228 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,272 | 226,031 | 3,647 | **0.97 (0.93, 1.01)** | **0.96 (0.92, 1.00)** | **0.96 (0.92, 1.00)** | **0.97 (0.93, 1.01)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Sensitivity analysis 8.** Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status women only.

Values are numbers (percentages) unless stated otherwise

| | **Study population** n=88,567 | **With oral antibiotic for acne** n=39,489 | **Without oral antibiotic for acne** n=49,078 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,155,165 | 493,169 | 661,996 |
| Median (IQR) duration of follow-up (years) | 11.6 (6.9-17.8) | 11.1 (6.7-17.0) | 12.1 (7.1-18.6) |
| **Sex** | | | |
| Female (%) | 88,567 (100.0%) | 39,489 (100.0%) | 49,078 (100.0%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,445 (1.6%) | 673 (1.7%) | 772 (1.6%) |
| 12-18 | 39,218 (44.3%) | 17,535 (44.4%) | 21,683 (44.2%) |
| 19-25 | 20,742 (23.4%) | 8,507 (21.5%) | 12,235 (24.9%) |
| 26-35 | 19,497 (22.0%) | 8,848 (22.4%) | 10,649 (21.7%) |
| 36+ | 7,665 (8.7%) | 3,926 (9.9%) | 3,739 (7.6%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 19,782 (22.3%) | 8,876 (44.9%) | 10,906 (22.2%) |
| 2 | 16,235 (18.3%) | 7,291 (44.9%) | 8,944 (55.1%) |
| 3 | 17,224 (19.5%) | 7,757 (45.0%) | 9,467 (55.0%) |
| 4 | 16,171 (18.3%) | 7,189 (44.5%) | 8,982 (55.5%) |
| 5(most deprived) | 19,155 (21.6%) | 8,376 (43.7%) | 10,779 (56.3%) |
| **Harmful alcohol use (%)***** | 1,285 (3.3%) | 537 (1.4%) | 748 (1.5%) |
| **Asthma (%)***** | 15,828 (40.1%) | 7,399 (18.7%) | 8,429 (17.2%) |
| **Diabetes (%)***** | 864 (1.0%) | 421 (1.1%) | 443 (0.9%) |
| **Ethnicity** | | | |
| White | 35,757 (40.4%) | 15,365 (38.9%) | 20,392 (41.6%) |
| South Asian | 1,999 (2.3%) | 823 (2.1%) | 1,176 (2.4%) |
| Black | 710 (0.8%) | 271 (0.7%) | 439 (0.9%) |
| Other | 444 (0.5%) | 160 (0.4%) | 284 (0.6%) |
| Mixed | 443 (0.5%) | 174 (0.4%) | 269 (0.5%) |
| Not stated or missing | 49,214 (55.6%) | 22,696 (57.5%) | 26,518 (54.0%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure

** Age at acne diagnosis - eligibility for entry to study population

*** Based on records closest to index date.

**Sensitivity analysis 8.** Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not in women only.

Fitted to patients with complete data for all variables included in each model*

| | | | | **Unadjusted model*** | **Model 1**** | **Model 2***** | **Model 3******** |
|---|---|---|---|---|---|---|---|
| | **Number** | **Person years at risk** | **Events** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** | **Hazard ratio (95% CI)^** |
| unexposed | 48,854 | 315,959 | 4,695 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 39,255 | 270,392 | 4,421 | **1.07 (1.03, 1.11)** | **1.07 (1.02, 1.11)** | **1.07 (1.02, 1.11)** | **1.07 (1.02, 1.11)** |

* Unadjusted model

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

## A3.7 – Appendix - corrections October 2023

1. Given the wide study period and potential for confounding by time period it would also be helpful to carry out an additional analysis adjusting for calendar time at index date (e.g., as a categorical variable with 5 year categories). Tables 1-3.

2. As an additional sensitivity analysis could you carry out a Cox model using time from index date as the underlying time scale instead of age, with adjustment for age as a covariate. Please would you do this with and without adjustment for calendar time (as above). Tables 4-9.

3. Add data on agegroup at diagnosis of infection in each cohort to Table 1. Tables 10-12.

4. Add information on how many people had the outcome by 30 days within each cohort (also with a % based on Kaplan-Meier estimates or rate) overall and split by exposure group (to indicate absolute risks). Figures 1-6.

**Table 1. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 49,572 | 384,215 | 5,096 | **1.08 (1.04, 1.12)** | **1.19 (1.14, 1.23)** | **1.19 (1.14, 1.24)** | **1.19 (1.15, 1.24)** | **1.19 (1.14, 1.23)** |

* Unadjusted model

** Adjusted for calender time interval at index date

*** Adjusted for sex and Index of Multiple Deprivation.

**** Additionally adjusted for harmful alcohol use.

***** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 2. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,944 | 218,780 | 4,841 | **1.12 (1.07, 1.16)** | **1.19 (1.14, 1.24)** | **1.19 (1.14, 1.24)** | **1.19 (1.14, 1.24)** | **1.18 (1.14, 1.23)** |

* Unadjusted model

** Adjusted for calender time interval at index date

*** Adjusted for sex and Index of Multiple Deprivation.

**** Additionally adjusted for harmful alcohol use.

***** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 3. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.** Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 41,656 | 288,595 | 4,790 | **1.06 (1.02, 1.11)** | **1.12 (1.07, 1.16)** | **1.11 (1.07, 1.16)** | **1.11 (1.07, 1.16)** | **1.11 (1.07, 1.16)** |

* Unadjusted model

** Adjusted for calender time interval at index date

*** Adjusted for sex and Index of Multiple Deprivation.

**** Additionally adjusted for harmful alcohol use.

***** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 4. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 49,572 | 384,215 | 5,096 | **1.05 (1.01, 1.09)** | **1.22 (1.17, 1.26)** | **1.22 (1.17, 1.26)** | **1.22 (1.17, 1.26)** | **1.21 (1.16, 1.26)** |

* Unadjusted model

** Adjusted for calender time interval at index date and age category at index date

*** Adjusted for sex and Index of Multiple Deprivation.

**** Additionally adjusted for harmful alcohol use.

***** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 5. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.** Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,944 | 218,780 | 4,841 | **1.06 (1.02, 1.11)** | **1.20 (1.15, 1.25)** | **1.20 (1.15, 1.25)** | **1.20 (1.15, 1.25)** | **1.19 (1.14, 1.24)** |

* Unadjusted model

* Adjusted for calender time interval at index date and age category at index date

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 6. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 41,656 | 288,595 | 4,790 | **1.07 (1.03, 1.12)** | **1.18 (1.14, 1.23)** | **1.18 (1.13, 1.23)** | **1.18 (1.13, 1.23)** | **1.18 (1.13, 1.22)** |

* Unadjusted model

* Adjusted for calender time interval at index date and age category at index date

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 7. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for LRTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 64,766 | 458,288 | 5,652 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 49,572 | 384,215 | 5,096 | **1.05 (1.01, 1.09)** | **1.10 (1.06, 1.14)** | **1.10 (1.06, 1.14)** | **1.10 (1.06, 1.14)** | **1.10 (1.05, 1.14)** |

* Unadjusted model

* Adjusted for age category at index date

** Adjusted for sex and Index of Multiple Deprivation.

*** Additionally adjusted for harmful alcohol use.

**** Additionally for asthma and diabetes.

^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 8. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for SSTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 40,411 | 251,198 | 5,023 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 32,944 | 218,780 | 4,841 | **1.06 (1.02, 1.11)** | **1.09 (1.04, 1.13)** | **1.09 (1.04, 1.13)** | **1.09 (1.04, 1.13)** | **1.07 (1.03, 1.12)** |

* Unadjusted model
* Adjusted for age category at index date
** Adjusted for sex and Index of Multiple Deprivation.
*** Additionally adjusted for harmful alcohol use.
**** Additionally for asthma and diabetes.
^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

**Table 9. Association (HR [95% CI]) between oral antibiotics for acne and antibiotic treatment failure for UTI: comparing risk of antibiotic treatment failure in those who have received oral antibiotics for acne to those who have not.**
Fitted to patients with complete data for all variables included in each model*

| | | | | Unadjusted model* | Model 1** | Model 2*** | Model 3**** | Model 4***** |
|---|---|---|---|---|---|---|---|---|
| | Number | Person years at risk | Events | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ | Hazard ratio (95% CI)^ |
| unexposed | 51,878 | 335,702 | 5,085 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| exposed | 41,656 | 288,595 | 4,790 | **1.07 (1.03, 1.12)** | **1.08 (1.04, 1.12)** | **1.08 (1.04, 1.12)** | **1.08 (1.03, 1.12)** | **1.07 (1.03, 1.12)** |

* Unadjusted model
* Adjusted for age category at index date
** Adjusted for sex and Index of Multiple Deprivation.
*** Additionally adjusted for harmful alcohol use.
**** Additionally for asthma and diabetes.
^ Estimated hazard ratios from Cox regression with current age as underlying timescale)

T**able 10.** Characteristics of the LRTI study population at cohort entry stratified by acne antibiotic exposure status.
Values are numbers (percentages) unless stated otherwise

| | **Study population** n=114,770 | **With oral antibiotic for acne** n=49,772 | **Without oral antibiotic for acne** n=64,998 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,704,070 | 678,578 | 1,025,492 |
| Median (IQR) duration of follow-up (years) | 13.6 (8.3-20.4) | 12.4 (7.6-18.5) | 14.7 (9.0-21.6) |
| **Sex** | | | |
| Female (%) | 72,186 (62.9%) | 30,962 (62.2%) | 41,224 (63.4%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,646 (1.4%) | 673 (1.4%) | 973 (1.5%) |
| 12-18 | 54,060 (47.1%) | 23,255 (46.7%) | 30,805 (47.4%) |
| 19-25 | 24,501 (21.3%) | 9,777 (19.6%) | 14,724 (22.7%) |
| 26-35 | 23,465 (20.4%) | 10,337 (20.8%) | 13,128 (20.2%) |
| 36+ | 11,098 (9.7%) | 5,730 (11.5%) | 5,368 (8.3%) |
| **Age at index date***** | | | |
| 8-11 | 370 (0.3%) | 98 (0.2%) | 272 (0.4%) |
| 12-18 | 23,102 (20.1%) | 11,882 (23.9%) | 11,220 (17.3%) |
| 19-25 | 30,118 (26.2%) | 14,636 (29.4%) | 15,482 (23.8%) |
| 26-35 | 32,641 (21.8%) | 12,359(24.8%) | 20,282 (31.2%) |
| 36-50 | 25,045 (21.8%) | 9,679 (19.5%) | 15,366 (23.6%) |
| 50+ | 3,494 (3.0%) | 1,118 (2.3%) | 2,376 (27.3%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 24,113 (21.0%) | 10,507 (21.1%) | 13,606 (20.9%) |
| 2 | 20,005 (17.4%) | 8,922 (17.9%) | 11,083 (17.1%) |
| 3 | 21,711 (18.9%) | 9,368 (18.8%) | 12,343 (19.0%) |
| 4 | 21,042 (18.3%) | 9,149 (18.4%) | 11,893 (18.3%) |
| 5(most deprived) | 27,899 (24.3%) | 11,826 (23.8%) | 16,073 (24.7%) |
| **Harmful alcohol use (%)***** | 3,189 (6.4%) | 1,235 (2.5%) | 1,954 (3.0%) |
| **Asthma (%)***** | 30,375 (26.5%) | 13,958 (28.0%) | 16,417 (25.3%) |
| **Diabetes (%)***** | 1,566 (1.4%) | 662 (1.3%) | 904 (1.4%) |
| **Ethnicity** | | | |
| White | 43,585 (38.0%) | 18,069 (36.3%) | 25,516 (39.3%) |
| South Asian | 2,529 (2.2%) | 1,016 (2.0%) | 1,513 (2.3%) |
| Black | 928 (0.8%) | 349 (0.7%) | 579 (0.9%) |
| Other | 525 (0.5%) | 190 (0.4%) | 335 (0.5%) |
| Mixed | 470 (0.4%) | 179 (0.4%) | 291 (0.4%) |
| Not stated or missing | 66,733 (58.1%) | 29,969 (60.2%) | 36,764 (56.6%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or LRTI antibiotic treatment failure.
** Age at acne diagnosis - eligibility for entry to study population.
*** Age at index date - start of follow up, date of antibiotic prescription within 7 days of infection diagnosis
**** Based on records closest to index date.

**Table 11**. Characteristics of the SSTI study population at cohort entry stratified by acne antibiotic exposure status.
Values are numbers (percentages) unless stated otherwise

| | **Study population** n=73,648 | **With oral antibiotic for acne** n=33,096 | **Without oral antibiotic for acne** n=40,552 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,054,645 | 437,111 | 617,533 |
| Median (IQR) duration of follow-up (years) | 13.1 (8.1-19.5) | 12.1 (7.4-17.8) | 14.1 (8.7-20.8) |
| **Sex** | | | |
| Female (%) | 43,418 (59.0%) | 19,283 (58.3%) | 24,135 (59.5%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,164 (1.6%) | 501 (1.5%) | 663 (1.6%) |
| 12-18 | 36,346 (49.4%) | 15,955 (48.2%) | 20,391 (50.3%) |
| 19-25 | 15,932 (21.6%) | 6,785 (20.5%) | 9,147 (22.6%) |
| 26-35 | 13,902 (18.9%) | 6,460 (19.5%) | 7,442 (18.4%) |
| 36+ | 6,304 (8.6%) | 3,395 (10.3%) | 2,909 (7.2%) |
| **Age at index date***** | | | |
| 8-11 | 218 (0.3%) | 68 (0.2%) | 150 (0.4%) |
| 12-18 | 14,336 (19.5%) | 7,360 (22.2%) | 6,976 (17.2%) |
| 19-25 | 21,199 (28.8%) | 10,478 (31.7%) | 10,721 (26.4%) |
| 26-35 | 20,820 (28.3%) | 8,246 (24.9%) | 12,574 (31.0%) |
| 36-50 | 14,863 (20.2%) | 6,207 (18.8%) | 8,656 (21.4%) |
| 50+ | 2,212 (3.0%) | 737 (2.2%) | 1,475 (3.6%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 15,499 (21.0%) | 6,883 (20.8%) | 8,616 (21.3%) |
| 2 | 12,929 (17.6%) | 5,931 (17.9%) | 6,998 (17.3%) |
| 3 | 14,038 (19.1%) | 6,369 (19.2%) | 7,669 (18.9%) |
| 4 | 13,403 (18.2%) | 6,036 (18.2%) | 7,367 (18.2%) |
| 5(most deprived) | 17,779 (24.1%) | 7,877 (23.8%) | 9,902 (24.4%) |
| **Harmful alcohol use (%)******** | 2,242 (6.8%) | 938 (2.8%) | 1,304 (3.2%) |
| **Asthma (%)***** | 15,322 (46.3%) | 7,328 (22.1%) | 7,994 (19.7%) |
| **Diabetes (%)***** | 1,255 (1.7%) | 604 (1.8%) | 662 (1.6%) |
| **Ethnicity** | | | |
| White | 28,544 (38.8%) | 12,313 (37.2%) | 16,231 (40.0%) |
| South Asian | 1,944 (2.6%) | 861 (2.6%) | 1,083 (2.7%) |
| Black | 813 (1.1%) | 301 (0.9%) | 512 (1.3%) |
| Other | 365 (0.5%) | 148 (0.4%) | 217 (0.5%) |
| Mixed | 306 (0.4%) | 117 (0.4%) | 189 (0.5%) |
| Not stated or missing | 41,676 (56.6%) | 19,356 (58.5%) | 22,320 (55.0%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or SSTI antibiotic treatment failure
** Age at acne diagnosis - eligibility for entry to study population
*** Age at index date - start of follow up, date of antibiotic prescription within 7 days of infection diagnosis
**** Based on records closest to index date.

**Table 12**. Characteristics of the UTI study population at cohort entry stratified by acne antibiotic exposure status.
Values are numbers (percentages) unless stated otherwise

| | **Study population** n=94,017 | **With oral antibiotic for acne** n=41,899 | **Without oral antibiotic for acne** n=52,118 |
|---|---|---|---|
| **Follow-up*** | | | |
| Total person-years | 1,250,025 | 530,444 | 719,580 |
| Median (IQR) duration of follow-up (years) | 11.9 (7.1-18.2) | 11.3 (6.8-17.2) | 12.3 (7.2-19.0) |
| **Sex** | | | |
| Female (%) | 88,567 (94.2%) | 39,489 (94.2%) | 49,078 (94.2%) |
| **Age at acne diagnosis**** | | | |
| 8-11 | 1,472 (1.6%) | 682 (1.6%) | 790 (1.5%) |
| 12-18 | 42,063 (44.7%) | 18,768 (44.8%) | 23,295 (44.7%) |
| 19-25 | 21,979 (23.4%) | 9,017 (21.5%) | 12,962 (24.9%) |
| 26-35 | 20,270 (21.6%) | 9,213 (22.0%) | 11,057 (21.2%) |
| 36+ | 8,233 (8.8%) | 4,219 (10.1%) | 4,014 (7.7%) |
| **Age at index date***** | | | |
| | 154 (0.2%) | 40 (0.1%) | 114 (0.2%) |
| | 18,416 (19.6%) | 9,474 (22.6%) | 8,942 (17.2%) |
| | 29,314 (31.2%) | 13,369 (31.9%) | 15,945 (30.6%) |
| | 26,790 (28.5%) | 10,909 (26.0%) | 15,881 (30.5%) |
| | 17,086 (18.2%) | 7,357 (17.6%) | 9,729 (18.7%) |
| | 2,257 (2.4%) | 750 (1.8%) | 1,507 (2.9%) |
| **Quintiles of Index of Multiple Deprivation** | | | |
| 1(least deprived) | 20,840 (22.2%) | 9,334 (22.3%) | 11,506 (22.1%) |
| 2 | 17,239 (18.3%) | 7,735 (18.5%) | 9,504 (18.2%) |
| 3 | 18,253 (19.4%) | 8,190 (19.6%) | 10,063 (19.3%) |
| 4 | 17,170 (18.3%) | 7,648 (18.3%) | 9,522 (18.3%) |
| 5(most deprived) | 20,515 (21.8%) | 8,992 (21.5%) | 11,523 (22.1%) |
| **Harmful alcohol use (%)******** | 1,529 (3.6%) | 641 (1.5%) | 888 (1.7%) |
| **Asthma (%)******** | 16,904 (40.3%) | 7,899 (18.9%) | 9,005 (17.3%) |
| **Diabetes (%)******** | 1,029 (1.1%) | 486 (1.2%) | 543 (1.0%) |
| **Ethnicity** | | | |
| White | 37,726 (40.1%) | 16,186 (38.6%) | 21,540 (41.3%) |
| South Asian | 2,126 (2.3%) | 888 (2.1%) | 1,238 (2.4%) |
| Black | 755 (0.8%) | 287 (0.7%) | 468 (0.9%) |
| Other | 468 (0.5%) | 170 (0.4%) | 298 (0.6%) |
| Mixed | 471 (0.5%) | 188 (0.4%) | 283 (0.5%) |
| Not stated or missing | 52,471 (55.8%) | 24,180 (57.7%) | 28,291 (54.3%) |

* Follow-up based on censoring at the earliest of: death, no longer registered with practice, practice no longer contributing to CPRD, or UTI antibiotic treatment failure
** Age at acne diagnosis - eligibility for entry to study population
*** Age at index date - start of follow up, date of antibiotic prescription within 7 days of infection diagnosis
**** Based on records closest to index date.

**Figure 1:** LRTI – Kaplan-Meier survival estimates by acne antibiotic exposure group

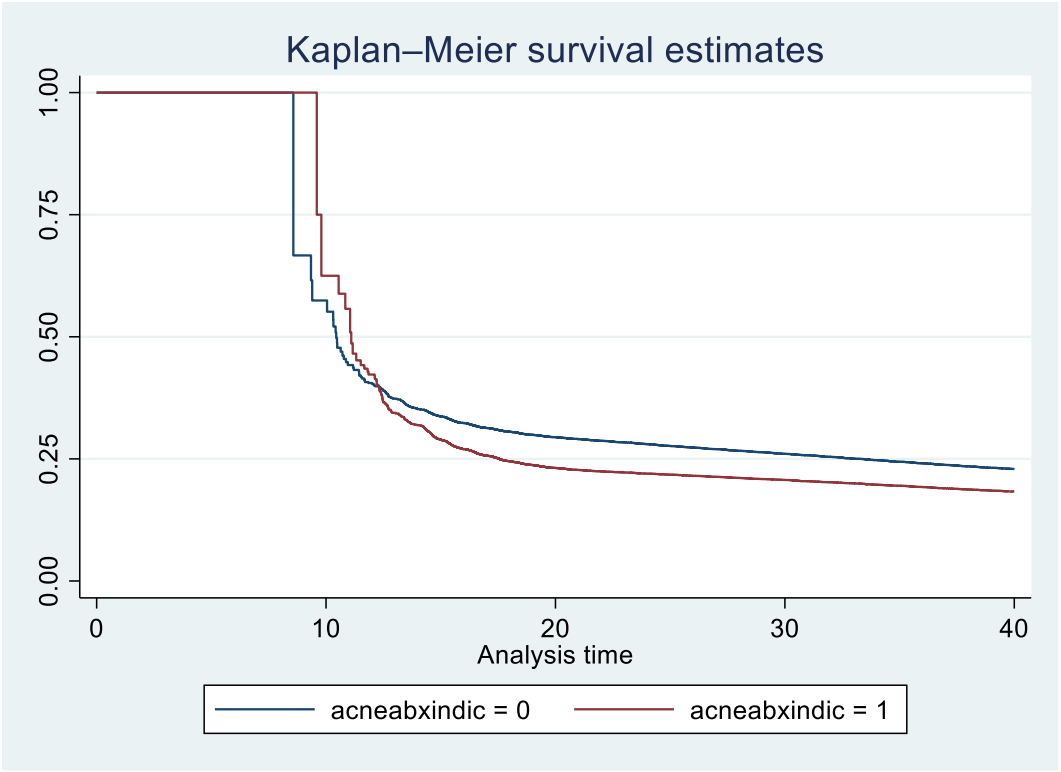


**Figure 2:** LRTI – Kaplan-Meier survival estimates overall

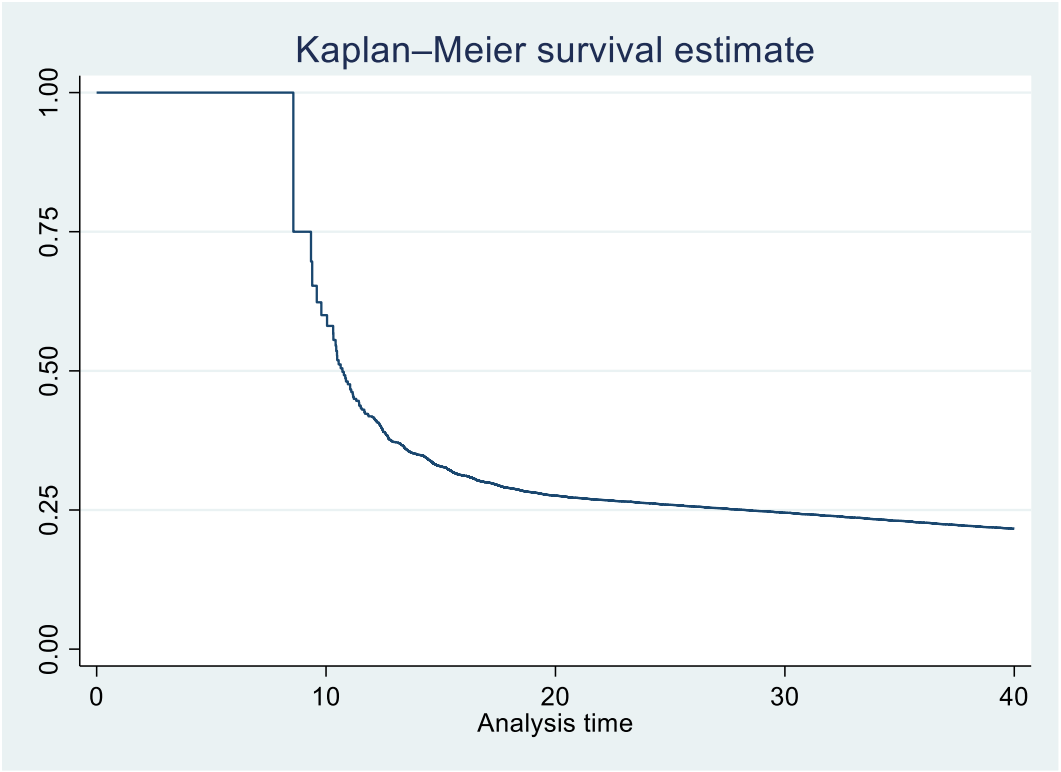


**Figure 3:** SSTI – Kaplan-Meier survival estimates by acne antibiotic exposure group

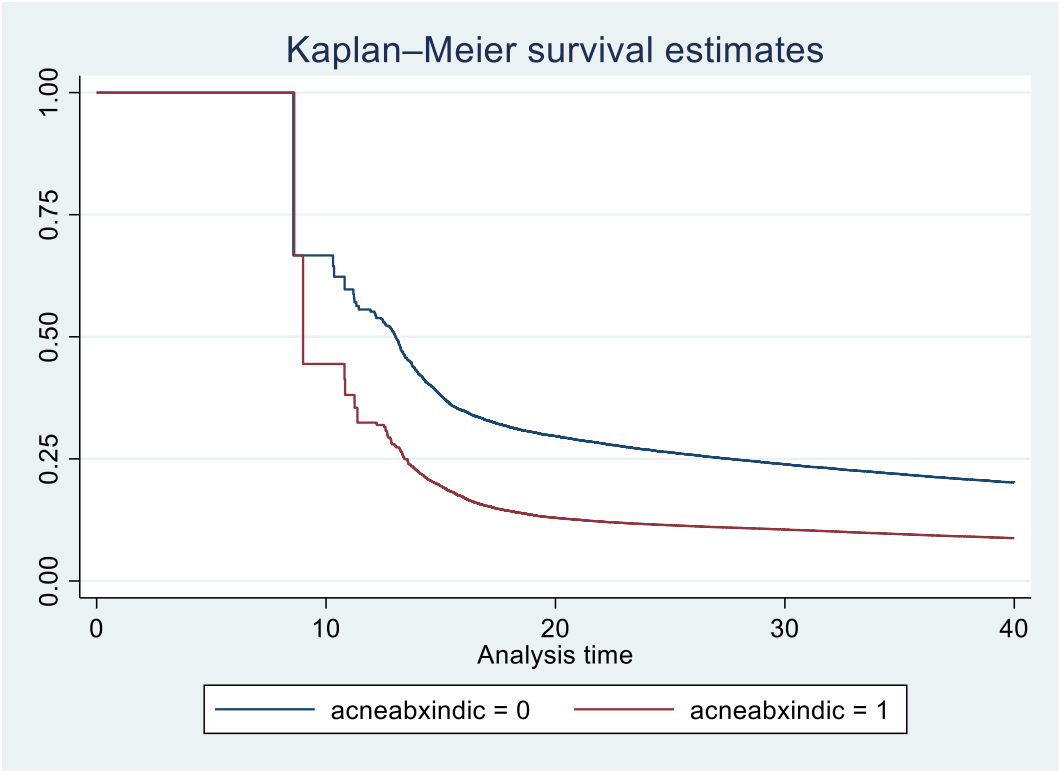


**Figure 4:** SSTI – Kaplan-Meier survival estimates by acne overall

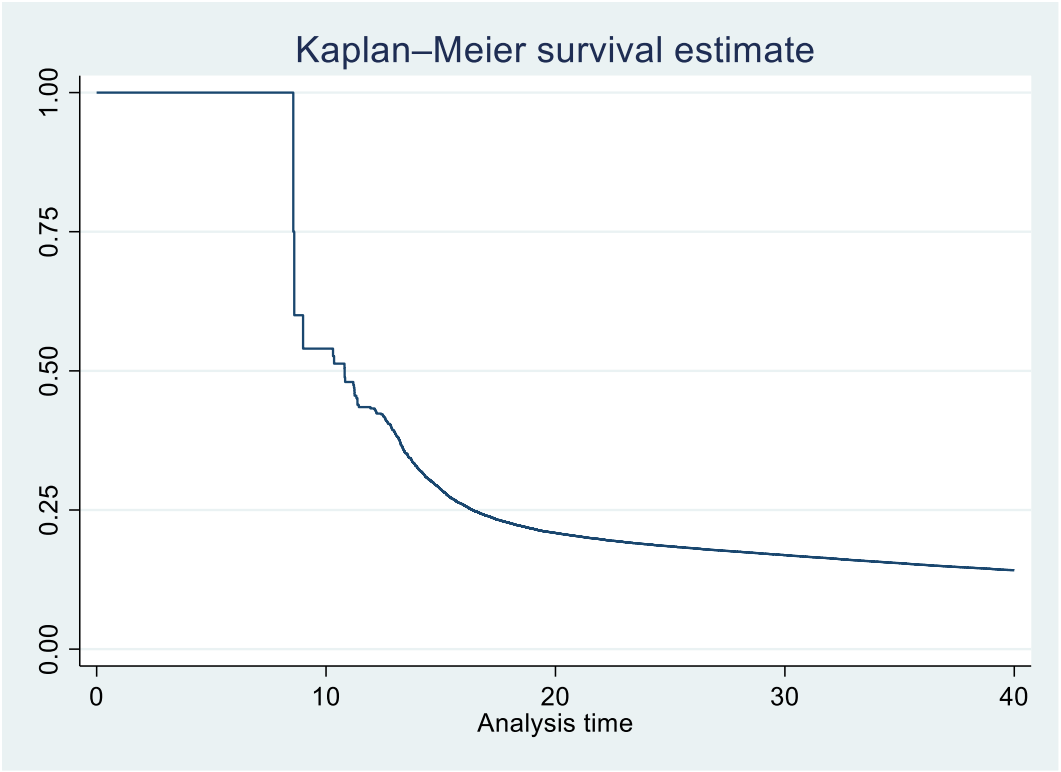


**Figure 5:** UTI – Kaplan-Meier survival estimates by acne antibiotic exposure group

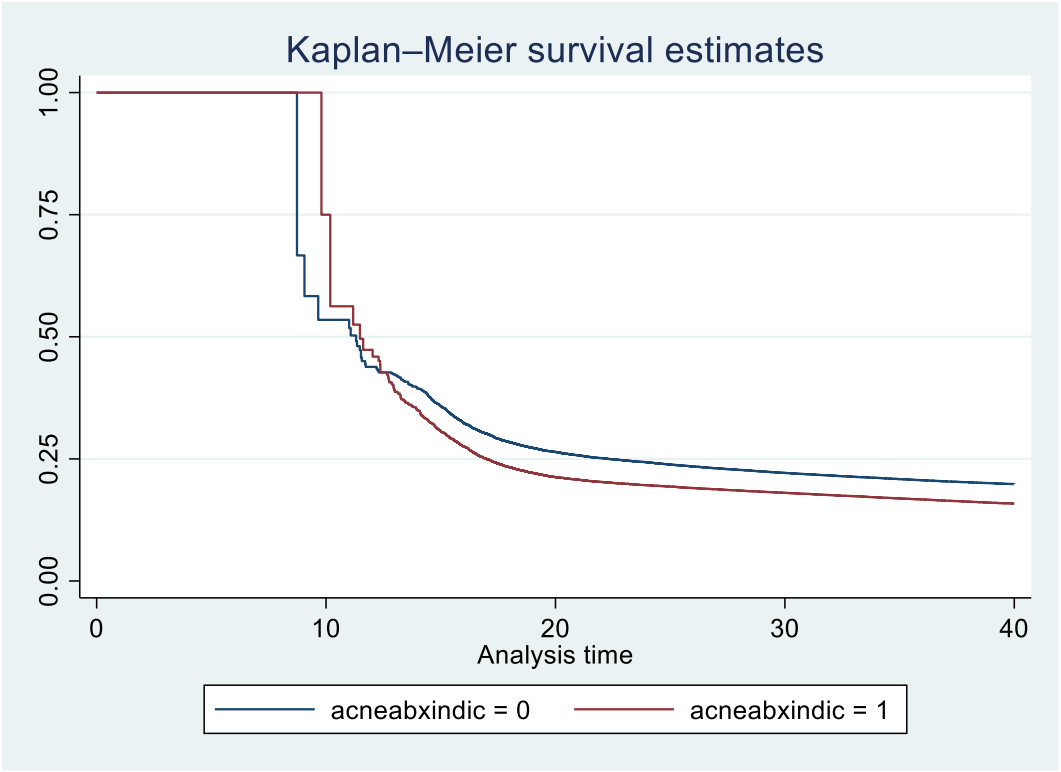
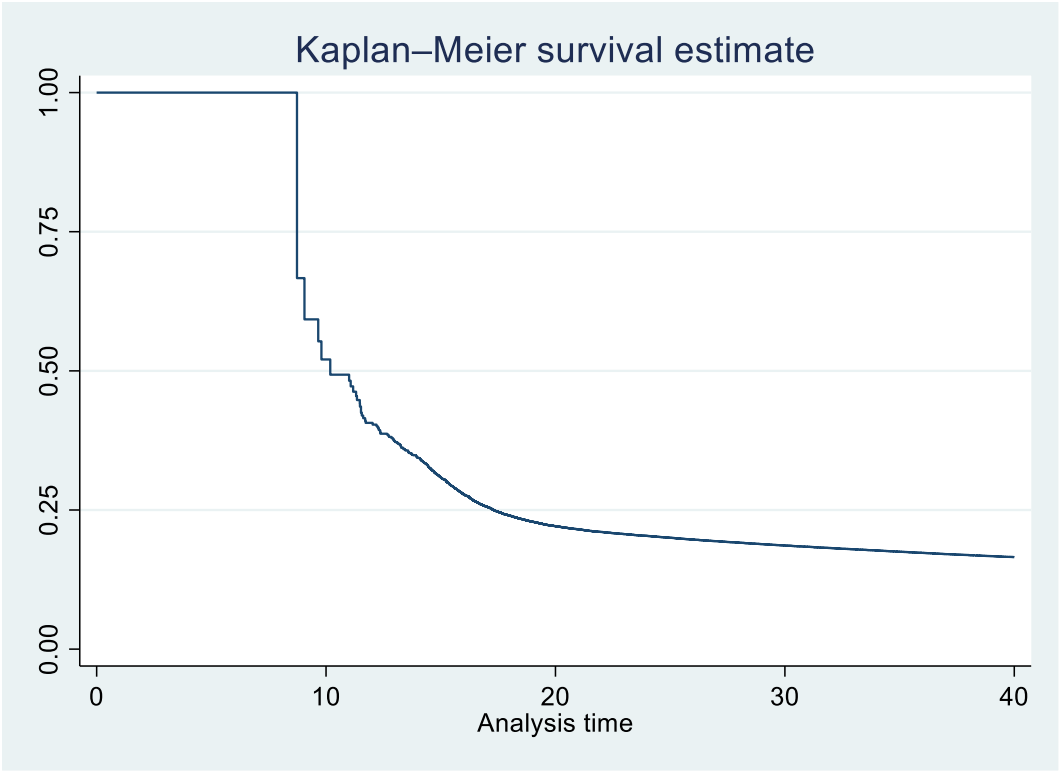


**Figure 6:** UTI – Kaplan-Meier survival estimates overall



ADDENDUM: at the time of submitting my thesis the results of the trial investigating spironolactone for acne were not published. The trial was a multicentre, phase 3, double blind randomised controlled trial comparing spironolactone for acne vs a placebo. The study found that spironolactone improved outcomes compared with placebo, with the greatest differences occurring at 6 months. The primary outcome measure was a self-reported score on the Acne-Specific Quality of Life (Acne QOL) symptom scale at week 12.(198)

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