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centre for the  
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modelling of  
infectious diseases

*The social and economic impact of community-based transmission  
of vaccine-preventable influenza and measles*

by Dominic Thorrington

Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

Thesis submitted for the degree of Doctor of Philosophy of the University of London

March 2016

Funded by



***National Institute for  
Health Research***

## **Declaration of own work**

I, Dominic Thorrington, 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.

# Acknowledgments

I have a number of people to thank for their help in taking this thesis from its infancy to this finished form.

I must start with my supervisors Ken Eames and Mark Jit. Ken accepted my application to study at the School and to be his first PhD student, so for that I am incredibly grateful. His attention to detail and creative mind helped me to identify the most interesting projects. Mark agreed to take me on as an additional PhD student mid-way through my studies, bringing new perspectives and approaches to problems, and his willingness to discuss work at any time and from any geographical location in which he found himself meant I always had someone backing me up. Thank you to you both, I'd have been lost without your support.

I would like to thank John Gibbon who first introduced me to mathematical modelling in infectious disease epidemiology during my mathematics degree at Imperial College. John proceeded to be my supervisor on both research projects that sparked my interest in the subject and subsequently supported both of my applications for postgraduate study in the subject. My life would be very different today if he hadn't supported me to study this fascinating subject further.

To my advisory committee: John Edmunds, Mary Ramsay, Albert Jan van Hoek, Peter White and Zia Sadique, I thank them for their helpful advice and expertise when they were called upon.

I am very grateful to the members of the Centre for the Mathematical Modelling of Infectious Diseases, but in particular to Esther van Kleef, Andrea Apolloni, Anton Camacho, Charlotte Jackson, Marc Baguelin, Katie Atkins, Roz Eggo and Gwen Knight for their conversations and advice during the past few years.

I'd like to offer special thanks to Katherine Stevens, Sherry Towers, Hawthorne Beyer, Roland Regoes, Florence Debarré, Niel Hens and Kathryn Glass who've logged-on to their emails in the morning and found annoying messages from me asking for clarification on research and analysis they had published many years ago.

To those who've had to share an office with me and put-up with my annoying habits: Helen McDonald, Kevin Wing, Michael Ranopa, Masao Iwagami and Seh Gumede, cheers!

To Mum, Dad, Adrian, Francis and Caroline: thank you for your incredible support throughout this journey. In particular, to both Mum and Dad who throughout my life have always told me that I can achieve anything that I set my mind to and have supported me in every adventure that I've been on.

To Linda, who has been on my journey at my side since my first year of this PhD; who has provided me with the most loving and invaluable emotional support throughout this period in my life; and half-way through made me the happiest man in the world by becoming my wife, thank you so very much. Je t'aime, *mucho beaucoup*!

Finally, to Maria Gloria-Basáñez: on the last day of my MSc studies at Imperial College she offered the most helpful advice for the future that's seen me through some pretty tough times. All of my academic and research achievements since have been motivated by her heartfelt words. I wouldn't have had the impetus to finish this research without that encouragement, so it is to her that I dedicate this thesis.

## **Publications and Presentations**

The following publications arose from sections of the thesis:

Thorrington D, Eames K, Ramsay M, Edmunds JW, van Hoek AJ, et al. (2013) The effect of measles on health-related quality of life: a population-based prospective study, in The Lancet Public Health Science Conference. The Lancet: 382, p. S12.

Thorrington D, Ramsay M, van Hoek AJ, Edmunds WJ, Vivancos R et al. (2014) The Effect of Measles on Health-Related Quality of Life: A Patient-Based Survey. PLoS ONE 9(9): e105153. doi:10.1371/journal.pone.0105153

Thorrington D and Eames K (2015) Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature. PLoS One, 10(8): p. e0135672. doi:10.1371/journal.pone.0135672

Thorrington D, Jit M and Eames K (2015) Targeted vaccination in healthy school children - can primary school vaccination alone control influenza? Vaccine, 33(41): p. 5415-5424.

Thorrington D, Balasegaram S, Cleary P, Hay C and Eames K (2016) Social and economic impacts of school influenza outbreaks in England: survey of carers. The Journal of School Health (accepted, in press)

Ghebrehewet S, Thorrington D, Farmer S, Kearney J, Blissett D et al. (2016) The economic cost of measles outbreaks: healthcare, public health and societal costs of the 2012-13 outbreak in Merseyside, UK. Vaccine, 34(15): p. 1823-1831

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Thorrington D and Eames K (2015) Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature. London School of Hygiene and Tropical Medicine Research Degree Poster Day, January 2015

Thorrington D, Jit M and Eames K (2015) Targeted vaccination in healthy school children - can primary school vaccination alone control influenza?, in Epidemics 5 conference. Tampa, FL USA, December 2015

Thorrington D and Eames K (2015) Mathematical modelling of heterogeneous influenza vaccination coverage in the community for a school-based vaccination programme, in Epidemics 5 conference. Tampa, FL USA, December 2015

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## Abstract

Children bear a considerable proportion of the impact of epidemics of influenza and measles and are a driving force in community-wide epidemics. This thesis considers this impact and the benefits of existing vaccination programmes.

First, we estimated the impact of seasonal influenza outbreaks in primary schools. To estimate the health-related impact we started by conducting a review of the literature to determine the methods used to estimate health utilities in children and adolescents, establishing that a wide variety of systems have been used without clear guidance on an optimal method. Mean absence from school was 3.8 days (95% CI: 3.0-4.8) and 3.7 days (95% CI: 2.7-4.8) off work for caregivers. The mean loss in HRQoL was 2.1 QALDs (95% CI: 1.5-2.7).

Next, we modelled the childhood influenza vaccination programme at a national- and community-level, exploring the impact of heterogeneous coverage. Nationally, a vaccination programme that focuses on primary school vaccination supplemented with fewer vaccinations in secondary schools is optimal from the perspective of the healthcare provider, but heterogeneous uptake within targeted populations consistently resulted in a larger total burden of disease at the community level, emphasising the importance of adherence to school-based vaccination policies.

Two studies of the measles outbreaks in England between 2012 and 2013 were conducted to further the understanding of the impact of measles infection. Significant work/school absence was reported by individuals with infection and their caregivers. Infection was associated with a mean loss of 6.9 QALDs (95% CI: 5.8-8.0). The total economic cost of the outbreak was £4.4m in Merseyside alone, compared to a total cost of £182,909 over the previous five years to achieve herd immunity through the MMR vaccination programme.

The findings demonstrate the importance of adherence to preventative vaccination programmes to reduce the potential for outbreaks of influenza and measles.

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## Chapter 1 - The structure of the thesis

This thesis considers the social and economic impact of measles and influenza outbreaks, focusing on issues surrounding the measurement of impact metrics as well as public health preventative measures and control measures for outbreaks. After a general introduction to this broad field of epidemiology, we consider methods and instruments used to estimate health utilities in a paediatric population, before discussing wider investigations on the topics of influenza outbreaks in primary schools, modelling school-based influenza vaccination programmes and the impact of measles outbreaks in England.

**Chapter 2** introduces concepts and ideas central to this thesis, including a look at the application of both mathematical modelling of infectious diseases and health economics to reducing the burden of both seasonal influenza and measles in England. Techniques employed in mathematical modelling are discussed with reference to research that follows in subsequent chapters dedicated to modelling seasonal influenza vaccination coverage.

**Chapter 3** considers the methods used to facilitate the accurate estimation of health utilities from both children and adolescents, presenting a systematic review of the literature reporting on the progress made in developing methods to gather health utilities from this age group for the purpose of economic evaluations. Estimating health utilities for children and adolescents is a key part of several studies included in this thesis so an exploration of the current practice was valuable.

An analysis of the impact of school-based influenza epidemics in England is presented in **Chapter 4**, including measuring health utilities for seasonal influenza in school children. We investigated the potential level of disruption at home for hypothetical school closures, in addition to both gauging acceptance for the childhood seasonal influenza vaccination programme and quantifying the impact of school-based influenza epidemics in the 2012-13 and 2013-14 influenza seasons in terms of QALYs and out-of-pocket expenses.

**Chapter 5** introduces mathematical modelling of seasonal influenza in England and aims to establish whether a policy of targeted vaccination in either primary or secondary schools would be more cost-effective than a programme across the two age groups. The concept of heterogeneous vaccination coverage is further investigated in **Chapter 6** with a modelling analysis of the impact of the burden of disease for school-based seasonal influenza vaccination programmes where school-level heterogeneity is simulated, this time using a stochastic SEIR-type model and a theoretical metapopulation framework.

**Chapter 7** describes an opportunistic undertaking to quantify the impact of measles infection in terms of QALYs during the 2012-13 nationwide measles epidemics. Questionnaires were distributed to

individuals with confirmed cases of measles in conjunction with Public Health England as part of their outbreak surveillance.

The societal cost of the measles outbreak in Merseyside is discussed in **Chapter 8**. The regional Public Health England office commissioned the development of a costing model for the initial four months of the outbreak, then subsequently requested that we use their report to estimate the total cost of the outbreak from the societal perspective.

**Chapter 9** proposes areas for further research then considers both wider issues in outbreak mitigation for both diseases and related challenges for public health institutions.

**Chapter 10** is the appendix, containing questionnaires used to gather primary data as well as scripts used in the mathematical modelling exercises and supplementary figures. **Chapter 11** contains print-outs of the publications arising from this thesis.

## **Chapter 2 - Background to concepts covered in the thesis**

### **THE MOTIVATION FOR STUDYING BOTH INFLUENZA AND MEASLES**

This chapter will introduce the different concepts covered in this thesis. The work in subsequent chapters overlays different topics within the main goal of understanding the impact of both influenza and measles outbreaks. However, before commencing with the background to these topics it is important first to understand the motivation for studying both influenza and measles.

### **VACCINE-PREVENTABLE DISEASES**

The United Kingdom has long-established publicly funded, free-at-the-point-of-delivery vaccination programmes that aim to reduce the burden of disease vaccine preventable diseases including both influenza and measles outbreaks. Influenza vaccinations have been available to those at high risk of serious morbidity and mortality since the late 1960s and the programmes have been extended several times to include more population groups: first to those aged 75 years and older in 1998 [1]; to those aged 65 years and older in 2000 [2]; and to pregnant women in their second and third trimester in 2006 [3]. The measles vaccination programme commenced in 1968 with a single vaccination against infection until the introduction of the combined measles, mumps and rubella vaccination (MMR) in 1988 [4], changing to a two-dose vaccination strategy in 1996 in line with World Health Organisation guidelines [5]. MMR is offered to all infants registered with a GP surgery as part of the NHS Childhood Vaccination Schedule [6].

Vaccination coverage for seasonal influenza varies according to risk-group. Public Health England reported mixed coverage levels during the 2014-15 influenza season with 72.7% coverage in individuals aged 65 years and older; 50.3% coverage in those clinically at-risk and aged between 6 months and 65 years; and 44.1% coverage in pregnant women. In addition, the vaccine was offered to children aged 2, 3 and 4 years with overall coverage of 38.5%, 41.3% and 32.9% respectively [7]. MMR vaccination coverage for individuals aged 5 years in England during the same period was 94.5% for the first dose and 88.6% for the second dose [8].

### **RECURRENCE OF NATIONWIDE OUTBREAKS**

Despite good vaccination coverage for both programmes, outbreaks can occur nationwide for both diseases as vaccine coverage for target groups falls below the targeted coverage levels for both the ECDC (75% seasonal influenza coverage for target groups [9] and 95% MMR coverage for target groups [10]). The 2012-13, 2013-14 and 2014-15 influenza seasons saw low-to-moderate activity with prolonged outbreaks across England and many community-level outbreaks occurring in settings such as schools and care homes [11-13]. During 2012 and 2013 a large nationwide outbreak of measles resulted in 3,873 laboratory-confirmed cases [14], with major outbreaks reported in Liverpool [15],

North-East England [16] and Manchester [17]. These outbreaks indicate that the achievements of both vaccination programmes have so far fallen short of eliminating sustained nationwide- and community-level transmission.

With both influenza and measles transmission still to be eliminated from the UK, this presents opportunities to study both the impact of outbreaks of these two diseases, as well as consider modifications to current vaccination programmes.

## **MAIN TOPICS OF STUDY**

The thesis focuses on four main themes:

1. Measuring health-related quality of life in children and adolescents

Cost-utility analyses estimate the cost-effectiveness of health technologies based on their costs and benefits using quality-adjusted life years (QALYs) as a measure of benefit, and are used to support a recommendation to introduce new health technologies such as new vaccination programmes to prevent infectious disease outbreaks. The accurate measurement of QALYs is dependent on using appropriate methods to elicit health utilities and conducting such a task for children and adolescents is particularly challenging [18]. We address this topic in greater detail in the systematic literature review in Chapter 3.

2. The social and economic impact of influenza outbreaks in schools in the community

Children attending schools are a large driver of community-wide influenza outbreaks [19-21], due to a variety of factors including a high number of close contacts [22] [23], poor hygiene habits [24] and a lack of acquired immunity in children [22, 25]. Therefore controlling outbreaks of influenza in school not only benefits those children and the members of their household but also members of the wider community [26-31]. To inform parents and guardians of both the risks of influenza infection as well as the benefits of preventative vaccination, we conducted a study in English primary schools to assess the impact of those outbreaks (Chapter 4).

3. The control of influenza outbreaks through preventative vaccination, both nationally and at a local level

The seasonal influenza vaccination programme in England was recently extended to include all healthy children attending primary or secondary schools [32]. Mathematical modelling demonstrates that the new programme is highly cost-effective [33] but failed to consider heterogeneities in vaccination coverage between primary and secondary schools at a national level, as well as potential heterogeneities in the community at a local level. Heterogeneity in vaccination coverage has the potential to be damaging to the overall success of the programme if sufficient numbers of susceptible individuals cluster in the community [34, 35], but if the appropriate target population for the vaccine

is selected then heterogeneous coverage may also be advantageous to the healthcare provider [36]. We sought to establish the impact of heterogeneous vaccination coverage in Chapters 5 and 6.

#### 4. The social and economic impact of measles infection

Measles is a highly contagious and potentially fatal disease, for which an effective vaccination programme exists that has already dramatically reduced the total burden of disease in England since its introduction [37]. However, measles outbreaks still occur within the community because vaccination coverage is not yet sufficient to provide herd immunity due to the clustering of susceptible individuals that have not been vaccinated [15]. To inform public health policy with the ultimate aim of increasing measles vaccination coverage through better educational materials on the risk of infection as well as the benefits of vaccination, we conducted two studies in Chapters 7 and 8 that sought to quantify the impact of measles infection on the individual, then separately on the community during an outbreak.

This chapter will provide some background information to the following subjects: The Epidemiology of Influenza and Measles; Mathematical Modelling of Infectious Diseases; Infectious Disease Outbreaks in Schools; The UK Influenza Vaccination Programme Extension to Healthy Children; and Heterogeneous Vaccine Coverage.

The subsequent chapter outlines the issues of measuring health-related quality of life in children and adolescents through a systematic literature review, before the findings of the review are then used to inform a wider research plan for the rest of the thesis.

### **THE EPIDEMIOLOGY OF INFLUENZA AND MEASLES**

This section will outline the main challenges posed by the burden of disease of both influenza and measles, both in the United Kingdom and worldwide.

#### **THE EPIDEMIOLOGY OF INFLUENZA: WORLDWIDE AND IN THE UNITED KINGDOM**

##### **ANNUAL BURDEN OF INFLUENZA**

Influenza is an infectious disease in both animals and humans that is transmitted through direct contact with nasal secretions, through contact with contaminated surfaces and through aerosols caused by coughing and sneezing containing the virus.

Influenza-like-illness (ILI) is a diagnosis of possible influenza infection based on clinical symptoms. Diagnosis of ILI requires the following criteria for those clinical symptoms:

- The sudden onset of symptoms
- At least one of the following four systemic symptoms:

- Fever
- Malaise (chills, feeling tired)
- Headache
- Myalgia (muscle or joint pain)
- At least one of the following three respiratory symptoms:
  - Cough
  - Sore throat
  - Shortness of breath

Case definitions for ILI vary worldwide and both the sensitivity and specificity of these case definitions are generally low, with low positive predictive values (23.3% to 59.7%) [38, 39]. Indeed, the case definition of ILI used by the ECDC (outlined above) is less sensitive than the definitions used by the WHO and CDC due to its reliance on self-reported fever rather than measured temperature [40].

Diagnosis of influenza, meanwhile, requires that the criteria for clinical symptoms for ILI be met with at least one of the following four laboratory criteria [41]:

- The isolation of influenza virus from a clinical specimen
- The detection of influenza virus nucleic acid in a clinical specimen
- Identification of influenza virus antigen by DFA test in a clinical specimen
- Influenza specific antibody response

Symptoms can start between 1 and 4 days after the influenza virus has entered an individual's body. Infected individuals are infectious up to 1 day before the symptoms develop, with the infectious period lasting up to 7 days in adults and longer in children [42].

Influenza belongs to the Orthomyxoviridae family of viruses which includes the A, B and C influenza virus types. In tropical regions, influenza epidemics can occur at any time of year but in more temperate climates influenza epidemics occur generally during the winter season and through circulation of influenza virus types A and B. Type A influenza is the main focus for public health officials because new and virulent strains of Type A tend to be both the cause of pandemics and the majority of the mortality burden for seasonal influenza [43]. In non-pandemic years influenza epidemics can cause 250,000 to 500,000 deaths [44], infecting 18% of unvaccinated individuals (95% CI: 16 – 22%) each influenza season [45]. Groups at risk of severe influenza infection include pregnant women, young children aged less than 5 years old, adults aged 65 years or older and those individuals with



underlying health conditions such as chronic disease to the heart, liver or kidneys as well as asthma and immunosuppression.

In addition to the burden of disease, influenza is associated with costs related to the loss of productivity in addition to hospitalisation, primary care and treatment costs. In 2003 the total economic burden of influenza epidemics in the United States was US\$87.1 billion [46].

Influenza epidemics are driven by the high attack rates in children, with 20-30% of this population group affected over the course of a typical influenza season as they lack prior immunity. Infants and young children are likely to be hospitalised with influenza infection [47] although mortality from influenza is greatest in the elderly population [48]. Influenza infection in children causes a high societal impact in terms of absence from school or day care and a loss of productivity in the workplace when parents or guardians are required to be absent from work in order to care for their children at home. Influenza infection is associated with a mean absence from school or day care of 2.8 – 12.0 days for children infected and 1.3 – 6.0 days for their siblings in addition to an absence from work of 1.3 – 6.3 days for their parents [49].

112 acute outbreaks were reported in care homes (49%), hospitals (39%), schools (9%) and other settings (3%) during the mild influenza season of 2013-14 [11] but virological testing shows that most outbreaks in care homes were caused by viral respiratory diseases other than influenza. Hospital outbreaks were caused by influenza A in the majority of cases. Very low levels of influenza B circulated (peak of 1.8% positive in week 18 of 2014), compared to 2012-13 (18.6% positive in week 52 of 2012). Influenza A (H1N1)pdm09 was the dominant circulating virus in 2013-14. Vaccine uptake reached 52.3% in clinical at-risk groups and 73.2% in those aged 65 years and older. In addition, 42.6% of GP-registered 2 year olds and 39.5% of GP-registered 3 year olds received the LAIV. A pilot programme in seven geographical areas saw 52.5% of primary school children receive the LAIV [50].

#### COMPLICATIONS FROM INFLUENZA INFECTION

Cromer et al. (2014) highlighted the risks of complications from influenza infection in England using laboratory reports and the NHS Hospital Episode Statistics database [51]. They reported the annual burden of disease attributable to influenza using the hospital admission rate, estimated number of deaths and GP consultations.

The highest influenza-attributable hospitalisation admission rate was for healthy children aged under 5 years, split by 333 per 100,000 (95% CI: 321 – 345) for children aged under 6 months and 176 per 100,000 (95% CI: 171 – 181) for children aged 6 months to 4 years. In comparison, healthy adults aged 65 years and older had an influenza-attributable hospitalisation admission rate of 46 per 100,000 (95% CI: 45 – 47). 72% of influenza-attributable deaths occurred in adults aged 65 years and older with co-morbidities. These figures show the uneven spread of the total burden of influenza infection within

an affected population. In addition, Rothberg and Haessler (2010) reported that patients with chronic medical conditions, such as heart disease, lung disease, diabetes, renal disease, rheumatologic disease, dementia, and stroke, are also at high risk for both seasonal and pandemic influenza complications, regardless of age [52]. These complications include primary viral pneumonia, secondary bacterial pneumonia as well as exacerbations of chronic underlying pulmonary diseases such as asthma and COPD.

Accurate estimation of the total burden of influenza in terms of hospitalisations and deaths is difficult as many cases will not be virologically confirmed, nor indeed will data sources listing hospital admissions and death registrations specify the virologically-confirmed causative organism [53]. There is inherent uncertainty in the estimates of the total burden of seasonal influenza, which must be accounted for when seeking to establish methods for controlling influenza outbreaks.

#### **THE EPIDEMIOLOGY OF MEASLES: WORLDWIDE AND IN THE UNITED KINGDOM**

##### **ANNUAL BURDEN OF MEASLES**

Measles is a highly infectious notifiable disease that can be severe in infants, pregnant women and immunocompromised individuals [37, 54]. It is caused by the measles virus, a member of the Paramyxoviridae family of viruses. It is highly contagious, spread by airborne droplets or direct contact with patient secretions. Measles is a leading cause of morbidity and mortality among young children, despite the availability of a safe and effective vaccine [55].

Measles infection is defined using the following criteria [56]:

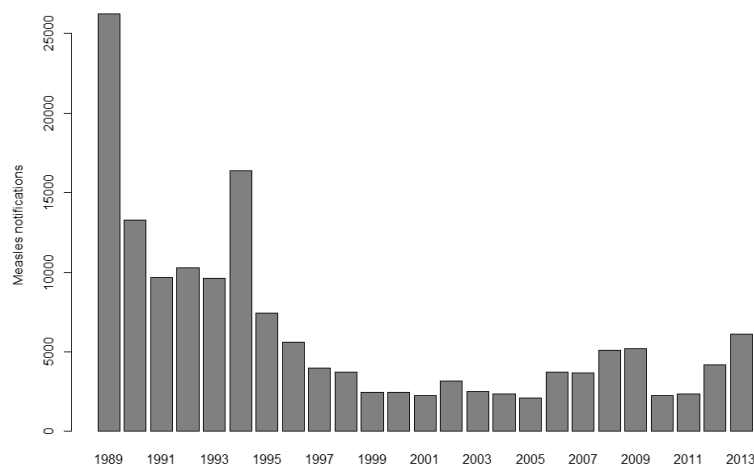
- Fever and maculopapular rash
- At least one of the following:
  - Cough
  - Coryza (Rhinitis)
  - Conjunctivitis
- At least one of the following laboratory criteria:
  - Isolation of measles virus from a clinical specimen
  - Detection of measles virus nucleic acid in a clinical specimen
  - Measles virus specific antibody response characteristic for acute infection in serum or saliva
  - Detection of measles virus antigen by DFA in a clinical specimen using measles specific monoclonal antibodies

Measles infection lasts between 7 – 10 days, with an incubation period of 10 – 12 days. Measles symptoms include:

- Cold-like symptoms
- Spot-like rash covering the body
- Red eyes, sensitivity to light
- A high temperature or fever
- Koplick’s spots inside the mouth

Measles is preventable through the measles-mumps-rubella vaccination programme (MMR), with measles vaccination introduced in the UK in 1968 [37]. In 1967, prior to the introduction of the vaccine, there was 460,407 notifications of measles infection and 99 deaths from the disease. By the mid-1990s the number of notifications had reduced to fewer than 20,000 with no deaths from measles recorded for the first time in 1994 [57].

The World Health Organisation (WHO) estimated that 122,000 deaths occurred from 226,722 cases worldwide due to measles infection in 2012, down from 562,400 deaths and 853,480 cases in 2000 [58]. The WHO aims to achieve elimination of measles infection in at least five WHO regions by the end of the year 2020 [59], though vaccination coverage is not yet reaching levels required to achieve this goal in any region [60].



*Figure 2.1 - Annual measles notifications in England and Wales from 1989 to 2013*

Figure credit: [14].

Public Health England reported 3,207 laboratory-confirmed cases of measles in England between January 2012 and June 2013, an increase over confirmed cases in previous years (*Figure 2.1*). Around 230,000 children aged 10 – 16 years in England were unvaccinated against measles as of 31 March

2013 [61] as uptake of the national measles-mumps-rubella vaccination programme (MMR) fell in the late 1990s from 92% in 1996 to 80% in 2003 [62] after the suggestion of a potential link between the vaccine and autism [63] that subsequently proved to be unfounded [64-66]. MMR uptake has since recovered to its highest levels (92.8%) since its introduction [67].

COMPLICATIONS FROM MEASLES INFECTION

Complication	Number of complications from measles infections (n = 66,800)	
Any	19,443	(29.1%)
Death	177	(0.3%)
Diarrhoea	5,473	(8.2%)
Encephalitis	96	(0.1%)
Hospitalisation	12,854	(19.2%)
Otitis media	4,875	(7.3%)
Pneumonia	3,948	(5.9%)

*Table 2.1 - Rates of complications from measles infections in the United States between 1987 and 2000*

Table credit: [68].

Measles infection can cause respiratory complications (otitis media, laryngotracheobronchitis and pneumonia), gastrointestinal complications (diarrhoea, mesenteric adenitis), neurological complications (febrile seizures, post-infectious encephalomyelitis and sub-acute sclerosing panencephalitis) and ocular complications (conjunctivitis and keratitis) (*Table 2.1*). Complications are more common in young children under the age of 5 years or in adults over the age of 20 years [68]. The rate of hospitalisation following measles infection can be high, with 42% of cases hospitalised in nine countries in the WHO European region in 2013, for those cases with a known hospitalisation status [69].

## MATHEMATICAL MODELLING OF INFECTIOUS DISEASES

This section will introduce the use of mathematical modelling in estimating the burden of disease and its use in economic evaluation. It will discuss both deterministic and stochastic modelling approaches and the use of social contact patterns to inform mathematical models of infectious disease transmission in populations.

Mathematical modelling plays a large and important role in the planning of public health interventions. When a controlled trial is too difficult to implement because of logistical, financial or ethical considerations the simulation of possible outcomes can make assessments of both the burden of disease and potential interventions possible.

When modelling the potential impact of new vaccination programmes, mathematical modelling provides the opportunity to study population-level outcomes (e.g. indirect protection offered to unvaccinated individuals and the overall impact on population-level burden of disease), the long-term

impact of the intervention and to assess several possible options for vaccination strategies. Estimating the impact of a population-wide vaccination programme would not be possible without the use of a mathematical model of disease transmission and the effect of vaccination.

The following section lists different approaches to mathematical models used to evaluate vaccination programmes: Static and Dynamic models; Deterministic and Stochastic models; and Aggregate models.

#### **STATIC AND DYNAMIC MODELS**

Dynamic models include the indirect effects of interventions such as vaccination, by assuming that the force of infection is dependent of the number of infectious individuals in the population, in contrast to static models that assume that the force of infection (or the per-susceptible rate of infection) is constant during the duration of the outbreak(s) simulated. Disease incidence simulated in dynamic models does not decline in proportion to the increase in vaccination coverage achieved because individuals not reached by the vaccination programme still experience some benefit from its existence due to a lower risk of infection [70]. Chapters 5 and 6 detail the use of dynamic models to examine the impact of the childhood seasonal influenza vaccination programme in England, taking into account the potential indirect protection offered to the general population by vaccinating healthy children.

#### **DETERMINISTIC AND STOCHASTIC MODELS**

##### **DETERMINISTIC MODELLING**

For a deterministic system, a model will continue to produce the same results if the initial conditions remain unchanged as the model does not use any degree of randomness or uncertainty in its computations. In the context of simulating infectious disease epidemics, the results of the model (e.g. final size, case fatality ratio, etc.) will be returned with each separate run of the model if the initial parameters (e.g. the proportion of susceptible individuals in the total population, the basic reproduction number, etc.) for each run remain the same. The behaviour of the system is limited by its history and the equations that govern the model.

##### **STOCHASTIC MODELLING**

A stochastic model will evolve over time using random variables. Even if the initial conditions remain the same for each simulation, the random variables that shape the progression of the system will ensure that the end results of each run will differ from the others. In infectious disease modelling a stochastic system will incorporate probability distributions in its parameters that permit important parameters to vary across the course of a simulation run, accounting for uncertainty in the estimation of this parameter.

An example of incorporating a random variable into a system describing the dynamics of an infectious disease outbreak is the Reed-Frost model [71]. The population is closed and time in the system is divided into discrete intervals. The probability that a susceptible individual becomes infectious at time  $i + 1$  depends on the number of infectious individuals at time  $i$ .

If we assume that the probability of escaping infection by an infectious individual is  $q$ , we can write the following:

$$Pr(I(j + 1) = n | S(j) = k, I(j) = l) = \binom{k}{n} (1 - q^l)^n (q^l)^{k-n}$$

*Equation 2.1 - The probability of  $n$  infectious individuals in a population at time  $j+1$ , as described by the Reed-Frost model*

The modelling exercise detailed in Chapter 6 used a stochastic model to simulate disease transmission dynamics between different schools in a small representative population. In contrast, the model used in Chapter 5 is a deterministic model that simulated influenza transmission in a much larger population, less dependent on stochastic processes.

#### **AGGREGATE MODELS**

When modelling an outbreak of an infectious disease in a large population a common approach to reduce computational resource use is to execute an aggregate model of the studied population [70]. That is the model calculates the proportion of susceptible individuals that become infectious per unit time; the proportion of infectious individuals that recover per unit time, etc. This type of model tracks groups of individuals, rather than the approach used in Individual-Based models that track each individual in the study population.

#### **INCLUDING SOCIAL CONTACT PATTERNS IN MODELS OF DISEASE TRANSMISSION**

The mixing patterns of the study population can be a critical determinant of the evolution of disease dynamics [72]. Therefore it is important that mathematical models of infectious disease outbreaks account for non-random mixing patterns by incorporating appropriate parameters into the system. It is also key that these parameters are informed by the accurate measurement of social mixing patterns.

Edmunds et al. (2006) [73] plotted the age of both primary and secondary cases of measles and meningococcal disease in England and Wales between 1995-1998 (*Figure 2.2*), demonstrating the largely assortative nature of social mixing patterns and age-clustering of cases of the diseases. This information can be used to inform models of infectious disease outbreaks by introducing data on social mixing patterns into the  $\beta$  parameter that describes the rate of contacts within a population.

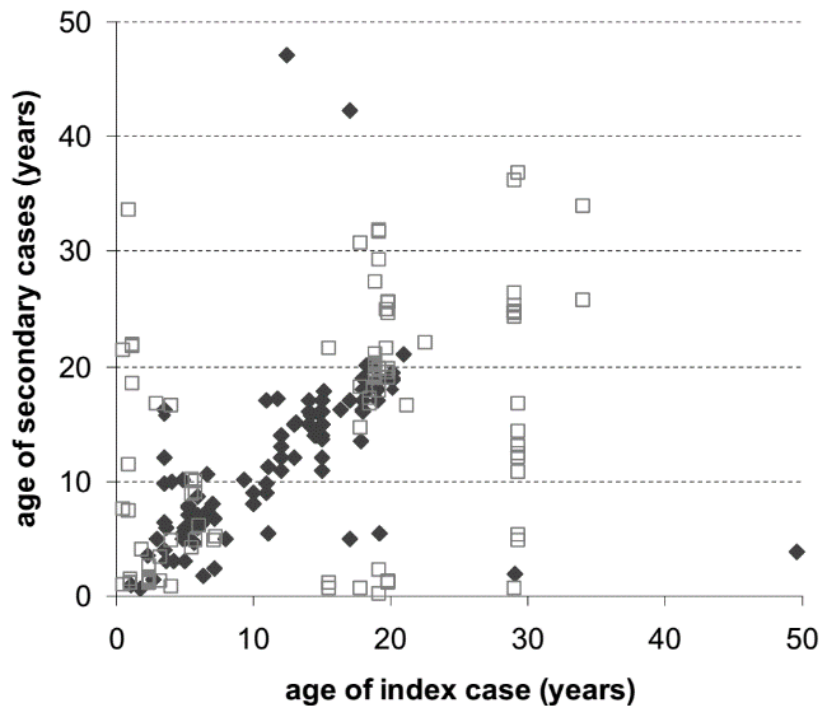
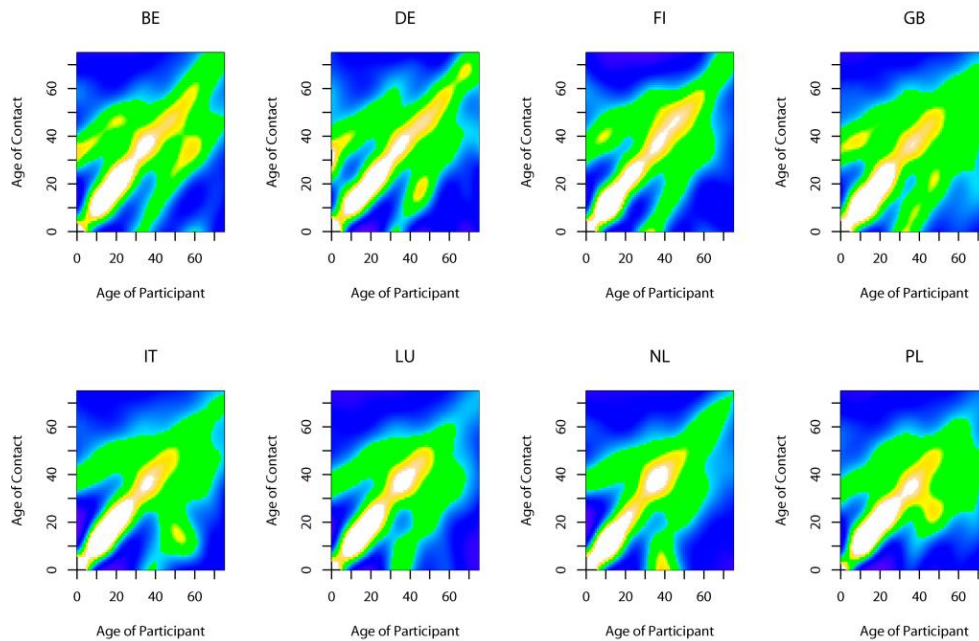


Figure 2.2 - The age of primary and secondary (based on date of onset) cases of measles (open squares) and meningococcal meningitis (filled diamonds) in clusters in England and Wales 1995-1998

Figure credit: [73].

Data on social mixing patterns can be gathered from a population using prospective surveys that require participants to complete regular diary entries listing the number of people they have been in contact with along with their age and other demographic parameters. The results of these surveys then permit the introduction of mixing matrices into mathematical models.

Mossong et al. (2008) [23] used contact diaries for one day in eight European countries, asking 7,290 recruited participants of all ages to record their contacts along with the appropriate demographic factors. They found that contacts made by children and adolescents are highly assortative (*Figure 2.3*) and may help to explain why this subpopulation is so important in understanding the transmission dynamics of certain diseases.



*Figure 2.3 - Smoothed contact matrices for eight European countries based on all reported contacts*

Figure credit: [23].

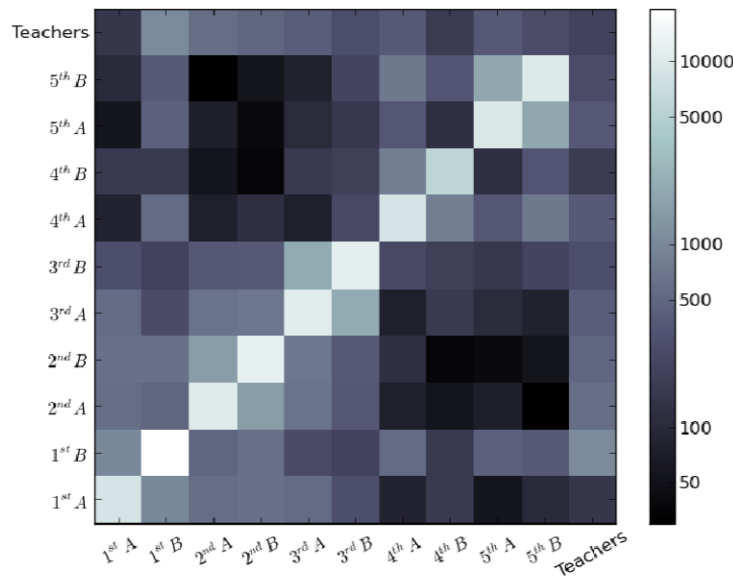
## **INFECTIOUS DISEASE OUTBREAKS IN SCHOOLS**

This section introduces the topic of school-based outbreaks and school-based vaccination programmes as one of the main themes of the thesis. The unique social dynamics within schools and the population-wide impact of infectious disease outbreaks within schools makes this subpopulation so important in the context of infectious disease outbreaks in the community.

### **SCHOOL SOCIAL DYNAMICS**

We've seen the use of social contact data in mathematical models of infectious disease dynamics to demonstrate how an infectious disease progresses through different age groups in a population based on the number of effective contacts between individuals of different age groups. Mossong et al. (2008) reported social contact data for age groups 0 to 4 years, 5 to 9, 10 to 14 and 15 to 19 with all age groups up to those individuals aged 70+ years. It was suggested that the high number of close contacts between school aged children can sustain the transmission of some infectious diseases within this subpopulation [23].





*Figure 2.4 - The number of contacts between individuals of classes A and B over two days of the study in French primary schools*

Figure credit: [74].

Further studies have sought to add detail to the contact patterns of school children. High-resolution contact patterns were recorded using radio frequency identification devices in French primary and secondary schools by Stehlé et al. (2011) and Fournet et al. (2014) respectively [74, 75]. *Figure 2.4* shows the contact matrix obtained from the primary school study and how the observed contact patterns differ from previously hypothesised homogeneous contact patterns due to a high degree of age assortativity.

School children, therefore, are an important subpopulation to consider when implementing a new preventative vaccination programme in the community [19-21]. Controlling outbreaks fuelled by children and adolescents attending schools can reduce the wider impact of outbreaks on the larger community. The next section will focus on exercises in the mathematical modelling of school-based outbreaks of disease and potential interventions (e.g. vaccination, or some social distancing policies) to reduce their impact.

## PREVIOUS OBSERVATIONAL STUDIES ON THE IMPACT OF SCHOOL-BASED INFECTIOUS DISEASE OUTBREAKS

Outbreak	Impact Measured	Reference
North Carolina, 2006	- 24% workplace absenteeism for adults acting as caregivers for children affected by school closure  - Childcare expenses for two families (\$100 and \$150 respectively)	[76]
Seattle, 2000-01	- 28% attack rate in school  - Influenza-attributable school absence rate of 62.9 days per 100 children  - 4.2 health care visits per 100 children  - 19.8 days of work missed by parents per 100 children	[77]
London, 2012-13	- Reported attack rates of 67.5%, 45.2% and 34.3% in schools	[78]
Odate City, 2012-13	- 70% of households experienced ILI transmission after a primary case in a school-attending child	[79]

*Table 2.2 - Measured impact of school-based seasonal influenza outbreaks*

Table 2.2 shows the measured impact of school-based seasonal influenza outbreaks for four separate outbreaks. Johnson et al. (2008) [76] distributed questionnaires to 220 households after an outbreak of influenza B in 9 schools during October and November 2006 in North Carolina; Neuzil et al. (2002) [77] used surveys to gather impact data from families with children attending an elementary school in Seattle for the 2000-01 influenza season; McCann et al. (2014) [78] described the impact of outbreaks of influenza B in primary schools within the Thames Valley region of London during the 2012-13 influenza season; and surveys were sent to households in Odate City, Japan during the 2012-13 influenza season [79]. These studies together demonstrate the impact in the community of infectious disease outbreaks that occur in schools, and show the importance of successfully mitigating this impact through previously-modelling social distancing policies or the implementation of new vaccination strategies targeting this subpopulation.

## OUTLINE OF STUDIES MODELLING OUTBREAKS IN SCHOOLS

### SOCIAL DISTANCING – SCHOOL CLOSURES AND CLASSROOMS CLOSURES

Social distancing policies in schools designed to mitigate infectious disease outbreaks have been studied using mathematical models, with varying predicted outcomes. In a recent review of mathematical modelling studies for school closures as a measure to mitigate seasonal and pandemic influenza outbreaks, the authors reported that peak incidence was typically predicted to fall by 20-60%, though some studies predicted an increase in this metric, usually determined by the duration and timing of the school closure [80]. The value of  $R_0$  was a key determinant in the effectiveness of the school closure, with higher values reducing the overall benefit.

Other studies have considered social distancing policies such as targeted class closure, targeted grade closure and whole school closure [81, 82], finding that targeted class closures can be as effective as whole school closures, and long school closures are unlikely to be cost-effective.

School children directly affected by a social distancing policy in their school would still have contacts within the wider community, and the unnecessary closure of classes or grades with no infectious individuals leads to the introduction of many susceptible individuals into the wider community. Therefore whole school closures can be less effective than a more targeted approach when the outbreak has spread to the wider community and is not just confined to the boundaries of the school.

#### VACCINATION STRATEGIES

Vaccinating school-age children against influenza greatly reduces the total burden of disease due to influenza infection by both direct and indirect effects of vaccination [36]. Seasonal influenza vaccination programmes in schools are likely to be very cost-effective [70], in part due to the substantial indirect protection offered to other individuals in the population not targeted by these programmes. A recent systematic review of mathematical modelling studies reported that the majority of these studies concluded that childhood influenza vaccination was cost-effective [83].

#### **THE UK INFLUENZA VACCINATION PROGRAMME EXTENSION TO HEALTHY CHILDREN**

Following on from the discussion of school-based outbreaks and studies examining cost-effective interventions for such outbreaks, we now introduce the extension to the UK seasonal influenza vaccination programme to healthy children.

#### **RATIONALE FOR SCHOOL-BASED SEASONAL INFLUENZA VACCINATION PROGRAMMES**

Children and adolescents attending schools play a large role in the spread of influenza in the community [19-21]. Children have a large number of contacts outside their household [22] and indeed transmission within schools is maintained because of the high number of close contacts between school children [23] as well as less acquired immunity in children [22, 25], poor hygiene habits [24] and a longer period of increased virus-shedding once infected [84, 85]. The advantage of administering a free-of-charge vaccination programme in schools is that easy access to a preventative medical intervention is offered to the community and commonly-cited barriers to vaccination such as time demands, inconvenience and cost are eliminated [86, 87].

#### OBSERVATIONAL STUDIES ESTABLISHING THE IMPACT OF SCHOOL-BASED PROGRAMMES

School children are an appropriate target for seasonal influenza vaccination due to their role in infectious disease transmission and their accessibility for vaccine administration, first demonstrated by Monto et al. (1970) in Michigan [88] then subsequently in many other communities [26-31]. The study conducted in Tecumseh reported reductions in the weekly mean rates of respiratory illness for

all age groups during the period of the Hong Kong influenza outbreak in 1968-69 after a school-based seasonal influenza vaccination programme that achieved mean coverage of 85.8% for enrolled children. The vaccination programme was credited with interrupting the influenza transmission chain, providing indirect protection to unvaccinated individuals in the community.

School-based influenza vaccination reduces excess mortality and influenza complications in the wider population [27, 89]. The studies conducted in US Navy day care centres in California [26] and in communities in the US [27], Italy [28], Brazil [29] and Canada [30] have demonstrated that vaccinating children has the potential to reduce influenza episodes both in the vaccinated individuals, but also in individuals of all age groups who were not vaccinated, or who did not successfully seroconvert following vaccination.

#### **MATHEMATICAL MODELLING OF THE IMPACT OF SCHOOL-BASED PROGRAMMES**

Annual influenza vaccination for healthy children has been repeatedly shown to be a cost-effective extension of existing national influenza vaccination programmes [83]. Indeed, many studies using dynamic transmission modelling have shown economic benefits in vaccinating healthy children for seasonal influenza [36, 70, 90-97]. The interruption of community-wide transmission to reduce the burden of disease in school children, as well as in the unvaccinated communities, is estimated to result in large reductions in healthcare resource use, costs, influenza-attributable deaths and QALYs lost due to influenza [94].

A systematic review published in 2008 examined the economic evaluations of influenza vaccination for children that included direct individual benefits and indirect societal benefits [96]. Ten of the 15 studies included in the review reported that such a vaccination strategy would be either cost-effective or cost-saving. 3 studies reported that vaccination was either cost-saving or cost-effective in certain conditions and 2 studies reported that vaccination provided no benefit regardless of the economic evaluation perspective considered.

#### **AN EXTENSION TO THE INFLUENZA VACCINATION PROGRAMME IN ENGLAND**

The Joint Committee on Vaccination and Immunisation (JCVI) in 2012 recommended extending the influenza vaccination programme to all children between the ages of 2-16 years [32]. This extension will be rolled out over several seasons and will see a live-attenuated influenza vaccination (LAIV) offered to children each year with the majority of vaccines administered in school settings.

The LAIV is more effective than inactivated vaccines in children and adolescents and may also offer protection against drifted strains of influenza as well as herd immunity effects seen in the elderly population even at low LAIV coverage levels in children and greater cost-effectiveness than the TIV alternative [98-102]. A recent cluster randomised trial in Canada found that LAIV administration in school-based vaccination programmes was associated with increased vaccine uptake when compared

to intra-muscular injection vaccines [103], and a large comparative trial of TIV and LAIV in children aged 6-59 months showed a 55% high relative efficacy for LAIV [99].

#### SUPPORTING THE JCVI RECOMMENDATION

The JCVI recommendation was supported by three studies. The first used mathematical models to assess a series of alternative vaccination scenarios to reduce transmission of seasonal influenza using infection surveillance data from 1995 to 2009 [104] and recommended that targeting children in addition to older adults was the most efficient use of the seasonal influenza vaccine. The second study estimated the total burden of seasonal influenza in England and demonstrated the benefit of a childhood vaccination programme in addition to older adults to offer both direct protection to children as well as indirect protection to the wider population [51]. The final study used the same models mentioned above to assess the cost-effectiveness of alternative vaccination programmes and reported that the most efficient strategy was to extend the previous vaccination policy to school-age children whilst maintaining good coverage in those individuals in a clinical at-risk group [33]. The inclusion of school-age children was the most cost-effective extension to the existing vaccination programme in an incremental cost-effectiveness analysis.

#### PILOTING THE EXTENSION TO THE INFLUENZA VACCINATION PROGRAMME IN ENGLAND, 2013-14

A pilot of the extended vaccination policy was implemented for the 2013-14 influenza season. Seven geographically discrete areas of England were chosen to offer vaccination against seasonal influenza (A/California/7/2009 (H1N1)pdm09-like strain, A/Victoria/361/2011 (H3N2)-like strain and B/Massachusetts/2/2012-like strain) to primary school age children between September 2013 to April 2014. Different models of delivery were included in the pilot, mainly focused on school-based and community-based administration.

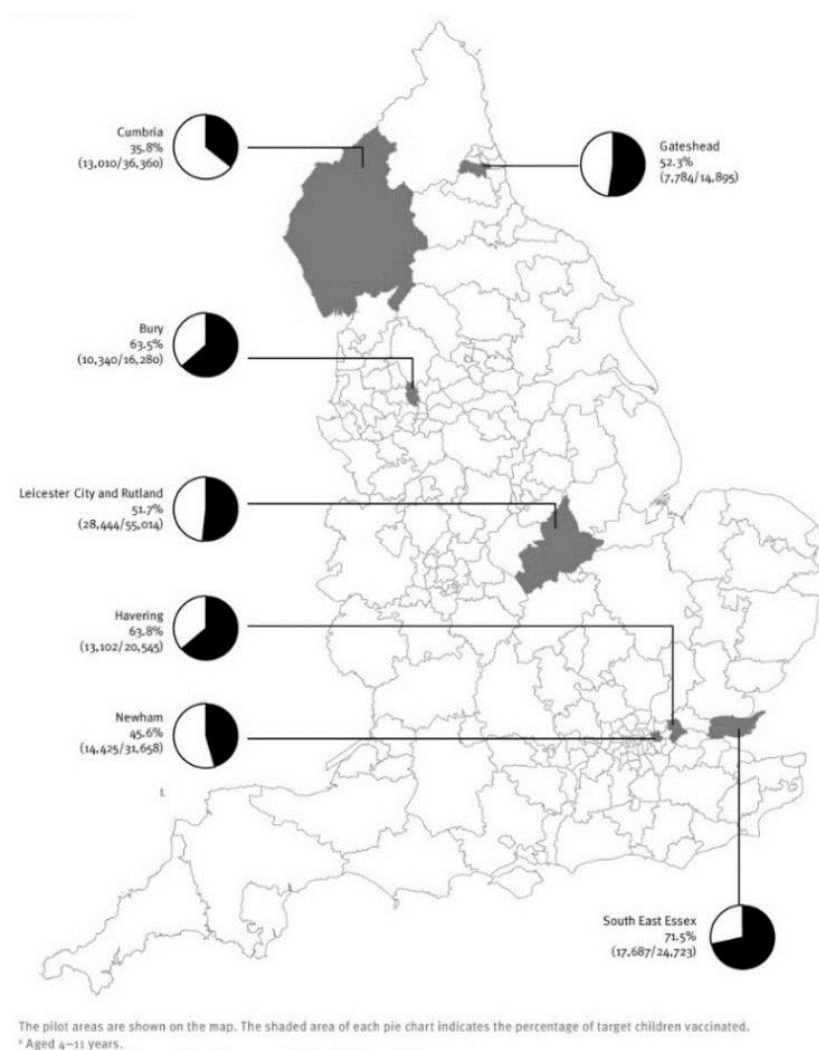
#### DEMOGRAPHICS

The 7 geographically discrete areas chosen for the pilot programme were Cumbria, Gateshead, Bury, Leicester City and Rutland, Havering, Newham and South East Essex counties. Children aged from 4 – 11 years were offered one dose of the live-attenuated influenza vaccination. 6 geographical areas implemented a school-based vaccination programme whilst 1 area delivered through pharmacies and primary care facilities.

#### COVERAGE ACHIEVED

Coverage in the seven areas varied from 35.8% (13,010/36,360) to 71.5% (17,687/24,723) with an average coverage level of 52.5% (104,792/199,475) for the pilot [50] (*Figure 2.5*). Six of the seven geographical areas used a school-based vaccination programme for which the overall average coverage level was 56.3% (91,782/163,115). In addition to the primary school cohort, children aged 2-3 years were offered vaccination via primary care. During the 2013-14 influenza season, provisional

vaccination uptake for this cohort was 42.6% and 39.5% respectively [105]. Uptake varied according to deprivation, ethnicity and religious belief [106].



*Figure 2.5 - Cumulative uptake of live attenuated influenza vaccine in primary school-age children in pilot areas, England, 2013-14 influenza season*

Figure credit: [50]. Contains Ordnance Survey data © Crown copyright and database right 2016. Contains National Statistics data © Crown copyright and database right 2016.

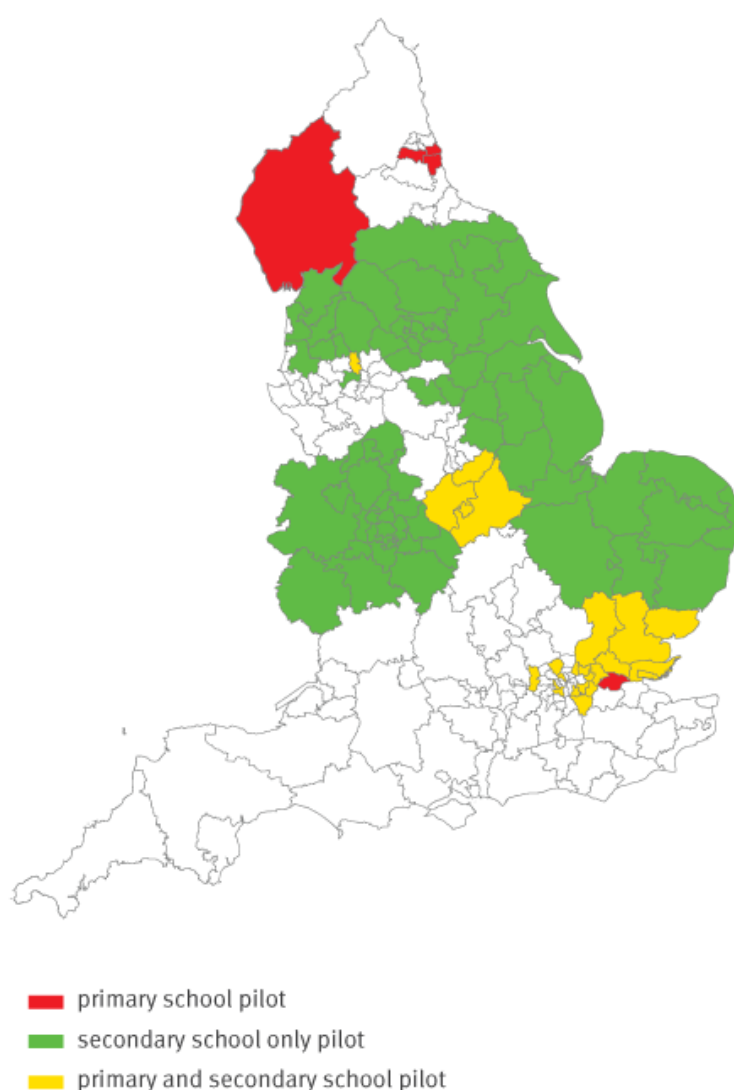
#### **PILOTING THE EXTENSION TO THE INFLUENZA VACCINATION PROGRAMME IN ENGLAND, 2014-15**

A further pilot of the extension to the influenza vaccination programme was conducted during the 2014-15 influenza season. All children aged 2 – 4 years in addition to children in primary schools (aged 4 – 11 years) and secondary schools (only 11 – 13 years) in pilot areas were offered a live-attenuated quadrivalent against seasonal influenza (A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Massachusetts/2/2012-like virus and B/Brisbane/60/2008-like

virus) between September 2014 and March 2015 [107]. Most pilot areas ran school-based administration, with two areas running a pharmacy-based model and one running a GP-based model.

#### DEMOGRAPHICS

Children attending primary schools in Cumbria, Greater Manchester, Leicestershire and Lincolnshire, London and Essex, Northumberland, Tyne and Wear formed part of the target population. The rest of the target population came from children of ages 11 – 13 years attending secondary schools in Arden, Birmingham and Black Country, Greater Manchester, East Anglia, Essex, Herefordshire and Worcestershire, Lancashire, London, North Yorkshire and Humber, Shropshire and Staffordshire, South Yorkshire and Bassetlaw and West Yorkshire (*Figure 2.6*).



*Figure 2.6 - Cumulative uptake of live attenuated influenza vaccine in primary school-age children in pilot areas, England, 2014-15 influenza season*

Figure credit: [107]. Contains Ordnance Survey data © Crown copyright and database right 2016.

## COVERAGE ACHIEVED

196,994 primary school children received one dose of the LAIV quadrivalent vaccine, giving an overall coverage level of 56.8%, though this varied from 32.3% to 63.1% across the pilot areas. 184,975 secondary school children received one dose of the vaccine, an overall coverage level of 49.8% that varied from 21.2% to 62.0% across pilot areas. The authors reported that school-based programmes consistently achieved higher coverage than pharmacy-based programmes in both age groups. In addition, 44.1% of children aged 2 – 4 years received their seasonal influenza vaccine.

## HETEROGENEOUS VACCINE COVERAGE

Previously we've discussed the uptake of the seasonal influenza vaccine in pilot areas during the 2013-14 and 2014-15 influenza seasons. Although encouraging mean coverage was achieved across the pilot as a whole the coverage varied between pilot areas. For example, coverage in one pilot area in 2013-14 reached 71.5% in primary schools whereas one pilot area in 2014-15 reported coverage of just 21.2% in secondary schools [50, 107]. The mathematical modelling and cost-effectiveness analysis that justified the JCVI recommendation to extend the vaccination programme to health children assumed that coverage would be 50% in both primary and secondary school groups [33].

It is unclear if the potential heterogeneous coverage between different areas of the United Kingdom would affect the effectiveness of the new vaccination programme. Before examining that issue, first we discuss heterogeneity in vaccination coverage in more detail.

## DEFINITION OF AND REASONS FOR HETEROGENEOUS COVERAGE

Damm et al. (2014) modelled the introduction of live-attenuated influenza vaccine for health children in Germany and when reporting their final estimate for the cost-effectiveness ratio they assumed uptake of 50% [90]. Baguelin et al. (2010) assumed that vaccination coverage against A/H1N1v would reach 70% in at-risk groups and 40% in all other groups targeted [108]. Both these modelling studies assumed a degree of homogeneity for the coverage of the new vaccination programme, but in vaccination coverage heterogeneity can occur for many different reasons. Lower vaccination uptake is associated with higher levels of deprivation in the community along with a higher proportion of non-white residents [109-111]. For some groups, religious beliefs can influence the decision to vaccinate children [112-115], for example fears over the new LAIV seasonal influenza vaccination during 2013-14 were raised within the Jewish and Muslim communities due to the porcine origin gelatin used in the manufacturing of the vaccine [116].

One major consequence of this heterogeneity is that some communities are more likely to experience infectious disease outbreaks than others if infection is introduced to an area of low coverage. Indeed, some studies confirm that areas with high rates of vaccine hesitancy have a greatly increased risk of outbreaks [34, 117]. Unvaccinated "pockets" or areas of low vaccination coverage have been



associated with outbreaks of vaccine-preventable diseases [34, 118]. Another consequence of vaccine refusal is that it negatively affects the health outcomes of those individuals who remain unvaccinated in the community and subsequently become infected in later life [119]. For infections like measles, varicella and rubella with health outcomes that increase in severity with age increases, vaccination programmes that target young children mean that the risk of being one of the last members of that community to be vaccinated directly increases the risk of complications from infection. Heterogeneity in vaccination coverage through vaccine refusal exposes unvaccinated individuals to an increased risk of hospitalisation and death.

#### **CONSEQUENCES OF HETEROGENEOUS COVERAGE**

Even when global vaccination coverage is high, local pockets of low vaccination coverage leave communities at risk of sustained infectious disease transmission. Omer et al. (2008) identified 23 clusters of low vaccination for pertussis in Michigan and six clusters of pertussis cases occurred during the study period, with significant overlap between the two [34]. Overall vaccine exemption clusters were three times more likely to be in a pertussis cluster than non-vaccine exemption clusters (odds ratio 3.02, 95% CI: 2.52-3.61). The community-level risk of pertussis outbreaks increased when vaccine-exemption clusters existed.

A similar situation was described in a study by van den Hof et al. (2001) when an outbreak of measles occurred in The Netherlands, a country with high measles vaccination coverage (96%) [35]. An orthodox reformed school of 412 pupils had a very low measles vaccination coverage of 7% and the introduction of the measles virus into the school caused an outbreak with an attack rate of 91% in the susceptible population. The authors concluded that clusters of unvaccinated individuals is a critical factor for measles elimination.

The level of heterogeneity in measles vaccination coverage and its implication for localised outbreaks was further explored by Choi et al. (2008) by modelling the potential for measles transmission in England after studying the vaccination uptake in the country [62]. They found that 99 former district health authorities had an increased risk of sustained measles epidemics due to their low MMR coverage and the subsequent impact on the number of susceptible individuals within their borders.

Low measles vaccination coverage was also responsible for an outbreak in Campania in Italy, where estimated coverage reached on 65% in 2002 [120]. Unvaccinated school-age children were most affected by the outbreak. Localised low vaccination coverage for measles infection was identified as a key factor for measles outbreaks in Germany by Herzog et al. (2010) [121].

## MODELLING HETEROGENEOUS COVERAGE

Metapopulation frameworks (the division of a population into smaller subpopulations, separate from each other but with interactions between the subpopulations) have provided new perspectives for mathematical modelling exercises that are used to evaluate the potential effectiveness of preventative vaccination programmes. The new seasonal influenza vaccination programme in England was implemented after mathematical modelling demonstrated that it was both highly effective at reducing the total burden of seasonal influenza [104], and that it was also very cost-effective [33]. However, the mathematical model did not anticipate heterogeneity in vaccination coverage, something seen in recent studies that reported on regional pilots [50, 107]. Therefore, it may be useful to consider methods of incorporating heterogeneous coverage for the national influenza vaccination programme to test the robustness of the conclusion that the programme will be very cost-effective, or to identify potential weaknesses in the programme caused by potential heterogeneous coverage.

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# **Chapter 3 - Measuring health utilities and health-related quality of life in children and adolescents: a systematic literature review**

Portions of this section were presented as a poster presentation at the London School of Hygiene and Tropical Medicine Research Degree Poster Day in January 2015 and published in PLoS ONE in August 2015 [1].

## **ABSTRACT**

### **BACKGROUND**

The objective of this review was to evaluate the use of all direct and indirect methods used to estimate health utilities in both children and adolescents. Utilities measured pre- and post-intervention are combined with the time over which health states are experienced to calculate quality-adjusted life years (QALYs). Cost-utility analyses (CUAs) estimate the cost-effectiveness of health technologies based on their costs and benefits using QALYs as a measure of benefit. The accurate measurement of QALYs is dependent on using appropriate methods to elicit health utilities.

### **OBJECTIVE**

We sought studies that measured health utilities directly from patients or their proxies. We did not exclude those studies that also included adults in the analysis, but excluded those studies focused only on adults.

### **METHODS AND FINDINGS**

We evaluated 90 studies from a total of 1,780 selected from the databases. 47 (52%) studies were CUAs incorporated into randomised clinical trials; 23 (26%) were health-state utility assessments; 8 (9%) validated methods and 12 (13%) compared existing or new methods. 22 unique direct or indirect calculation methods were used a total of 137 times. Direct calculation through standard gamble, time trade-off and visual analogue scale was used 32 times. The EuroQol EQ-5D was the most frequently-used single method, selected for 41 studies. 15 of the methods used were generic methods and the remaining 7 were disease-specific. 48 of the 90 studies (53%) used some form of proxy, with 26 (29%) using proxies exclusively to estimate health utilities.

### **CONCLUSION**

Several child- and adolescent-specific methods are still being developed and validated, leaving many studies using methods that have not been designed or validated for use in children or adolescents.

Several studies failed to justify using proxy respondents rather than administering the methods directly to the patients. Only two studies examined missing responses to the methods administered with respect to the patients' ages.

## **INTRODUCTION**

### **BACKGROUND**

Evaluation of healthcare interventions and technologies commonly assess both the cost and consequences of interventions, in addition to effectiveness and safety. Economic evaluations are increasingly being used by healthcare systems around the world before a decision is made on whether to recommend a new intervention. In the United Kingdom, for example, the National Institute for Health and Care Excellence (NICE) requires that the appraisal of new interventions and technologies includes a cost-effectiveness analysis containing an assessment of benefits and resource use [2]. A requirement in the evidence submitted is a cost-utility analysis (CUA) that compares costs with benefits using quality-adjusted life years (QALYs), a measure incorporating the length of life and quality of life.

Quality of life is measured using health utilities that take values between 0 and 1, corresponding to utilities for dead and perfect health respectively. These utilities measured pre- and post-intervention are combined with the time over which the health states are experienced to calculate the QALYs that can be gained from new interventions. When evaluating several new health technologies the ratio of expected additional total costs to the expected additional QALYs gained incrementally is estimated for each technology, then cost-effectiveness is evaluated by comparing the incremental cost-per-QALY ratio against a pre-determined cost-effectiveness threshold, which in the UK is between £20,000 and £30,000 per QALY gained [2].

A CUA is also the recommended economic evaluation for submissions to the Canadian Agency for Drugs and Technologies in Health (CADTH) [3]; in Australia with submissions to The Pharmaceutical Benefits Advisory Committee (PBAC) [4]; in Sweden with submission to The Swedish Council on Health Technology Assessment (SBU) [5]; in New Zealand with submissions to The Pharmaceutical Management Agency (PHARMAC) [6] and other countries [7].

Health state utility values are usually obtained from one of two sources. Either the relevant health states are directly valued, using techniques such as Time Trade Off (TTO) or Standard Gamble (SG), or an existing tariff is applied. This latter approach is generally used when valuing generic health states (such as the EuroQol EQ-5D [8]). The tariff to be applied is usually based on valuations of a general population sample again using techniques such as TTO and SG. The TTO is a choice-based method that establishes for an individual how much time in full health is equivalent to a specified period of time spent in a particular ill-health state. The SG is another choice-based method that identifies the

probability of being in a better health state that makes an individual indifferent between the certainty of being in an intermediate health and a gamble between a worse health state and a better health state.

Measuring utilities for health-related quality of life (HRQoL) for children and adolescents is a developing field of research. Methods used to obtain health utilities from adults are well established but many have not been validated for use in children and adolescents. NICE states that the EQ-5D is the preferred method for use in CUAs that focus on the adult population [2], but no specific guidance has been given to help health economists choose an instrument designed for children and adolescents. Indeed, NICE did not make a specific recommendation for a particular instrument in the publication of their most recent guidance on technology appraisal [2].

There is evidence that children and adolescents are able to report on the state of their own health [9]. Children aged 3 years can report on feelings of nausea and pain that are reliable and clinically meaningful [10-12]. If children can convey the state of their health using a standardised method such as EQ-5D or HUI-2 then accurate and meaningful health utilities may be obtained for a range of childhood illnesses and conditions, which would be highly desirable for conducting CUAs.

It is important to recognise that methods suitable for young children may not be applicable to adolescents [13, 14], in the same way that adult-specific methods may not be appropriate for recording health utilities of adolescents [15]. Children may lack the cognitive ability to evaluate their health using abstract concepts in adult-specific indirect methods and direct methods such as TTO and SG. In addition, young children may lack the required linguistic skills to answer questions about their preferences for health using systems designed for self-completion by older children. The understanding of disease and its effect on HRQoL changes with the child's age, consequently both the measurement and valuation of changes in health due to disease need to be facilitated using age-specific instruments [13, 16].

Some methods have been developed for use exclusively in children and adolescents, and some existing adult-specific methods have been modified to make them child-friendly. The EQ-5D has been amended so that the questions for each dimension of health are easier to read and more accessible to children, resulting in a new child-friendly method called the EQ-5D-Y [17]. However, this uses the same utility weights in each dimension as the adult version, so does not yet incorporate child and adolescent preferences for health states. Adult preferences for health states may be different from the preferences of children and adolescents and the dimensions included may not cover all dimensions of health relevant to children and adolescents [18].

#### GENERIC AND DISEASE-SPECIFIC CALCULATION METHODS

Direct and indirect methods for the calculation of health utilities fall into two distinct domains – generic and disease-specific. Generic methods can be used to measure HRQoL in adults, children and adolescents (where appropriate) for a range of conditions, both chronic and acute. Commonly used generic methods include the EQ-5D and HUI-2. Disease-specific methods measure HRQoL with reference to a particular condition, such as the Asthma Control Questionnaire (ACQ) [19] and the Pediatric Asthma Health Outcome Measure (PAHOM) [20].

The advantage of using generic calculation methods in CUAs is that results can be compared across populations, conditions, and for different treatments or interventions [21]. Disease-specific methods have the benefit of being more sensitive to small changes in the condition of the patient in question and may describe the functioning of a patient with the condition with greater clarity than a generic classification system that may overlook some aspects of HRQoL [22], but utilities calculated using these instruments lack comparability across different diseases.

#### MEASUREMENT BY PROXY

When measuring the HRQoL of young children some authors prefer to gather the health utilities via proxies as young children may not have the cognitive ability to evaluate their health and/or complete the required measurement tasks [18]. Proxy respondents include the child's parents, clinicians and teachers. Parents are deemed to be the most useful proxies as they are the most familiar with their child's health and life [23, 24], though it has been suggested that parents may misjudge the health of their child owing to their own anxiety during the illness [25, 26] and further studies have shown differences between parent and child ratings for the child's health [27-29]. Clinicians' knowledge of children's conditions, symptoms, and functioning makes them useful proxies when evaluating HRQoL, though they will not have the same contact with children during their time away from clinics at home or in school [23, 30] so results are of questionable validity [31]. Teachers will not be able to provide HRQoL assessments for the child at home or in clinics [23] but will be able to evaluate a child's emotional and physical functioning.

In a systematic review published in 2005, Griebisch et al. [32] concluded that methods for measuring health utilities in children need further development. They noted the lack of methods that account for the development of the child, methods for children aged younger than 5 years, and a full understanding of the role of proxies in the evaluation of HRQoL in children and adolescents. Ravens-Sieberer et al. (2006) concluded that HRQoL of children and adolescents can and therefore should be ascertained by self-rating [33].

When performing a CUA in children and adolescents researchers must determine the best way to obtain utilities: expert opinion, measurement using patients or measurement using proxies. Each option will impose limitations on the study, and if the protocol calls for measurement then the

researchers need to choose the appropriate method. The method used in CUAs should be justified as each has limitations relevant to the estimation of health utilities and QALYs.

## RESEARCH QUESTIONS

The objective of this review was to evaluate the application of direct and indirect methods used to measure health-related quality of life in children and adolescents in the context of cost-utility studies. In doing so, we aimed to answer the following questions:

1. What direct and indirect methods have been used to obtain health utilities from children and adolescents in the context of cost-utility studies? How frequently have they been used?
2. If the method has not been validated for use in the study population do the authors acknowledge the limits of the method and therefore the study?
3. For study populations that include adults with children and adolescents, did the younger participants complete the calculation method to the same level as the adult participants?
4. When proxies have been used to obtain health utilities have the authors acknowledged the problems related to obtaining such utilities from proxies rather than patients?
5. How many studies have used HRQoL classification systems to obtain utilities for infectious diseases?

## PREVIOUS REVIEWS

<b>From whom were health utilities measured in the study?</b>	<b>Direct measurement methods used</b>	<b>Indirect measurement methods used</b>
Child (n = 5)	Time trade-off	EuroQol EQ-5D
Parent as proxy (n = 10)	Standard Gamble, Time trade-off, Visual Analogue Scale	EuroQol EQ-5D, Health Utilities Index, Quality of Well-Being Scale
Health care provider as proxy (n = 3)	None	EuroQol EQ-5D, Health Utilities Index, 16D-questionnaire
Adults as proxy (n = 1)	Time trade-off	None
Parent as unit of analysis (n = 1)	Time trade-off	None

*Table 3.1 - Results from Kromm et al. (2012) for studies that measured health utilities as part of a cost-utility analysis*

Kromm et al. (2012) [15] used the Pediatric Economic Database Evaluation (PEDE) project's online database to find a total of 213 CUAs for children and adolescents published in English between 1997 and 2009 to use in a quality appraisal. Citing that CUAs were 8% of all published economic evaluations between 1976 and 2001 [34] and also that 10% of economic evaluations for children and adolescents published between 1980 and 1999 were CUAs [35], they assessed the quality of such CUAs using the

57-item Pediatric Quality Appraisal Questionnaire (PQAQ) [36]. Only 16 (8%) of the studies included in the review gathered health utilities as part of the analysis (Table 3.1).

Other studies used health utilities from the researchers or literature (63%), health care provider opinion (6%), disability-adjusted life years (DALYs) (25%) and the remainder did not state the source of the utilities (1%). Kromm et al. (2012) argued that utilities gathered from the published literature might not be valid [37]. Study authors may assume that adult health utilities apply to children and adolescents and assume a uniform utility throughout childhood and adolescence, ignoring the child's development [13, 14]. In conclusion, the authors stated that new instruments should be developed to obtain utilities from children, rather than relying on adult utilities from the literature and utilities gathered via proxy.

Ladapo et al. (2007) [38] concentrated on CUAs in the United States, comparing analyses for adult, children and adolescent interventions. Using a database developed by the Tufts-New England Medical Center in Boston, they compared various aspects of 35 CUAs for children and adolescents with 491 adult CUAs. They found that generic classification systems (EQ-5D, Quality of Well Being (QWB) and HUI only) were used in 29% of analyses for children and adolescents and such CUAs are methodologically similar to adult CUAs. The leading primary disease category for CUAs for children and adolescents was infectious, representing 31% of all such CUAs. Finally, the authors noted that published cost-utility ratios tend to be lower for children and adolescents than for adults.

Griebsch et al. (2005) [32] considered all CUAs for patients aged younger than 17 years published until April 2004 in the Medline, Embase, Econlit, York Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database, the Harvard Cost-Utility Analysis Database and the Database of the PEDE project. 63 direct or indirect calculation methods were used to estimate health utilities, of which 22 (35%) used a generic method. The authors concluded that the variation in methods for estimating health utilities in children and adolescents meant that the process was not yet standardised. They called for the clear justification of the choice of methods for measurement.

Recently, Adlard et al. (2014) [39] discussed how the practice of paediatric CUAs has evolved over time, with reference to methods described in the NICE reference case [2]. The review considered 43 studies published between May 2004 and April 2012, of which only 11 obtained health utilities from children with the remaining 32 studies using utilities published in the literature. The authors noted that since NICE suggested investigators use the HUI-2 to obtain health utilities from children there has been no increase in use of this instrument, with many authors seeking to use the EuroQol EQ-5D or its derivatives. Adlard et al. recommended that research funding be targeted at those studies seeking to estimate health utilities directly from children, given a lack of published data specific to this age group and wide variation in the methods used to obtain these data in previous work.

In contrast to the reviews cited, this review examined the methods used by researchers and health economists to estimate health utilities for children and adolescents and the extent of the variation between them. Details of all methods administered in each study were collated to evaluate the suitability of each system given the age of study participants, mode of completion and the stated justification for use of each calculation method.

## **METHODS**

### **CONDUCTING THE REVIEW**

#### **ELIGIBILITY CRITERIA**

Studies eligible for inclusion in the final review needed to include primary data to measure health utilities from patients aged 17 years or under, through the administration of at least one direct or indirect method completed by either the patients or their proxies. Studies that included adult patients were not excluded, but studies that gathered HRQoL data exclusively from adults were excluded. We did not exclude studies based on language of publication, date of publication, journal or disease.

Studies that used other methods to calculate HRQoL scores that are incapable of generating utilities without a further mapping process were excluded unless the study also used a method to calculate health utilities.

Eligibility was not restricted to CUAs using primary data for HRQoL; studies detailing the validation of methods and studies that calculated health utilities for specified conditions but stopped short of collecting data related to healthcare resource use and patient-borne costs to calculate a cost-per-QALY ratio were eligible for inclusion.

Studies using health utilities gathered from previous studies were excluded, as were reviews, comment pieces and conference abstracts. All studies included in the full-text review had their references checked for additional studies to include in the review that did not were found through the online database search.

#### **INFORMATION SOURCES**

We searched for articles in the following databases: CAB Abstracts, Global Health, Ovid MEDLINE(R), Econlit and Embase Classic+Embase.

#### **SEARCH**

The search terms were taken from a systematic review published in 2005 by Griebisch et al. [32], appraising published CUAs in child and adolescent health care and looking at further issues still in doubt within the measurement of HRQoL in children and adolescents:

1. Infant, newborn/

2. Infant/
3. Child, preschool/
4. Child/
5. Adolescent/
6. 1 or 2 or 3 or 4 or 5
7. *expand* quality-adjusted life years/
8. cost-utility or cost utility
9. cost-effectiveness or cost effectiveness
10. 7 and 9
11. 8 or 10
12. 11 and 6

The search was performed on 30<sup>th</sup> September 2014.

#### DATA ITEMS

The following data were extracted from papers included in the full-text review:

1. Reference
2. Year of publication
3. Country
4. Direct or indirect calculation method(s) used
5. Health condition (if applicable)
6. Sample size
7. Age range of participants
8. Mode of assessment:
9. Self-completion of questions



10. Completion of questions via proxy (parents, clinicians, primary caregivers, etc.)

- a. Patient interviews
- b. Interviews with proxies (parents, clinicians, primary caregivers, etc.)
- c. Other methods
- d. Methods not stated

11. Study type:

- a. Validation of calculation method
- b. CUA
- c. Health utility assessment
- d. Comparison of calculation methods

12. Investigation of infectious disease HRQoL impact

We classified each study as one of four study types by the primary aim of each study: validations of calculation methods sought to validate or derive an instrument for estimating health utilities; CUAs first estimated health utilities then used these utilities in an economic evaluation; health utility assessments measured the burden of disease in individuals using health utilities; and comparisons of calculation methods used two or more instruments to measure health utilities then compared results.

In addition, each paper was analysed to ascertain whether or not the method(s) used had been justified for use in the cohort, along with the acknowledgment of any data collection issues that were related to the participants' understanding of the calculation method.

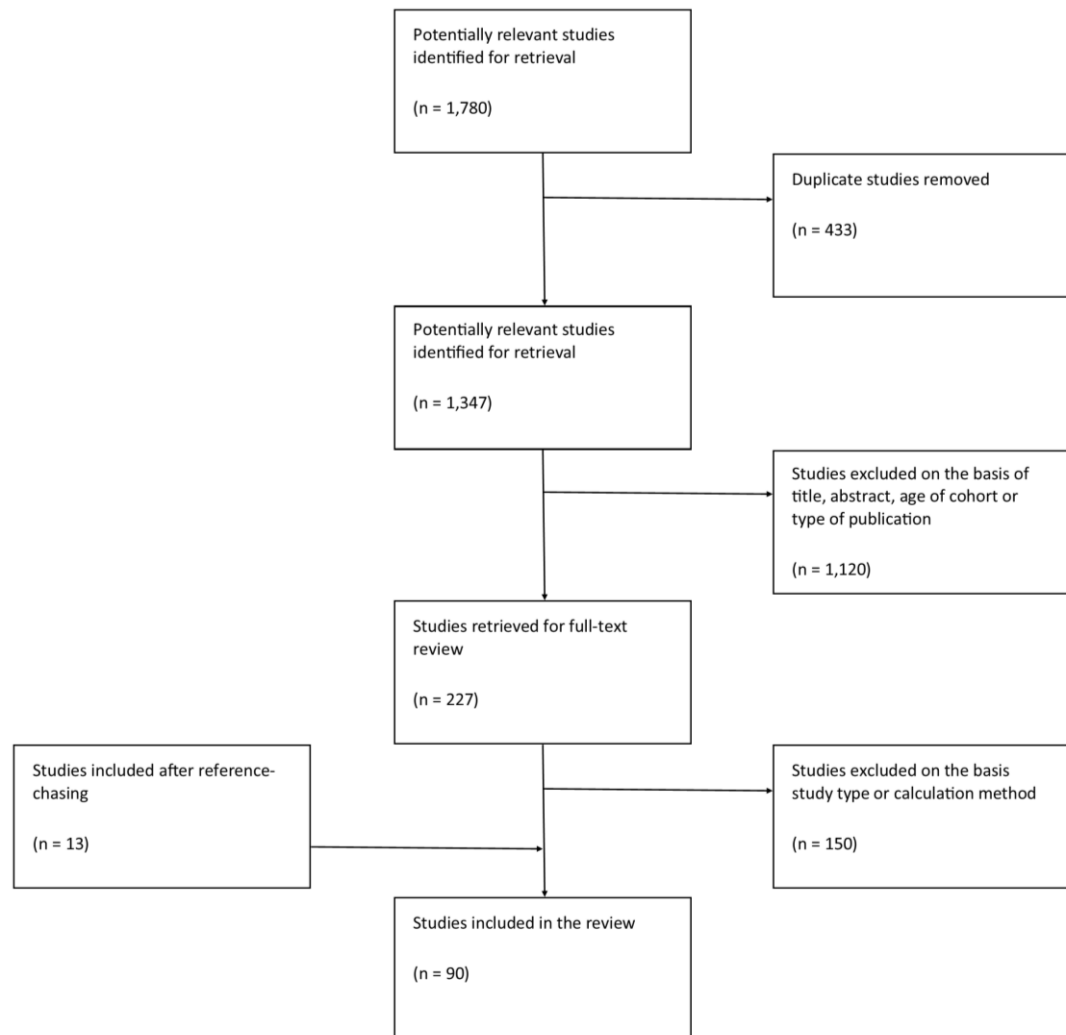
## **RESULTS**

### **STUDY SELECTION**

#### **INCLUSION AND EXCLUSION OF STUDIES**

Study selection: 1,780 studies were retrieved from an online database search and were imported into an EndNote X7 library. 433 studies were removed from the list as duplicates. The remaining 1,347 studies underwent a title, abstract and type of publication review to exclude studies that did not meet the inclusion criteria. The remaining 227 studies were submitted for a full-text review. 150 studies were excluded from the full-text review as they did not use direct or indirect methods to gather

primary data for HRQoL in children and adolescents, whilst an additional 13 studies were found in the list of references. In total, 90 studies were included in the review (Figure 3.1).



*Figure 3.1 - Identification of studies of measuring HRQoL in children and adolescents*

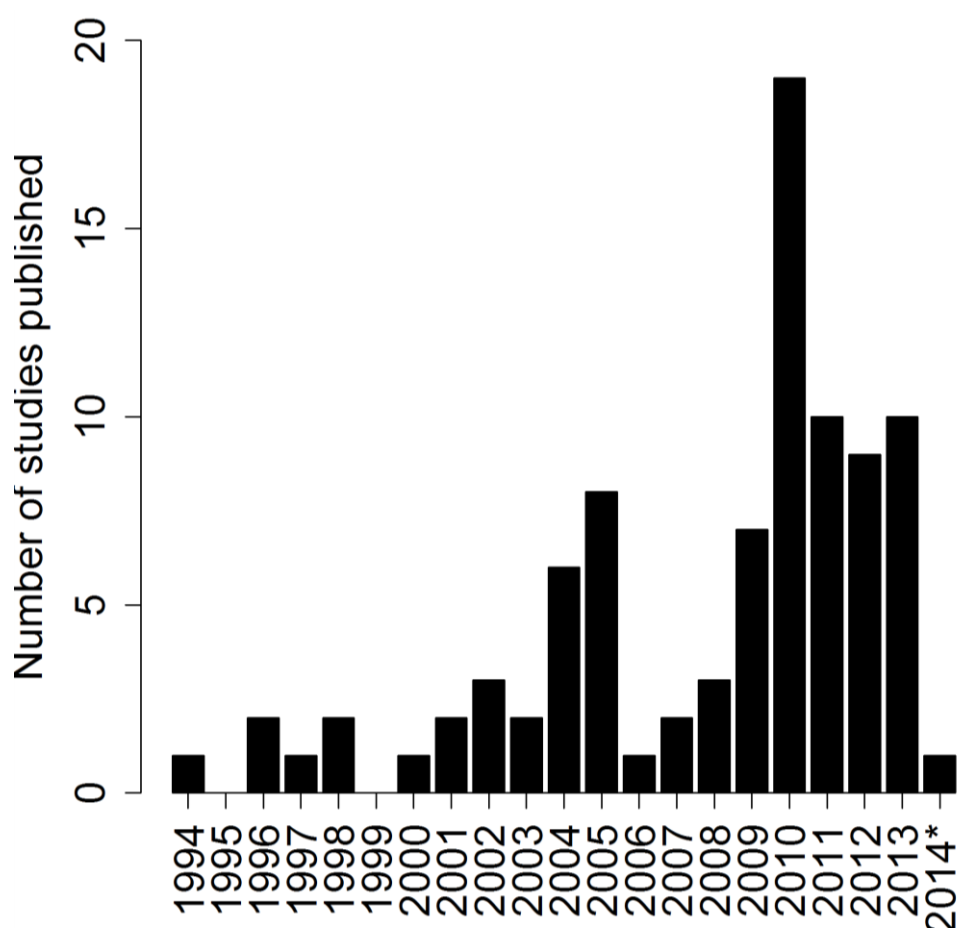


Figure 3.2 - Year of publication for studies included in the review

The earliest publication date for a study included in the review was 1994 (Figure 3.2). Since then the publication of measurements of health utilities in children and adolescents has steadily increased. The year with the most publications was 2010.

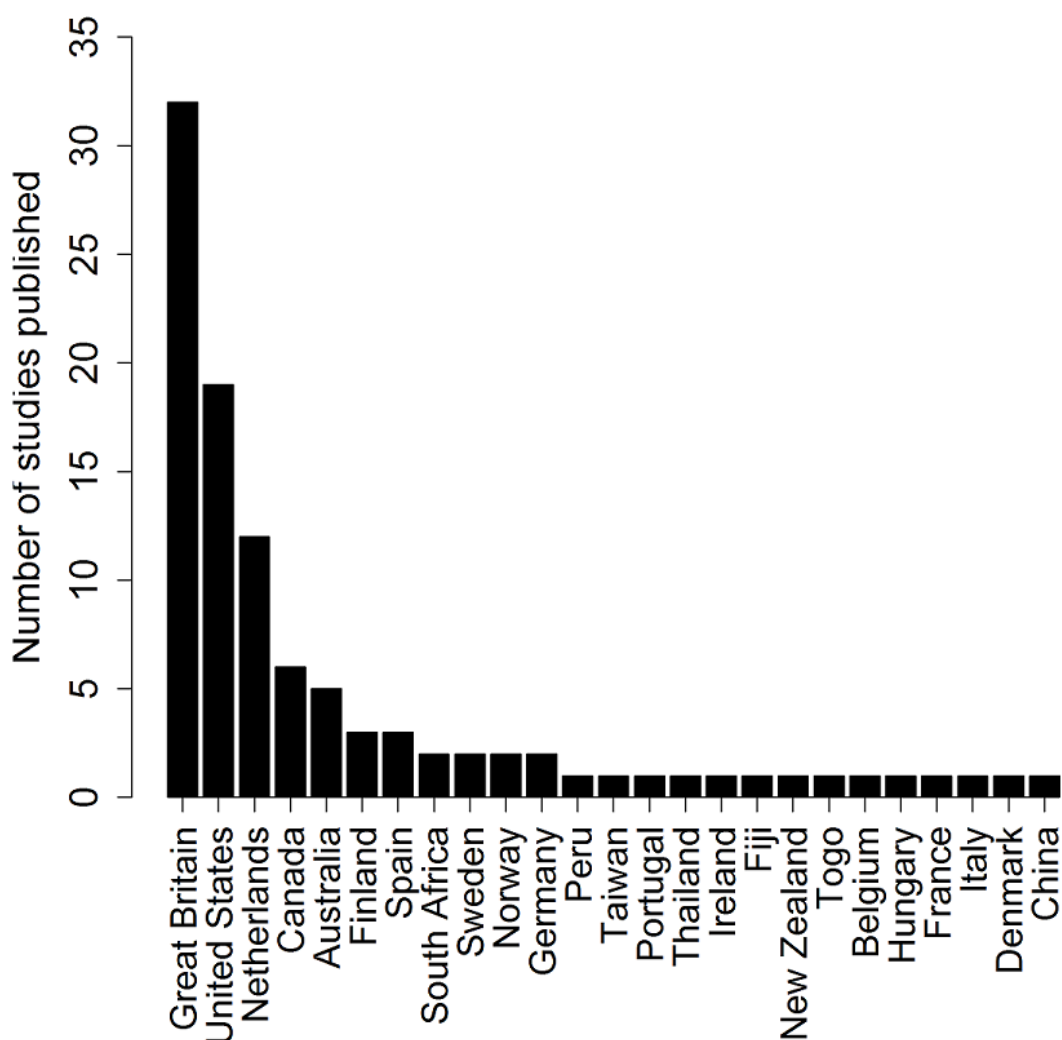


Figure 3.3 - Countries featured in studies using direct or indirect calculation methods for obtaining health utilities from paediatric patients

25 different countries were featured in the studies included in the review (Figure 3.3). The UK was featured the most. Three studies included multiple countries [40-42].

#### STUDY CHARACTERISTICS

##### TYPE OF STUDY

47 studies (52.2% of 90) were CUAs of which 21 [43-63] (44.7% of 47) were incorporated into randomised controlled trials for interventions. 23 [40, 41, 64-84] studies (25.6% of 90) were health-state utility assessments. Eight [20, 85-91] studies (8.9% of 90) were validations of calculation methods. The remaining 12 [63, 92-102] studies (13.3% of 90) were comparisons of calculation methods. 11 studies (12.2% of 90) had secondary aims of either comparing calculation methods (seven studies [63, 70, 72, 76, 78, 85, 89]) or providing health-state utility assessments (four studies [20, 42, 94, 103]).

#### CALCULATION METHODS USED

Family of calculation method	Number of methods in family	Frequency of use
Direct Calculation	3	32
EuroQol	3	52
Health Utilities Index	2	26
Short Form	3	8
Other	11	19
	<b>22</b>	<b>137</b>

*Table 3.2 - Frequency of use for calculation methods found during the review*

The 90 studies used 22 unique calculation methods to gather health utilities, with the total frequency of use in all studies being 137. 7 calculation methods were disease-specific and were used 11 times (8.0% of 137) in all. The 15 generic calculation methods were used 126 times (92.0% of 137). The EuroQol collection of indirect calculation methods was the most widely used, accounting for 38.0% of the total frequency of use (Table 3.2). The EQ-5D was used 41 times with its derivatives the EQ-5D-Y (used 10 times) and EQ-5D+ (a modification of the EQ-5D to include an additional dimension for cognitive functioning, used once) used separately. Direct calculation methods were also common, used 24.4% of the time. The stand-alone Visual Analogue Scale (VAS) was used 14 times, with the direct calculation methods of the SG and TTO each used nine times. The Health Utilities Index collection of indirect calculation methods was used 26 times (Table 3.3).

11 studies did not specify the age range of all participants. Four of these studies stated the mean age of participants; one study used a hypothetical cohort of child and adolescent patients but did not specify any demographic details of this hypothetical cohort; three did not give any details of the ages at all but the title and/or study details refer to child and adolescent patients; the three remaining studies indicated in aggregated results tables that some children and adolescents participated without elaboration of demographic details.

The number of participants varied from small studies of six children and adolescents [104] to studies sampling from large national databases of patients that included 84,443 patients of all ages [66] in their evaluation.

35 studies gathered health utilities exclusively from child and adolescent patients. 48 studies administered the calculation methods to adults whilst the remaining seven studies did not specify the age range of patients or did not present enough detail about the age range to determine the overall age of the cohort. 10 studies did not specify how the calculation methods were completed.

Abbreviation	Methods of obtaining utilities	Generic or disease-specific	Freq. of use
15D	15D Instrument [105]	Generic	1
ACQ	Asthma Control Questionnaire [106]	Disease specific	3
AQoL-6D	Assessment of Quality of Life 6D [107]	Generic	1
CAVE	Escala de calidad de vida del niño con epilepsia [108]	Disease specific	1
CHU-9D	Child Health Utility 9D [109]	Generic	3
EQ-5D	EuroQol 5D [110]	Generic	41
EQ-5D+	Expanded EuroQol 5D	Disease specific	1
EQ-5D-Y	EuroQol 5D Youth Version [111]	Generic	10
HALex	Health and Activities Limitation Index [112]	Generic	1
HUI-2	Health Utilities Index 2 [113]	Generic	10
HUI-3	Health Utilities Index 3 [113]	Generic	16
Mini AQLQ	Mini Asthma Quality of Life Questionnaire [114]	Disease specific	2
PAHOM	Pediatric Asthma Health Outcome Measure [20]	Disease specific	2
PAQLQ	Paediatric Asthma Quality of Life Questionnaire [115]	Disease specific	1
QLQ-C30	EORTC Quality of Life Questionnaire-Core 30 [116]	Disease specific	1
QWB	Quality of Well Being [117]	Generic	3
SF-12	Short Form 12 [118]	Generic	2
SF-36	Short Form 36 [119]	Generic	4
SF-6D	Short Form 6D [120]	Generic	2
SG	Standard Gamble [121]	Generic	9
TTO	Time Trade Off [122]	Generic	9
VAS	Visual Analogue Scale [123]	Generic	14

*Table 3.3 - Direct and indirect calculation methods to obtain health utilities from the paediatric population*

#### **ANALYSIS OF THE USE OF DIFFERENT CALCULATION METHODS**

##### **MEASUREMENT BY PROXY**

54 studies administered calculation methods directly to children and adolescents in line with previous recommendations that they are able to evaluate their own health states [9-12], although 22 of these also used at least one method of proxy completion for at least one of the calculation methods. Of these 22 studies, 16 used parental proxies; four used clinician proxies; and three used caregiver proxies.

26 studies used proxies exclusively, with 17 using parental proxies, six using clinician proxies and five other proxies. One study used a combination of different proxies to obtain health utilities.

Some studies commented on the use of proxies to obtain health utilities: Cheng et al. (2000) [124] acknowledged that proxy reporting may overestimate health utility gains for cochlear implants; Chiou et al. (2005) [20] discussed issues around the use of parental proxies in their study, stating that parental preference for health may be different from child preferences; Jelsma & Ramma (2010) [98] recommended the use of self-reporting rather than proxy-reporting, acknowledging the potential issues with proxy-reporting; Oostenbrink et al. (2002) [101] stated that health utilities for CUAs should be measured from patients rather than proxies, as proxies may have difficulty evaluating the impact

of conditions on dimensions of health such as pain and emotion; Tilford et al. (2005) [80] called for more research to be conducted on calculation methods for young child when discussing the issues surrounding the use of proxies; Tilford et al. (2012) [103] cite the use of proxies as a limitation in their study; Wasserman et al. (2005) [83] acknowledged a potential discrepancy between patient- and proxy-reported health utilities in their study.

However, several other studies argued that proxy-reporting was appropriate: Bichey et al. (2002) [125] said that clinician-proxy was suitable due to the clinicians' familiarity with each case; Bodden et al. (2008) [43] referred to previous studies that used EQ-5D through proxies; Chadha et al. (2010) [94] stated that their results showed no difference between self- and proxy-reported utilities; Friedman et al. (2004) [65] claimed that parental-proxy is consistent in evaluating HRQoL for children with atopic dermatitis; Gerald et al. (2012) [89] claimed that clinician-proxy reporting of health utilities is the gold standard; Hollman et al. (2013) [68] referred to previous studies to justify their use of proxy-reporting; Matza et al. (2005) [72] claimed that SG methods through parental-proxies are a suitable method for obtaining health utilities from children; Petrou & Kupek (2009) [74] claimed that there is no consistent evidence that parental- or caregiver-proxies either over-estimate or under-estimate health utilities for their children; Poley et al. (2001) [126] cite previous studies to support the use of proxies. van Litsenburg et al. (2013) stated that the HUI-3 calculation method is a parental-proxy method by design [82].

#### USE OF CHILD- OR ADOLESCENT-SPECIFIC CALCULATION METHODS

Six calculation methods found in this review were designed specifically for use in the child and/or adolescent population (Table 3.4). The number of health dimensions included ranges from three to nine. Three methods are disease-specific with two focusing on asthma and one focusing on epilepsy. The remaining three methods are generic systems.

Some studies discussed the short-comings of the calculation methods used. For example, Canaway et al. (2012), Oluboyede et al. (2011) and Wu et al. (2010) all discussed the lack of an appropriate tariff for the EQ-5D-Y [84, 93, 100], acknowledging that existing utilities have been taken from the adult-specific EQ-5D, finally stating that the current EQ-5D-Y is not yet complete without the child-focused tariff. Thorrington et al. (2014) also commented on the lack of a child-specific tariff for the EQ-5D-Y [79]. It has previously been noted by Kromm et al. (2012) [15] that slow progress is being made in developing age-specific utility weights.

Abbreviation	Name of calculation method	Dimensions of health	Studies found using this method
AQoL-6D	Assessment of quality of life (adolescent version)	Independent living Relationship Mental health Coping Pain Senses	[69]
CAVE	Escala de calidad de vida del niño con epilepsia	Behaviour School compliance Learning Autonomy Social relations Frequency of seizures Intensity of seizures Parents opinions	[127]
CHU-9D	Child health utility, 9 dimensions	Worried Sad Pain Tired Annoyed School work Sleep Daily routine Joining with activities	[90, 91, 93]
EQ-5D-Y	EuroQol 5 dimensions, youth version	Mobility Self-care Usual activities Pain or discomfort Worried, sad or unhappy	[64, 79, 81, 84, 87, 93, 95, 97, 98, 100]
PAQLQ	Paediatric asthma quality of life questionnaire	Symptoms Activity limitations Emotional function	[67]
PAHOM	Pediatric asthma health outcome measure	Symptoms Emotion Activity	[20, 89]

*Table 3.4 - List of child- and/or adolescent-specific calculation methods used*

Many other studies opted to administer calculation methods designed for a wide range of ages, such as the HUI-2 or the HUI-3. In addition, the EQ-5D system (originally designed for use in adults) was used 41 times, with the child-specific EQ-5D-Y version used only 10 times. Few studies adopting this approach discussed the suitability of their methods by evaluating the number of missing values for each returned calculation method. Hollmann et al. (2013) [68], Jelsma (2010) [97], Radford et al. (2013) [54], Thorrington et al. (2014) [79] Tilford et al. (2012) [103] and Wyatt et al. (2012) [63] all present data for missing or incomplete responses for their respective calculation methods, but only Jelsma (2010) [97] and Thorrington et al. (2014) [79] discuss these data with respect to the age of the respondents.



11 studies obtained HRQoL to assess the impact of infectious diseases or complications arising from infectious diseases [50, 60, 64, 68, 70, 79, 81, 94, 101, 128-130]. A list of these studies and their calculation methods is presented in Table 3.5. Methods for measuring the temporary deterioration in HRQoL were not consistent within the studies. For example, four studies focused on either H1N1 influenza or measles but gathered their data using different methods: Baguelin et al. [64] and van Hoek et al. [81] administered the EQ-5D (and derivatives) for the worst day of influenza infection then two weeks later for a baseline HRQoL reading. Thorrington et al. [79] used a similar methodology to estimate the impact of measles infection, but collected data points three weeks apart rather than two. Authors for all three studies assumed that HRQoL and duration are directly correlated both before and after the worst day of infection. In contrast, Hollman et al. [68] measured HRQoL during infection and assumed the drop from baseline was constant throughout infection.

Reference	Condition	Calculation method(s) used
Baguelin et al. (2010)	H1N1 Influenza	EQ-5D EQ-5D-Y
Chadha et al. (2010)	Juvenile-onset recurrent respiratory papillomatosis	HUI-3 VAS
Hollman et al. (2013)	H1N1 Influenza	EQ-5D
Lee et al. (2005)	Pertussis	TTO
Oh et al. (1996)	Acute otitis media	VAS
Oostenbrink et al. (2002)	Permanent sequelae after bacterial meningitis	EQ-5D HUI-2 HUI-3
Petrou et al. (2010)	Otitis media with effusion	HUI-2 HUI-3 EQ-5D
Prosser et al. (2004)	Pneumococcal infection	TTO
Thorrington et al. (2014)	Measles	EQ-5D EQ-5D-Y EQ-5D proxy
van Hoek et al. (2011)	H1N1 Influenza	EQ-5D EQ-5D-Y
Williamson et al. (2009)	Persistent otitis media	HUI-2 HUI-3 EQ-5D

*Table 3.5 - Health-state calculation methods used to gather HRQoL data for the impact of infectious diseases*

## DISCUSSION

### SUMMARY OF EVIDENCE

There is extensive variation in the methods used to estimate health utilities from children and adolescents. Issues that were raised by Kromm et al. (2012) and Griebisch et al. (2005) relating to the

need for a standardised method to collect health utilities from children and adolescents are yet to be fully resolved. Though this review found 22 different calculation methods that have been used between 1994 and 2013, many adult-specific methods have been used with children and adolescents without justification. Although several child- and adolescent-specific methods are currently in development, some existing adult-specific systems have been modified in order to fill the current gap.

#### **CURRENT CHILD- AND ADOLESCENT-SPECIFIC CALCULATION METHODS**

This review found six calculation methods designed for use in children and adolescents of which the most frequently used was the EQ-5D-Y, used 10 times. Another 16 methods either designed for a wide range of ages or designed specifically for use in adults but applied to younger patients. Development and use of child- and adolescent-specific methods is steadily increasing, though several issues of suitability still surround these methods. For example, this review found that the EQ-5D-Y has been used ten times even though the EQ-5D-Y does not differentiate between adult and child or adolescent preferences for health. Several authors acknowledge this discrepancy with some calling for further research and development of child- and adolescent-specific calculation methods. At the time of writing, EuroQol has not explored child-specific utility weights that use children's preference for health states for use in the EQ-5D-Y [111].

#### **USE OF PROXY RESPONDENTS**

Justification for the use of proxy respondents was mixed, and there is no consensus for the advisability of proxy-reporting in obtaining health utilities from children and adolescents. Several studies stated that proxy-reporting may differ from self-reporting in their studies, but others claimed that their use of proxy-reporting was justified by citing previous CUAs or health utility measurements. Some studies in this review did not discuss the use of proxy-reporting vs. self-reporting and how their results may have been influenced by proxy reporting from different sources.

The use of proxies has been justified because of lack of verbal capacity of the children being evaluated [18]. Nevertheless responses should be elicited directly from those children being evaluated when verbal capacity is not a barrier [33].

#### **USING MULTIPLE CALCULATION METHODS AND RESPONDENTS**

Only four studies compared self- and proxy- reported health utilities. Chadha et al. 2010 [94] found no difference between utilities. Gerald et al. (2012) [89] reported that PAHOM scores for parental proxies were significantly lower than self-reported scores from children. Jelsma & Ramma (2010) [98] found agreement with the EQ-5D-Y scores. Lock et al. (2010) [48] presented the mean and range of estimated utilities but did not perform a statistical test to verify that self-reported scores were different to proxy-reported scores.

## **MISSING DATA**

Discussions of missing data are essential in any study. In the case of the EQ-5D, a missing response to any of the five dimensions of health means that the response cannot be converted into a health utility. Analysis of missing responses would be helpful in deducing which aspects of measuring HRQoL in children and adolescents are particularly difficult and in developing new systems to minimise missing data in responses.

## **RELIANCE ON ADULT-SPECIFIC CALCULATION METHODS**

Perhaps because the EQ-5D-Y still needs an appropriate tariff for children and adolescents, some authors continue to use an adult-specific method for children and adolescents in preference to a method under development for the appropriate age group. The first use of the EQ-5D-Y in this review was in 2009 [95], and since then 18 studies have used the standard EQ-5D system in children and adolescents or patients outside of the appropriate age range for the system [42, 46, 49, 52-57, 61, 62, 68, 71, 74, 85, 92, 131, 132].

## **INFECTIOUS DISEASES**

Few studies gathered HRQoL data to assess the impact of infectious disease. 11 studies administered a mixture of different generic calculation methods for only 8 conditions. HRQoL with respect to infectious disease is still a developing field of research, especially in the child and adolescent populations. Methods to measure deterioration in HRQoL due to infectious disease were inconsistent, even when different studies measured the impact of the same condition.

## **LIMITATIONS OF THIS REVIEW**

This review only concerned published literature, which may be a source of bias as the gray literature was not considered. However, Griebisch et al. (2005) [32] argued that by not including unpublished works, they avoided reducing the overall quality of studies included in their review.

It was the decision of the authors that focused the qualitative assessment on the use and justification of different calculation methods to measure HRQoL in children and adolescents. There are several other ways to assess the quality of a CUA, notably the PQAQ [36] and the checklist for economic analysis outlined by Drummond et al. (2005) [133]. However, we have not sought to assess the quality of each CUA in the review but instead to evaluate the use of each direct or indirect calculation method in addition to understanding the justification for different methods of eliciting health utilities from children and adolescents.

## CONCLUSIONS

Many authors examining child and adolescent HRQoL have relied on tools developed exclusively for adults. Further development of child- and adolescent-specific calculation methods is required to ensure that CUAs using health utilities of children and adolescents are valid, without relying on the assumption that adults, children and adolescents all have the same health preferences.

Previous studies measuring HRQoL in children and adolescents have relied on proxy respondents without sufficient justification for their use. There is considerable debate in the literature about whether proxies can be used (and if so, which proxies). No clear consensus was found in the literature from this.

Several calculation methods are in development that will facilitate the measurement of QALYs in children. These systems are needed by health economists as the application of adult-specific systems is of questionable validity. Adults, children and adolescents measure HRQoL, perceive and value health differently, so the assumption that adult-specific health utilities are valid in adolescents or young children is potentially misleading.

Measuring children's health states is extremely challenging and requires a suitable instrument for the estimation of paediatric health utilities that NICE can recommend for use to ensure the validity of future child- and adolescent-focused CUAs.

## FUNDING

This work was funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

## ACKNOWLEDGEMENTS

We would like to thank colleagues at both the London School of Hygiene & Tropical Medicine for discussions on the manuscript. In particular, we would like to thank John Cairns for his help.

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## **Chapter 4 - The social and economic impact of school influenza outbreaks in England**

Portions of this chapter were submitted to The Journal of School Health in October 2015 (accepted, in press).

### **ABSTRACT**

#### **BACKGROUND**

Seasonal influenza is a cause of considerable morbidity in England, particularly among young children. 39% of all influenza-attributable GP consultations and 37% of all influenza-attributable hospital admissions occur in those aged under 15 years. The impact of influenza outbreaks has been studied at population level but fewer studies have quantified the impact on families whose children become infected with influenza.

#### **OBJECTIVE**

Here we sought to assess this impact in England during the 2012-13 and 2013-14 influenza seasons.

#### **METHODS AND FINDINGS**

We used paper-based and online questionnaires to obtain data from parents of children in three primary schools that reported an outbreak of an influenza-like-illness (ILI). We sought data on the impact of illness in terms of loss of productivity, costs borne by families and loss in health-related quality of life. Influenza-like-illnesses were identified using the reported symptoms and the symptoms criteria from both the European Centre for Disease Prevention and Control and the UK Flusurvey.

For children with ILI, the mean absence from school was 3.8 days (95% CI: 3.0 – 4.8) with mean total time off work for all caregivers reported as 3.7 days (95% CI: 2.7 – 4.8). The mean loss in health-related quality of life was 2.1 quality-adjusted life days (95% CI: 1.5 – 2.7), compared to 2.92 QALDs for H1N1v influenza. The estimated total paediatric burden of disease for all reported school-based outbreaks during the two influenza seasons was 105.3 QALYs (95% CI: 77.7 – 139.0).

#### **CONCLUSION**

This study shows the potential social and economic benefit of vaccination of children during mild influenza seasons.

## **INTRODUCTION**

### **BACKGROUND**

Influenza epidemics are associated with a substantial socio-economic impact in terms of direct and indirect costs [1, 2], loss of productivity in the workplace, health-related quality of life and illness [3].

Seasonal influenza can cause a significant health burden in the United Kingdom. It is estimated that approximately 10% of all respiratory admissions and deaths can be attributed to influenza. The highest admission rates for both influenza A and B strains are in children under five years of age and the highest influenza-attributed deaths rates occur in the group of elderly patients with co-morbidities [4].

In England, seasonal influenza is estimated to account for over one million GP consultations per year and a large proportion of this burden comes from children aged under 15 years. 39% of all influenza-attributable GP consultations and 37% of all influenza-attributable hospital admissions occur in this age group. Estimated annual hospital mortality from influenza in this age group is low at 1.3 per million but school-age children still account for a substantial proportion of the full burden of seasonal influenza [4].

School children play an important role in the spread of influenza in the community [5-7]. The 2009 H1N1 pandemic emphasised the importance of public health policies that tackle transmission within children and the school-age population [8] and the pandemic has since generated debate about the appropriate response to future outbreaks with respect to children and schools. Suggested interventions range from school-based initiatives that restrict contacts between children within schools [9] and school closures [10] to new vaccination strategies that target school-age children [11, 12].

Infectious disease outbreaks in schools will have both a health-related and an economic impact in the community. The health-related impact concerns the illness suffered by school children and any subsequent spreading of infection in the wider community [4]. The costs will include loss of earnings for those families where a parent or guardian must stay at home to supervise their children, along with the cost of medicines, etc. [1, 2]. Indirect costs may include the travel costs for friends and family members who help by supervising children who cannot attend school.

This impact will be felt by families who must adjust their working and social schedules to stay at home with children either too ill to attend school or those sent home due to a reactive closure [13]. In order to assess the benefits of potential interventions for these outbreaks first the impact of such outbreaks must be quantified.

Including societal costs into an analysis to evaluate the cost-effectiveness of an intervention can be difficult as these costs can be difficult to obtain. Because of this, cost-effectiveness analyses may be restricted to including only direct costs (e.g. the cost of medical intervention to the healthcare provider) without considering the costs and impact on families, or the analyses may use estimates for childcare costs, loss of productivity, etc. from other data sources.

QALY-loss assessment associated with infectious disease outbreaks can be examined by employing HRQoL measures aimed at patients infected [3]. The measure recommended by NICE is the EuroQol EQ-5D-3L [14]. This questionnaire has also been used in children to examine their health and inform cost-utility analyses for interventions [3, 15, 16] but QALYs and health utilities relating to infectious disease outbreaks in children barely feature in the published literature, as this is a developing field of research [17]. As a result from this, it is difficult to evaluate the cost-effectiveness of interventions for infectious disease outbreaks in children as the direct impact on the children's quality of life is not understood.

The previous chapter discussed the issues surrounding the accurate estimation of health utilities from children and adolescents – the extensive variation in methods and instruments available has led to authors and analysts using many different instruments, several of which may not be suitable or justified for use in the population at hand.

#### PARENTAL ATTITUDES TO ANNUAL INFLUENZA VACCINATION

The Joint Committee on Vaccination and Immunisation (JCVI) in 2012 recommended extending the influenza vaccination programme to all children between the ages of 2-16 years [12]. Parents' or guardians' knowledge of the recommendation from the JCVI for influenza are not understood. These attitudes may impact on the uptake of the offered vaccination programme, subsequently affecting regional preparedness for outbreaks in schools and communities.

Surveys mailed to families with children attending elementary schools in 2001 were used by Nettleman et al. [18] to report that vaccine non-acceptance was low (13% of 954 responses) and a higher acceptance rate among parents or guardians of children whose child had been absent from school with a winter respiratory illness than those children not absent (33% vs. 24%,  $p < 0.01$ ). In addition, parents or guardians required to miss work due to childcare responsibilities were more likely to accept a vaccine for a winter respiratory illness than those parents who were able to work during their child's illness (35% vs. 25%,  $p < 0.01$ ).

Understanding the potential heterogeneity in the uptake of the offered vaccinations will help the healthcare authorities evaluate the cost-effectiveness of the proposed programme. Factors determining vaccine acceptance will help public health officials in designing programmes to improve vaccine uptake in low-coverage areas.

## **EPIDEMIOLOGY OF SEASONAL INFLUENZA IN 2012-13 AND 2013-14**

The influenza season of 2012-13 saw prolonged influenza activity in GP practices and hospitals [19]. 460 acute outbreaks were reported in schools (36%), care homes (52%), hospitals (9%) and other settings (3%). Where data were available the majority of school outbreaks were attributable to influenza B. 112 acute outbreaks were reported in care homes (49%), hospitals (39%), schools (9%) and other settings (3%) during the influenza season of 2013-14 [20]. Influenza A (H1N1)pdm09 was the dominant circulating virus in 2013-14 [21].

### **RESEARCH QUESTIONS**

1. What was the impact of illness at home caused by an ILI outbreak in a child's school in terms of disruption due to childcare, cost and HRQoL?
2. How would parents and guardians arrange childcare in the event of a school closure for potential future outbreaks?
3. What is the willingness-to-pay threshold for parents and guardians paying for childcare provided by a third party?
4. What would be the likely uptake of an annual influenza vaccination offered to children? For what reasons might parents or guardians decline the offer of a vaccination offered to their children?

### **METHODS**

The study was a population-based retrospective survey taking place in primary schools in three geographically distinct areas of England during the influenza seasons of 2012-13 and 2013-14: the South (excluding London), the Midlands and the North West.

#### **IDENTIFICATION AND RECRUITMENT OF SCHOOLS**

A local health protection team (HPT) in England received notification from a school of an outbreak. If the Head Teacher agreed their contact details were passed to the researchers at LSHTM so that a full discussion of the study could take place at a later time. The local HPT acted as facilitator by sending the contact details to LSHTM. These details were collected in a pro forma then sent to LSHTM via email.

The LSHTM researchers contacted the Head Teacher to invite them to participate in the study. A sample questionnaire was sent to the Head Teacher and full details of the study aims, protocol and proposed outcomes, along with the plans for distribution of the online questionnaires were discussed.

If the school agreed to participate in the study then LSHTM sent the links to the online questionnaires to the school within one week of the notification or paper questionnaires in sealed blank envelopes along with stamped-addressed envelopes for return to LSHTM. The links consisted of a questionnaire for each child at the school in addition to a letter addressed to the parents or guardians of the children explaining the details of the study and what they needed to do if they wish to take part.

#### **HPT INVOLVEMENT AND RESPONSIBILITIES**

Existing working relationships between Public Health England, especially local HPTs and schools in England helped facilitate participation of schools in this study. Because QALYs should be gathered as quickly as possible during an outbreak it was essential that the study packs were sent to the school soon after the notification of an outbreak.

FES and HPT involvement in this study was essential to recruit sufficient schools. Once a school notified the HPT of the outbreak and expressed an interest in participating then the management of the schools involvement was the responsibility of LSHTM who invited the school to participate before sending the links, collecting the responses and analysing the data.

Further details of the responsibilities of the FES and local HPTs were agreed in discussions with PHEC Influenza Leads.

#### **INCLUSION CRITERIA**

Inclusion criteria analysis:

- Notification from HPT of an influenza-like-illness (ILI) outbreak affecting a school

#### **EXCLUSION CRITERIA**

- Notification of an outbreak of ILI in a special needs education establishment
- Patients identified as not suitable for recruitment; recent mortality in the family, inclusion in previous studies from PHE; other reasons identified by the HPT or school

#### **DISTRIBUTION AND COLLECTION OF QUESTIONNAIRES**

Head teachers were offered a choice of paper-based or online questionnaires. Paper-based questionnaires were posted in a batch to the school each with a letter explain more about the study; instructions for completing the questions; contact details of the lead investigators; and a self-addressed envelope to return the questionnaire to the lead investigators. School staff distributed one questionnaire to each child at the school.



Online questionnaires took the form of a Google Form linked to a Google Docs spreadsheet. Schools that requested the use of online questionnaires emailed the link to all parents and guardians of children in the school.

All responses to both forms of the questionnaire were anonymous.

#### **FINANCIAL INCENTIVES**

No financial incentives were given.

#### **LANGUAGES**

The questionnaires were written in English.

#### **DATA MANAGEMENT**

The final data files (as a csv file) were stored as a Google Sheet accessible only to Dominic Thorrington, the primary investigator based in LSHTM. The Google Doc spreadsheet was downloaded to a secure network drive for analysis once data collection has ceased. Only the investigators based in LSHTM had access to this file.

Online questionnaires took the form of a Google Form linked to a Google Sheet. Schools that requested the use of online questionnaires emailed the link to all parents and guardians of children in the school.

All responses to both forms of the questionnaire were anonymous.

#### **THE FORM OF THE QUESTIONNAIRES**

Paper-based and online questionnaires were used to gather data from parents and guardians of children attending schools that had reported an outbreak of suspected influenza to their local Health Protection Team during that influenza season. The paper-based and online questions were identical and are available from the authors on request.

Questionnaires were offered to all parents and guardians, whether or not their children were ill during the outbreak. We sought information about parents' attitudes towards childhood influenza vaccination; likely childcare arrangements in the case of a future school closure; and, for those parents whose children were ill during the outbreak, information about the children's symptoms and the impact of the episode on the family.

Copies of the questionnaires are available in the Appendix.

## IMPACT OF ILLNESS

We asked parents and guardians of children who were sick during the recent outbreak at their school to complete a section on their child's illness. ILI was separated from other potential illness by asking parents or guardians to indicate the symptoms experienced during illness from a list provided from Flusurvey. ILI was identified according to the definition from the European Centre for Disease Prevention and Control [22], specifically:

- The sudden onset of symptoms
- And at least one of the following four systemic symptoms:
  - Fever
  - Malaise (chills, feeling tired)
  - Headache
  - Myalgia (muscle or joint pain)
- And at least one of the following three respiratory symptoms:
  - Cough
  - Sore throat
  - Shortness of breath

We asked about the duration of perceived symptoms; absence from school; and contacts with the health services during infection. Further data were requested on any childcare arrangements made during the child's illness as well as an estimate of additional costs to the child's primary caregivers and others who helped with childcare.

We asked parents and guardians to complete a EuroQol EQ-5D assessment [23] on both the worst day of the child's infection and then another on the date of completion of the questionnaire, to establish the loss of HRQoL. The version of the EQ-5D used for primary schools was the proxy version [24], to be completed on behalf of the child. The EQ-5D was chosen because it is the instrument of choice for Public Health England for use in outbreak investigations. Results from Chapter 3 indicate that it has been used extensively in the paediatric population and in particular in estimating the impact of pandemic influenza. To calculate the impact of infection in terms of QALYs we adopted the approach taken by van Hoek et al. (2011) [3] when estimating the impact of the 2009 H1N1 pandemic in England. 95% confidence intervals of the mean loss of HRQoL were based on 1,000 bootstrap replications.

Parents and guardians were asked what childcare arrangements they would make if the school were closed for a future influenza outbreak for a period of one day, one week and one month and whether it would affect a normal working schedule to organise this childcare; a measure of potential disruption for each possible school closure through a 0-10 Likert scale [25, 26] (0 corresponding to “not disruptive” and 10 for “very disruptive”); whether the child was considered old enough to look after themselves at home; and how much parents and guardians would be willing to pay for childcare per day.

Parents and guardians were asked if they would accept an annual influenza vaccination for their children. Those parents and guardians who indicated that they would accept the vaccination were asked where they would prefer the vaccination to be administered: the child’s school; the child’s GP practice; or no preference. Those parents that would refuse the vaccination were asked to indicate why they would choose to do so using a list of reasons for vaccine denial from the UK Flusurvey [27].

#### **ETHICAL APPROVAL**

Ethical approval was obtained from the ethics committee at the London School of Hygiene & Tropical Medicine in addition to approval from the Public Health England Research and Development office. PHE has ethical approval to investigate the impact of an infectious disease outbreak in a community setting, including QALY data along with details of absence from school and work. However, PHE did not have such approval to collect data on the financial burden suffered by families affected by the outbreak.

#### **ANALYSIS OF DATA**

Data were analysed using R version 3.0.2 [28].

#### **QUESTIONNAIRES USED IN THE STUDY**

1. For children
  - i) HRQoL for those directly affected by the outbreak
  - ii) Children attending secondary schools received the EQ-5D-Y. Children attending primary schools received the EQ-5D proxy version.
2. For adults
  - i) Response to a hypothetical school closure to all parents or guardians of children where an outbreak has occurred

- ii) Knowledge and attitudes to the recommended changes to the annual influenza vaccination programme to offer the vaccine to children attending schools and preschools
- iii) Economic burden of the outbreak for those directly affected through their children's illness

#### **DELIVERY METHOD AND FOLLOW-UP**

Online questionnaires were sent by LSHTM to the schools within a few days of the notification to the local HPT, with paper-based questionnaires sent to the school in bulk within one week from LSHTM. Head Teachers emailed the links to parents or guardians at their convenience and paper-based questionnaires were distributed to school children via their classroom teachers. Patient consent was implied through the return of a completed questionnaire.

Parents or guardians who did not respond to the questionnaire were not followed-up. Schools that chose not to participate in the study were not followed-up. Schools that experienced a low rate of return for the questionnaires were not followed-up.

#### **COSTS**

Pre-paid postage envelopes were already available to the LSHTM researchers as existing stock from a previous study, therefore no costs were incurred in the administration of the study.

### **RESULTS**

#### **DEMOGRAPHICS AND EMPLOYMENT**

##### **DEMOGRAPHICS**

Three schools participated in our study – one in south east England after a reported outbreak in February 2013 and two in North West England after reported outbreaks in January 2014. All three schools were state-run primary schools. 87 responses were received, of which 85 were paper-based questionnaires and 2 were questionnaires completed online. Table 4.1 displays the response rate for each school and the gender breakdown of the respondents. 85.1% of respondents belonged to a two-parent family.

	<b>Response rate (total distributed)</b>	<b>Male respondents</b>
School 1	26.3% (n=99)	46.2%
School 2	12.8% (n=204)	46.2%
School 3	14.6% (n=240)	62.9%
Overall	16.0% (n=543)	52.9%

*Table 4.1 - Response rate and gender breakdown for participating schools*

## EMPLOYMENT

74 questionnaires (85.1%) were completed by two-parent families and 13 (14.9%) by single parent families. Of the 160 adults identified as parents or guardians in the survey, 78 were in full-time employment (48.8%) (Table 4.2). Comparing our sample to the UK labour market statistics [29] we determined that those individuals unemployed or retired are overrepresented and students are underrepresented.

Employment category	Adults in the survey	UK labour market statistics [29]	
Full-time employment	78 (48.8%)	52.5%	p = 0.3472
Part-time, shift or casual employment	33 (20.6%)	19.0%	p = 0.6031
Self-employed	25 (15.6%)	12.1%	p = 0.1738
Unemployed	18 (11.3%)	6.5%	p = 0.0139
Retired	11 (6.9%)	3.6%	p = 0.0251
Student	4 (2.5%)	6.3%	p = 0.0477

*Table 4.2 - Employment breakdown of adults identified in the survey*

## ILLNESS

### REPORTED ILLNESS AND SYMPTOMS

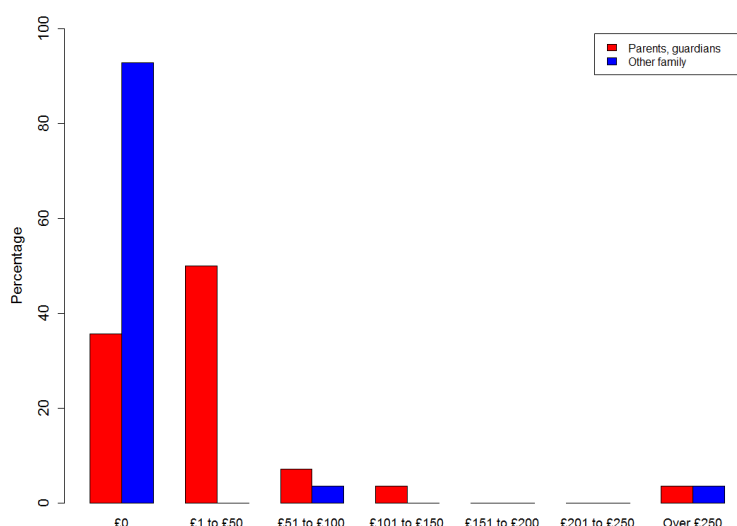
43 (49.4%) parents or guardians reported that their child was absent from school with illness during the outbreak period at their child's school. 34 of these children (79.1%) reported symptoms consistent with the ECDC case definition of ILI (Table 4.3).

Reported symptoms for children reporting illness	All children (n = 43)	Children with symptoms consistent with ILI (n = 34)
Fever	33 (76.7%)	28 (82.4%)
Chills	20 (46.5%)	19 (55.9%)
Feeling tired or exhausted	33 (76.7%)	29 (85.3%)
Headache	24 (55.8%)	21 (61.8%)
Myalgia	12 (27.9%)	11 (32.4%)
Cough	29 (67.4%)	27 (79.4%)
Sore throat	27 (62.8%)	25 (73.6%)
Shortness of breath	5 (11.6%)	5 (14.7%)

*Table 4.3 - Reported symptoms for those children who reported illness during an outbreak of suspected ILI at their primary school*

Five individuals with symptoms not consistent with ILI met the ECDC case definition of acute respiratory infection (ARI) [22] (i.e. at least from the list of cough, sore throat, shortness of breath, and coryza). Three individuals with symptoms not consistent with ILI had fever but no additional ILI-specific symptoms, and the remaining individual reported tiredness with vomiting.

## COSTS



*Figure 4.1 - Costs attributable to ILI outbreak in schools for those families reporting their child had symptoms consistent with ILI*

For costs incurred by the parents or guardians of a child with symptoms consistent with ILI, 10 respondents (35.7%) reported no additional costs due to their child's illness; 14 (50.0%) reported spending up to £50 during their child's period of illness; two respondents (7.1%) spent up to £100; one (3.6%) spent up to £150; and one (3.6%) spent over £250. For costs incurred by other family members 26 respondents (92.9%) reported no additional costs, one (3.6%) reported costs up to £100 and one reported costs over £250 (Figure 4.1).

## HEALTH-RELATED QUALITY OF LIFE

The overall health-related quality of life loss associated with infection consistent with ILI was 0.006 QALYs per individual (95% CI: 0.004 – 0.008) or 2.1 QALDs per individual (95% CI: 1.5 – 2.7) (Table 4.4). The mean duration of perceived symptoms consistent with ILI was 5.3 days (95% CI: 4.4 – 6.3). The EQ-5D proxy questionnaires had no blank responses except for one individual who did not complete the VAS scores for both the worst day and background measurements.

Children with symptoms consistent with ILI were absent from school for a mean duration of 3.8 days (95% CI: 3.0 – 4.8). During this time they were looked after by a mean of 1.7 caregivers (95% CI: 1.4 – 2.0) who were absent from work for a total time of 3.7 days (95% CI: 2.7 – 4.8). Only one respondent sought professional childcare, employing two child minders. All other respondents organised childcare between parents and other family members

Using the Wilcoxon test we found no evidence that the health-related quality of life loss metrics differed between those individuals with symptoms consistent with ILI and those individuals with

symptoms not consistent with ILI except for strong evidence for a difference between the background VAS scores ( $W = 71.5$ ,  $p = 0.0181$ ).

	<b>Symptoms consistent with ILI (n = 34)</b>	<b>Symptoms not consistent with ILI (n = 9)</b>	<b>Wilcoxon Test Statistics</b>
Mean duration of perceived symptoms (95% CI)	5.3 days (4.4 – 6.3)	5.0 days (2.8 – 7.2)	$W = 174.5$ , $p = 0.5283$
Mean duration of absence from school (95% CI)	3.8 days (3.0 – 4.8)	3.8 days (3.0 – 4.8)	$W = 96.5$ , $p = 0.6885$
Mean number of caregivers used during absence (95% CI)	1.7 (1.4 – 2.0)	1.7 (1.3 – 2.1)	$W = 60.0$ , $p = 0.1347$
Mean total time off work for all caregivers (95% CI)	3.7 (2.7 – 4.8)	3.7 (2.8 – 4.8)	$W = 88.5$ , $p = 0.9658$
Mean VAS score, worst day (95% CI)	39 (31 – 45)	54 (33 – 74)	$W = 107.0$ , $p = 0.2071$
Mean VAS score, background (95% CI)	88 (81 – 94)	98 (97 – 100)	$W = 71.5$ , $p = 0.0181$
Mean EQ-5D score, worst day (95% CI)	0.2 (0.02 – 0.3)	0.3 (0.1 – 0.6)	$W = 111.5$ , $p = 0.2205$
Mean EQ-5D score, background (95% CI)	0.9 (0.8 – 1.0)	1.00 (1.00 – 1.00)	$W = 139.5$ , $p = 0.3796$
Mean QALY loss (95% CI)	0.006 (0.004 – 0.008)	0.006 (0.002 – 0.009)	$W = 174.0$ , $p = 0.5405$
Mean QALD loss (95% CI)	2.1 (1.5 – 2.7)	2.0 (0.8 – 3.5)	$W = 174.0$ , $p = 0.5405$

*Table 4.4 - Health-related quality of life scores reported for both individuals with symptoms consistent with ILI and those with other symptoms. 95% confidence intervals of the mean are based on 1,000 bootstrap replications*

#### ESTIMATED TOTAL PAEDIATRIC BURDEN OF DISEASE IN QALYS

Public Health England reported 165 acute influenza outbreaks occurring in schools during the 2012-13 season and 10 in 2013-14 [19, 20]. Assuming that the estimated ILI attack rate from this sample (34/87 respondents, 39.1%) is representative of the attack rate from the reported 175 school-based outbreaks of the two influenza seasons and that the mean number of pupils in a state-funded primary school is 263 [30], the estimated total paediatric burden of disease for transmission in those primary schools reporting suspected ILI outbreaks during the two influenza seasons was 105.3 QALYs (95% CI: 77.7 – 139.0) or 38,309 QALDs (95% CI: 28,165 – 49,844).

#### SOCIAL IMPACT OF INFLUENZA OUTBREAKS

##### HEALTHCARE SERVICE CONTACT

13 (38.2%) parents or guardians of children reporting symptoms consistent with ILI visited their GP. 4 (11.8%) spoke to a GP surgery receptionist over the telephone, 3 (8.8%) telephoned NHS Direct, 2 (5.9%) spoke to a GP over the telephone and 1 (2.9%) used another unspecified NHS service. No

parents or guardians reported visiting Accident and Emergency departments with their child due to symptoms consistent with ILI.

#### CHILDCARE OPTIONS AVAILABLE FOR HYPOTHETICAL SCHOOL CLOSURES

The preferred option for childcare during hypothetical school closures was for a parent to stay at home. 82.1% of respondents preferred this option for a one day closure, decreasing to 60.5% in the event of a month long closure (Figure 4.2). The preferred alternative option for childcare for all three scenarios was another family member, selected 56.9%, 58.2% and 43.5% of the time for one day, one week and one month closures.

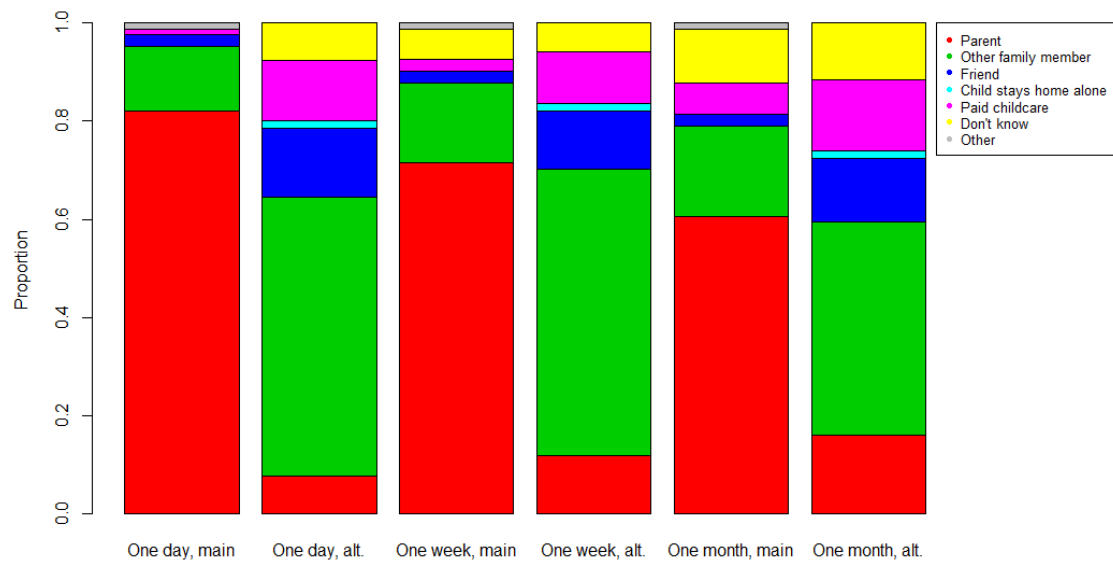


Figure 4.2 - Preferred main and alternative options for childcare for three school closure scenarios

49.3% of parents or guardians indicated that someone would have to take time off work for their main option for childcare for a one day school closure, with 47.8% for a one week closure and 46.4% for a one month closure. 96.4% of respondents thought that their child was not old enough to be alone at home; the remaining children able to be alone at home were all 11 years old.

A potential future one day closure had a mean score of 3.4 (95% CI: 2.7 – 4.2) on the 10-point Likert scale for perceived disruption. Potential future week-long and month-long closures had mean scores of 6.1 (95% CI: 5.3 – 6.9) and 7.7 (95% CI: 6.8 – 8.3) respectively.

#### WILLINGNESS-TO-PAY FOR CHILDCARE

Families with one parent or guardian were prepared to pay a mean of £21.43 per day of childcare per child if their child's school was closed at short notice. For families with two parents or guardians the mean was £36.92 per day of childcare per child (Figure 4.3). Using the Wilcoxon test there is good evidence of a difference in the willingness-to-pay for childcare based on the number of parents or guardians at home ( $W = 81$ ,  $p = 0.01$ ).



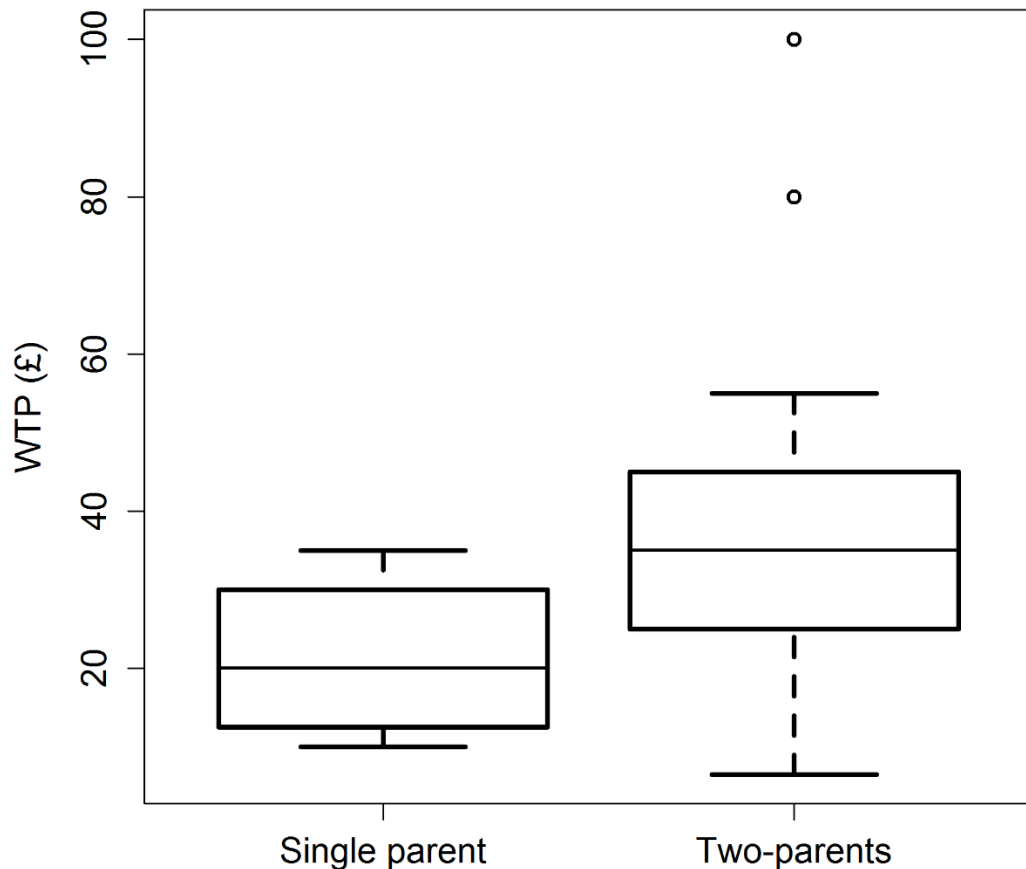


Figure 4.3 - Willingness-to-pay for one day of childcare for one child for single parents and two-parent families

#### VACCINATIONS

71 (81.6%) of parents or guardians stated that they would accept the offer of an annual influenza vaccine for their children. Of those answering the question about the location of vaccine administration, receiving the vaccine at their local GP surgery was the preferred option with 28 (40.6%) responses. 14 (20.3%) preferred to have the vaccine administered at their child's school and 27 (39.1%) stated no preference between the two options.

88.2% of parents or guardians whose child had symptoms consistent with ILI expressed a preference that their child received annual influenza vaccinations. The three most common reasons given by those expressing a preference for their children not to be given influenza vaccination for all parents or guardians were a preference for building natural immunity (78.6%), safety fears over the new vaccine (42.9%) and a belief that their child was unlikely to get influenza (28.6%).

## **DISCUSSION**

### **RESPONSE RATE**

We have used both paper-based and online questionnaires to examine the impact on families of ILI outbreaks in schools, with responses recorded during the 2012-13 and 2013-14 influenza seasons in England. Our response rate was typical of postal surveys [31].

### **ILLNESS AND HEALTH-RELATED QUALITY OF LIFE**

For those children with symptoms consistent with ILI, their illness did not have a large financial impact on families. 35.7% of respondents reported no additional costs to themselves and 92.9% reporting no additional costs for others; mainly because parents and family were the preferred carers. The main socio-economic impact of influenza in schools is seen in the total loss of productivity due to illness: the mean absence from school was 3.8 days (95% CI: 3.0 – 4.8) with mean total time off work for all caregivers reported as 3.7 days (95% CI: 2.7 – 4.8). Therefore the total loss of productivity per child with symptoms consistent with ILI was approximately 7.5 days off both work and school. McCann et al. (2014) [32] investigated three outbreaks of laboratory-confirmed influenza B in schools in the Thames Valley during the 2012-13 influenza season and reported that the mean length of absence from each school was 3.5 days, 2.6 days and 2.8 days respectively, similar to our findings.

The mean duration of perceived symptoms was 5.3 days (95% CI: 4.4 – 6.3) and mean loss of HRQoL was 2.1 QALDs per individual (95% CI: 1.5 – 2.7), both smaller than the estimates provided for H1N1v influenza (8.8 days duration and a loss of 2.92 QALDs [3]). For comparison with other diseases, the mean loss of HRQoL for measles was 6.90 QALDs [33] and 0.99 QALDs for natural varicella [34]. Seasonal influenza has a greater impact on HRQoL in children than varicella, though less than H1N1v pandemic influenza and measles.

### **COSTS INCURRED BY FAMILIES**

35.7% of parents and guardians of children with symptoms consistent with ILI reported that their child's illness did not result in additional financial costs on the family. 50% of parents and guardians of children with symptoms consistent with ILI reported spending up to £50 on out-of-pocket expenses with few parents or guardians reporting greater expense. 92.9% of other family members reported no additional costs due to the child's illness. These figures suggest that two-thirds of families affected by seasonal childhood influenza in primary schools experience a small economic burden in terms of out-of-pocket expenses, and that this burden usually does not extend to the wider family.

## **EQ-5D COMPLETION RATE**

The EQ-5D proxy questionnaires had no blank responses except for one individual who did not complete the visual analogue scale scores for both the worst day and background measurements. This is a very high completion rate for the EQ-5D health-state classification system as other studies have reported several respondents having difficulty in completing all aspects of the system [33], which in turn reduces the size of the cohort used to calculate the impact in HRQoL.

## **ESTIMATE OF THE TOTAL PAEDIATRIC BURDEN OF DISEASE**

Our estimate of the total paediatric burden of disease in primary schools reporting suspected ILI outbreaks for the two influenza seasons of 105.3 QALYs (95% CI: 77.7 – 139.0) was much lower than the 22,267 discounted QALYs reported for total burden of disease during the H1N1v pandemic influenza in England [3]. We used the number of schools reporting a suspected acute influenza outbreak but the total number of such outbreaks in schools is unknown. We assumed a conservative overall attack rate of 39.1% from our sample in comparison to a mean attack rate of 53.0% from McCann et al. (2014) [32]. Also, we only considered the impact of infection associated with school transmission by excluding the potential secondary transmission of ILI to household members, which is likely to have occurred as previous studies have indicated [35, 36].

## **HEALTHCARE SERVICE CONTACT AND INTENTION TO VACCINATE**

The proportion of parents or guardians taking their child to their local GP (38.2%) was much higher than estimates provided by Flusurvey (10.0%) [27]. With a mean cost per GP appointment of £45 [37] this result would increase the cost of healthcare resource use in economic evaluations of strategies to manage both seasonal and pandemic influenza.

Potential vaccination uptake for the annual influenza vaccination could be high in primary schools with 81.6% of parents or guardians willing to consent to vaccination for their children. This figure is much higher than the mean uptake of 52.5% seen in the 2013-14 pilot programme [21], which may be indicative of response bias for this question – parents or guardians will be asked to consent to the annual influenza vaccination long before the majority of influenza transmission occurs. When compared to vaccination uptake for a long-running seasonal influenza vaccination programme in the United States, 39.4% of parents or guardians responding to a survey on attitudes to vaccination for seasonal influenza reported that they vaccinated their children each year, with another 28.2% said their children were vaccinated sometimes [38].

Policy makers should note the reasons for vaccine refusal and address the attitudes of parents and guardians, particularly the commonly-held belief that acquiring immunity through influenza infection is a viable and positive alternative to vaccination (78.6%). Nearly half (42.9%) of vaccine refusers cited

vaccine safety fears as a reasons for potentially refusing an annual influenza vaccine for their child, in contrast to just 17.0% of non-NHS workers indicating in 2009 that they would refuse their own seasonal influenza vaccination [39]. Further work on communicating vaccine safety and efficacy to the parents and guardians of those children eligible for seasonal influenza vaccination is required, though correcting myths held by vaccine-hesitant individuals about the seasonal influenza vaccination is known to be difficult, as tackling such misconceptions about the vaccine can be counter-productive if the intention is to increase the intention to vaccinate [40].

## **LIMITATIONS**

### **SMALL SAMPLE SIZE**

This study was conducted over two influenza seasons of mild severity compared to many previous seasons. In conjunction with mainly paper-based questionnaires with no incentive for completion offered to the parents or guardians it means the sample size is smaller than other published analyses using surveys in schools with ILI outbreaks. Head teachers of schools were recruited via the health protection teams, so we do not know how many were offered participation or declined.

It should also be noted that the study was conducted over a period of substantial managerial reorganisation in Public Health England, which may have impact on staff time to recruit schools to the study. However, even with a small number of schools participating in the study, we have conducted an important and novel study that describes the social and economic impact of influenza outbreaks in schools from the perspective of families affected.

### **GENERALISING RESULTS TO WIDER COMMUNITY-BASED TRANSMISSION**

We sought to estimate the impact of influenza outbreaks in schools and to understand parental attitudes to seasonal influenza vaccination, but our study was conducted only within the context of a school-based outbreak rather than with wider community-based transmission occurring. The potential for sustained background transmission without large school-based outbreaks is not an unrealistic scenario, and in such a scenario it is possible that parents or guardians of children attending schools would not be as likely to obtain seasonal influenza for their children if they perceive the risk of infection to be low. Our results can therefore only be generalised to scenarios with community-based transmission that also includes school-based outbreaks that would come to the attention of parents and guardians.

### **SAMPLE REPRESENTATIVENESS AND SEVERITY BIAS**

In our sample the unemployed and retired individuals were overrepresented and students were underrepresented when compared to UK labour market statistics for the same period. This is likely to have biased our results for the willingness-to-pay for childcare and for the costs incurred during a child's infection.

Nearly half of the responses to our questionnaires came from parents or guardians of children reporting illness during the outbreak period in their child's school, but it is possible that the parents or guardians of the children with the most severe illness returned their questionnaires, introducing a potential severity bias to our study that we could not control for.

#### NO LABORATORY TESTING OF SUSPECTED INFLUENZA CASES

We did not confirm influenza infection using laboratory testing. The study would have been improved with the presence of this testing but in its absence we are confident that we have correctly identified ILI infection using the same list of symptoms as the UK Flusurvey and in turn from the ECDC.

#### UNSUCCESSFUL IMPLEMENTATION ON ONLINE QUESTIONNAIRES

Our study used data from 87 questionnaires of which only two were returned online. The process of printing, packaging and sending paper-based questionnaires was time consuming so we had hoped that more schools would request online questionnaire distribution only. In addition, the distribution of paper-based questionnaires along with the data entry process once paper-based questionnaires were returned to LSHTM meant that a study using online questionnaires exclusively would be a more attractive proposition for researchers, schools and research subjects alike. If the study were to be taken forward in future years with increased influenza activity then the protocol would be improved by moving all data collection to online survey tools.

The poor online questionnaire response rate for our study may have been because of the combination of a hyperlink shortening service redirecting internet traffic across their server to our Google Forms survey tool. In order to allow head teachers to send a short hyperlink in an email to parents and guardians we used a service that shortens hyperlinks from the standard hyperlink provided by Google Forms (approximately 100 characters) to a shorter length of approximately 20 characters. The service may have triggered in-browser anti-virus software that prompted users to check whether they wanted to be redirected to a hyperlink with a very different address, which may have discouraged some users attempting to complete the questions online.

After noticing a low response rate for online questionnaires we distributed the shortened hyperlink to colleagues at LSHTM who anecdotally reported the activation of their in-browser anti-virus software after clicking the hyperlink sent via email.

#### MEASURING COSTS

Costs incurred due to a child's ILI infection were discretely grouped. Indicating costs using discrete groups was judged to be easier than requiring parents or guardians to list all individual costs incurred during ILI infection. Due to time delays in sending paper-based questionnaires to schools we thought that itemised costs would have been too difficult to report and therefore the exercise would be subject to substantial recall bias.

The grouped cost data obtained during the study showed that the majority of parents and guardians did not incur many out-of-pocket expenses due to their child's ILI infection. This result is important as it can be used for economic analyses of different measures to mitigate seasonal influenza epidemics conducted from the societal perspective and may avoid overestimating the total costs incurred. However, for those parents and guardians that did incur such costs during infection, the lack of description about different potential costs meant it may have been difficult to estimate the total costs incurred.

Rapid distribution of online questionnaires to the parents and guardians affected by a suspected ILI outbreak in their child's school would reduce the potential for recall bias when reporting costs incurred. Additional information provided to parents and guardians to help them consider all potential costs would reduce the risk that they do not include all potential costs.

#### INTENTION TO VACCINATE VS. SUCCESSFUL VACCINATION

81.6% of parents and guardians expressed a preference for their child to receive an annual influenza vaccination in our study. However, uptake of the seasonal influenza vaccination was considerably lower than this, with Pebody et al. (2014) reporting 52.5% uptake in a pilot of seven discrete geographical areas in England during the 2013-14 influenza season [21].

There is a distinction between those parents and guardians who would look favourably on an annual influenza vaccination for their child and those parents and guardians who consent to the administration of such a vaccine to their child. There may be many different reasons why those previously in favour of influenza vaccination do not subsequently consent to vaccine uptake, but the parents and guardians that do not vaccinate their child after previously expressing an interest to do so do not fall into the recognised category of "vaccine hesitant" caregivers.

Understanding the reasons why parents or guardians have previously expressed their desire to vaccinate their child but ultimately failed to do so could be used to increase vaccination uptake in those parents and guardians not consenting to vaccination but who're also not vaccine hesitant. If the difference between the 81.6% preference for vaccination reported in our study and the 52.5% uptake reported in the seasonal influenza vaccination pilots is due to more than just responder bias in our study then this would be a worthwhile study to pursue.

#### INTERPRETATION FOR SCHOOLS

The impact of ILI outbreaks in primary schools is mainly seen in the total loss of productivity due to illness. We did not find a large financial impact, but ILI infection contracted in school will have a socio-economic impact at home. In the event of a suspected ILI outbreak occurring at a primary school, staff should contact their local Public Health England centre for advice on mitigating the outbreak to minimise this impact.

At the time of writing, a children's influenza vaccine is available for primary school children in school years 1 and 2 which will offer direct protection to those children vaccinated as well as indirect protection for their family, carers and the wider population. Parents and guardians of children in these school years should be made aware of the benefits of annual influenza vaccination for their children.

## FUNDING

This work was funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

## ACKNOWLEDGEMENTS

We would like to thank colleagues at both the London School of Hygiene & Tropical Medicine and Public Health England for their help in setting up this study. We would particularly like to thank the parents, guardians and teachers at each of the schools that took part in the study.

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## **Chapter 5 - Modelling seasonal influenza vaccination programmes, part I: targeted vaccination at a national level**

Portions of this section were published in *Vaccine* in August 2015 [1], tabled at the meeting of the Joint Committee on Vaccination and Immunisation on 3<sup>rd</sup> June 2015 [2] and presented at the Epidemics 5 conference in Tampa, FL USA in December 2015. © 2015 Elsevier Ltd.

### **ABSTRACT**

#### **BACKGROUND**

The UK commenced an extension to the seasonal influenza vaccination policy in autumn 2014 that will eventually see all healthy children between the ages of 2-16 years offered annual influenza vaccination. Models suggest that the new policy will be both highly effective at reducing the burden of influenza as well as cost-effective.

#### **OBJECTIVE**

We explore whether targeting vaccination at either primary or secondary schools would be more effective and/or cost-effective than the current strategy.

#### **METHODS AND FINDINGS**

An age-structured deterministic transmission dynamic SEIR-type mathematical model was used to simulate a national influenza outbreak in England. Costs including GP consultations, hospitalisations due to influenza and vaccinations were compared to potential gains in quality-adjusted life years achieved through vaccinating healthy children. Costs and benefits of the new JCVI vaccination policy were estimated over a single season, and compared to the hypothesised new policies of targeted and heterogeneous vaccination. All potential vaccination policies were highly cost-effective. Influenza transmission can be eliminated for a particular season by vaccinating both primary and secondary school children, but not by vaccinating only one group. The most cost-effective policy overall is heterogeneous vaccination coverage with 48% uptake in primary schools and 34% in secondary schools.

#### **CONCLUSION**

The Joint Committee on Vaccination and Immunisation can consider a modification to their policy of offering seasonal influenza vaccinations to all healthy children of ages 2 to 16 years.

## **INTRODUCTION**

The previous chapter details the investigation of the societal and economic impact of seasonal influenza infection as felt at home by those parents and guardians with children attending primary schools in England. The results from the investigation will be crucial to understanding the impact of influenza outbreaks on the community, providing an additional perspective on the far-reaching consequences of infectious disease outbreaks typically overlooked by cost-effectiveness analyses that use a more narrow perspective on overall benefits and costs.

However, preventative measures for influenza outbreaks take the form of nationwide vaccination programmes. In England, cost-effectiveness analyses for new vaccination programmes are conducted from the healthcare provider perspective. The national influenza vaccination programme in England was introduced in Chapter 2 and is discussed further in the following section. Here, we investigate options to modify the planned roll-out of the school-based vaccination programme by considering the optimal vaccination coverage for both primary and secondary school populations, from the perspective of the healthcare provider.

## **BACKGROUND**

### **THE UK SEASONAL INFLUENZA VACCINATION PROGRAMME**

The UK has had a long-standing seasonal influenza vaccination programme. Originally available to those in at-risk groups including those with underlying health conditions such as chronic heart disease, the programme was extended in 1998 to include people aged 75 years and over. Two years later it was extended again to include people aged 65 years and over. Pregnant women were included in 2010. Any proposed alterations to a national vaccination programme should be accompanied by a cost-effectiveness analysis using quality-adjusted life years (QALYs) as the measured benefit, according to guidelines written by both The National Institute for Health and Clinical Excellence (NICE) and the JCVI [3, 4]. A cost-effective vaccination policy would have a cost per QALY ratio less than £20,000 per QALY, from the perspective of the healthcare provider [3]. In 2013 Baguelin et al. (2013) reported that it would be cost-effective to offer vaccination to children in addition to the other groups currently offered the vaccine [5].

### **EXTENSION TO THE SEASONAL INFLUENZA VACCINATION PROGRAMME**

Subsequently, the Joint Committee on Vaccination and Immunisation (JCVI) in 2012 recommended extending the influenza vaccination programme to all children between the ages of 2-16 years [6]. This extension would see a live-attenuated influenza vaccination (LAIV) offered to children each year with the majority of vaccines administered in school settings, and would become the largest vaccination programme in the UK measured in terms of number of doses administered. The LAIV is

more effective than inactivated vaccines in children and adolescents and may also offer protection against drifted strains of influenza [7, 8].

Children and adolescents attending schools play a large role in the spread of influenza in the community [9-11]. Transmission within schools is maintained because of the high number of close contacts between school children [12], as well as less acquired immunity in children [13] and a longer period of virus-shedding once infected [14, 15]. Vaccinating children has the potential to reduce influenza episodes both in the vaccinated individuals, but also in individuals of all age groups who were not vaccinated, or who did not successfully seroconvert following vaccination. Several countries now offer annual influenza vaccination to healthy children as it has been repeatedly shown to be a cost-effective extension of existing national influenza vaccination programmes [16, 17].

Previous modelling analyses demonstrating the cost-effectiveness of vaccinating healthy children have consistently assumed that children in both primary schools (aged 4 – 11 years) and secondary schools (11 – 16 years) would be simultaneously vaccinated [18, 19]. For infectious diseases such as seasonal influenza, which has a low potential for transmission, it is possible to vaccinate a proportion of a population to eliminate the potential for sustained transmission (the threshold for “herd immunity” [20]). This threshold could be achieved with a successful vaccination policy implemented in only one of the two school groups. Indeed, the planned roll-out of the vaccination programme involves vaccinating the youngest children in primary schools (those aged 4-5 years) in autumn/winter 2014-15, with each successive influenza season seeing vaccination offered to successive age groups. With this plan, autumn/winter 2020-21 will be the first year that all primary school children are vaccinated against seasonal influenza. Therefore, if successful vaccination in this cohort is capable of stopping large nationwide outbreaks of seasonal influenza the subsequent vaccination of children in secondary schools may not be required.

This study aims to establish whether a programme of targeted vaccination in either primary or secondary schools would be more cost-effective than a programme stretching across both school groups, and whether it will be able to eliminate influenza transmission for that season. Given a range of coverage levels we also investigate how high coverage needs to be in order to maximise cost-effectiveness. For comparability, we have used epidemiological and economic parameters from previous influenza vaccination analyses to inform national immunisation [5, 21], but adopted a simpler model to highlight key results related to optimally targeting age groups for paediatric vaccination.

## RESEARCH QUESTIONS

1. Can the JCVI-recommended extension to the UK seasonal influenza vaccination programme be extended without homogenous vaccination between primary and secondary schools?

2. Would a targeted vaccination programme in either primary or secondary schools be cost-effective? Would a heterogeneous vaccination policy be cost-effective?

## METHODS

### THE AGE-STRUCTURED MODEL

This study uses a discrete time age-structured deterministic model with SEIR structure written in R version 3.0.2 using the tcltk2, mc2d, mgcv, MASS and lattice packages [22-27] to estimate the burden of disease. The model has age-structured compartments representing individuals susceptible to influenza infection (S), latently infected (E), infectious (I) and recovered (R). The model is linked to a decision tree model also written in R to determine the cost-effectiveness of each proposed vaccination policy in comparison to the old UK policy.

The SEIR framework has been modified to include classes of those vaccinated (V) as well as individuals assumed to have immunity from influenza due to exposure in previous seasons and therefore have associated antibodies in their immune systems (A). An individual in the model who has recovered from infection is assumed to have immunity from influenza for the remainder of the simulation (i.e. one influenza season). Persons successfully immunised also acquire immunity for the duration of the simulation but a fraction of those vaccinated were non-responders and remain susceptible [28]. All vaccination is assumed to take place at random within the targeted age groups before the annual influenza season commences when the first infection occurs.

$$\frac{dS_i}{dt} = -\lambda_i S_i$$

$$\frac{dE_i}{dt} = \lambda_i S_i - \gamma E_i$$

$$\frac{dI_i}{dt} = \gamma E_i - \delta I_i$$

$$\frac{dR_i}{dt} = \delta I_i$$

*Equation 5.1 - The SEIR-type age-structured transmission model*

$S_i$  represents the number of susceptible individuals in age group  $i$  in the population  $N$ ;  $E_i$  represents the number of exposed but not yet infectious individuals;  $I_i$  represents the number of infectious individuals and  $R_i$  represents the number of individuals whose period of infectiousness has ceased (either by recovery or death from infection).  $\gamma^{-1}$  is the time that an individual is exposed but not yet infectious and  $\delta^{-1}$  is the time that an individual is infectious.  $\lambda_i$  is the force of infection for age group  $i$ .

$$\lambda_i = \sum_j \frac{\beta_{ij} I_j}{N_j}$$

*Equation 5.2 - The age-dependent force of infection*

$\beta_{ij}$  is the matrix of the mean daily number of contacts between an individual of age group  $i$  with age group  $j$ .  $\sigma_i$  is the age-specific proportion of individuals in the S compartment who have not acquired immunity from clinical at-risk vaccination; from the new vaccination programme; or from previous influenza seasons.

Contact rates between age groups in the population can be critical for determining model outcomes [29]. In our model the population of England is divided into 5 age groups (0 – 3, 4 – 10, 11 – 16, 17 – 64 and 65+ years old) using 2011 mid-year estimates [30] (Table 5.1). Individuals have close contacts with others in the model according to the POLYMOD survey of contact frequency in Europe [12].

Age group	Total population [30]	At-risk population [21]	Vaccinated (baseline) [31]
0 – 3 years	2,680,335	138,573	71,504
4 – 10	4,221,738	218,264	112,624
11 – 16	3,771,682	194,996	100,618
17 – 64	33,703,747	1,742,484	899,122
65+	8,729,667	8,729,667	6,459,954

*Table 5.1 - Total population of England, at-risk population and the number of seasonal influenza vaccinations administered before new JCVI vaccination policy is implemented*

The mathematical model was informed with the age-dependent mixing patterns measured from the Great Britain arm of this eight-country survey in the form of a matrix of close contacts,  $\beta_{ij}$  (Figure 5.1).

A significant proportion of influenza infections are subclinical. The definition of clinical influenza is fever with one other influenza-related symptom [32]. Clinical influenza incidence was estimated as a proportion of total infections generated by the model, derived from a review of volunteer challenge studies that found that 35% of individuals with influenza had fever, thereby providing an estimate of clinical influenza cases from suspected influenza infections [33].

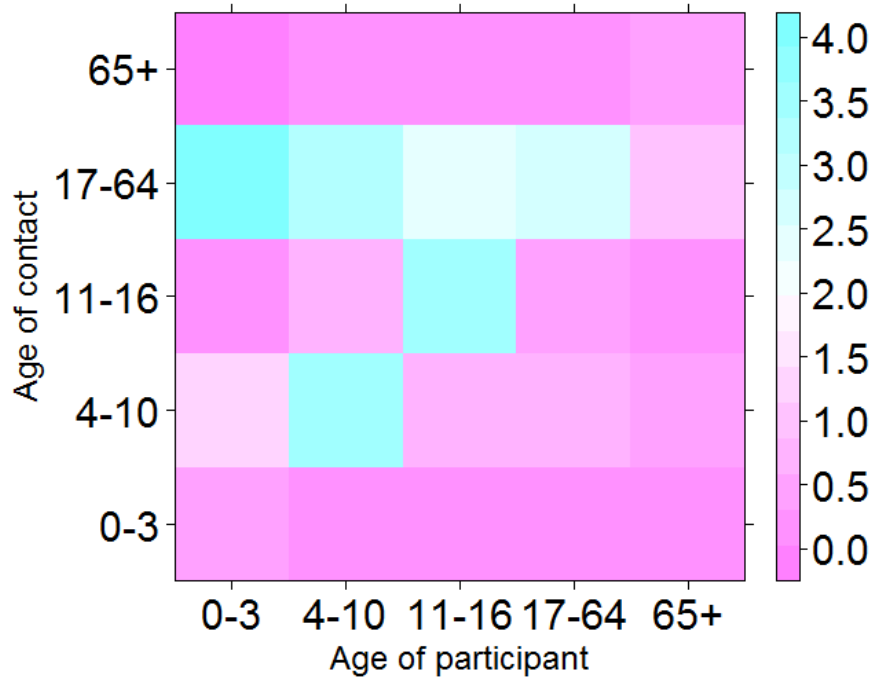


Figure 5.1 - Weighted social contact matrix from POLYMOD contact survey, showing the mean number of long-duration physical contacts per day for participants in Great Britain. The age group of participants and their contacts are shown on the axes.

#### MODEL CALIBRATION

The model was calibrated by fitting the incidence of clinical influenza to final size data of the 2006-07 influenza season in England to ensure our model produced results comparable to the model of Baguelin et al. (2012) used to inform England's original decision to vaccinate children [18]. Parameters for the proportion of each age group with prior immunity to influenza were estimated using Latin Hypercube sampling and binomial maximum likelihood estimation (Table 5.2). We drew 25,000 Latin Hypercube samples from uniform distributions over [0,1] for each of these parameters, and then selected those which minimised the binomial log-likelihood using the observed final size and the simulated final size for each age group.

Parameter	Value	Source
R <sub>0</sub> , initial reproduction number †	Triangular with min=1.30, max=1.59, mode=1.46	[18]
Vaccine efficacy †	70% (95% CI: 57 – 78) for 0 – 64 years 46% (95% CI: -17 – 75) for 65+ years	[28]
Latent period	1.46 days	[18]
Infectious period	1.28 days	[18]
Susceptible proportion of 0-3 group †	0.7837	Calibration exercise
Susceptible proportion of 4-10 group †	0.8943	Calibration exercise
Susceptible proportion of 11-16 group †	0.9819	Calibration exercise
Susceptible proportion of 17-64 group †	0.9496	Calibration exercise
Susceptible proportion of 65+ group †	0.9736	Calibration exercise

*Table 5.2 - Transmission model parameters*

In fitting the expected final size of ILI epidemics to the observed final size of the 2006-07 epidemics we sampled 25,000 sets of parameters for the age-specific proportion of susceptibles in the population using uniform Latin Hypercube sampling to cover the possible parameter space. Each of the 25,000 parameter sets was used in the model to estimate the expected final size in each age group. The parameter values used in the simulation of the model that minimised the binomial log-likelihood, defined below.

$$\ln \mathcal{L} = \sum_{i=1}^5 y_i \ln p_i + (n_i - y_i) \ln(1 - p_i)$$

*Equation 5.3 - The binomial log-likelihood minimised to estimate the age-specific proportion of individuals with previously acquired immunity*

$n_i$  represents the number of individuals in the population;  $y_i$  represents the observed final size of the 2006-07 epidemic; and  $p_i$  represents the estimated final size from the model using the 5 parameters for age-specific prior immunity sampled using Latin Hypercube sampling.

## MODELLING VACCINATION

We assumed that vaccination administered using LAIV requires one dose per individual. The baseline for all modelling scenarios was a continuation of the influenza vaccination policy in the UK prior to the introduction of paediatric vaccination (i.e. at-risk groups and adults ≥65 years only). The outputs from this scenario were then compared to modelling outputs from the following scenarios:

1. Targeting primary schools only



2. Targeting secondary schools only
3. Targeting both primary school and secondary school age groups, and achieving the same (homogeneous) level of coverage in both
4. Targeting both primary school and secondary school age groups, and achieving different (heterogeneous) levels of coverage in either

For each scenario the vaccination coverage achieved prior to the start of each influenza season was varied from 0-100%. The economic impact of such coverage was analysed in the economic evaluation.

Individuals in at-risk clinical and age groups were vaccinated according to the previous influenza vaccination programme, with uptake data taken from Public Health England [31]. At-risk individuals were assumed to have the same pre-vaccination susceptibility and mixing patterns as not-at-risk individuals of the same age. We assumed that those school-age individuals vaccinated due to their at-risk status were not vaccinated again at school because their parents or guardians would be aware of their vaccination status and would not need to consent to a second vaccination.

For homogenous coverage vaccination occurred in both age groups at the same level. For targeted vaccination only one age group was vaccinated. For the heterogeneous policy we allowed coverage in primary schools to vary from 0-100% then at each level examined the effect of supplementary vaccination in secondary schools from 0-100%, including the homogenous case.

#### **ECONOMIC EVALUATION**

From the estimates of the burden of disease from the epidemiological model a proportion of infections were assumed to result in clinical infections. Individuals with clinical influenza then use health services during their period of infection with each health service having an associated cost to the health care provider. Clinical influenza was associated with a risk of consultation with their GP, hospitalisation, intensive care admission and death.

We compared the total costs and number of QALYs saved for each possible vaccination coverage level for each of the four scenarios, arranging each coverage level by total cost in ascending order. The incremental cost-effectiveness ratio was calculated by comparing the ratio of an increase in the cost of a different coverage level achieved with the difference in QALYs saved. Those coverage levels that saved fewer QALYs than a less costly coverage level were dominated and therefore eliminated from the analysis.

Parameters used in the economic evaluation were first used by Baguelin et al. (2010) [21] with sources updated where possible (Table 5.3). Estimates of the use of GP services and the risk of hospitalisation due to influenza infection were taken from the published literature. We used the ratio of consultations

and hospitalisations from Cromer et al. (2014) [34]. We also assumed at all deaths due to influenza infection occur after a hospital admission and that all intensive care admissions also require first an admission to hospital.

Parameter	Value	Source
Proportion of infected cases with clinical 'flu	0.35	[33]
Hospitalised case fatality ratio	0.0009 for 0 – 3 years 0.0012 for 4 – 16 0.0258 for 17 – 64 0.1486 for 65+	[34]
Quality-adjusted life expectancy	67.34 quality-adjusted life years at birth	2009 data
Proportion of ILI cases visiting their GP	0.1	[36]
Proportion of GP visits subsequently requiring hospitalisation †	0.0375 for 0 – 3 years 0.0036 for 4 – 16 0.0105 for 17 – 64 0.1087 for 65+	[34]
Proportion of hospitalised cases requiring intensive care	0.0557	RMN, FluZone
Cost of GP consultation †	Log normal from $N(\mu=£45, \sigma=£8.4)$	[37]
Cost of hospital admission (non-elective) †	Log normal from $N(\mu=£1,489, \sigma=£192.1)$	[38]
Cost of admission to intensive care †	Triangular with min=£1,449, max=£2,300, mode=£2,034	[38]
Cost of vaccine per dose †	£14	[39]
Cost of vaccine delivery and administration per dose †	£3.03	[40]
QALY loss (not hospitalised) †	$N(\mu=0.0074, \sigma=0.00085)$ for 0 – 16 $N(\mu=0.0082, \sigma=0.00180)$ for 17+ years	[18, 35]
QALY loss (hospitalised) †	$N(\mu=0.0160, \sigma=0.00180)$ for 0 – 16 $N(\mu=0.0180, \sigma=0.00180)$ for 17+ years	[18, 41]
Discount rate	3.5% per annum	[3]

*Table 5.3 - Economic evaluation model parameters*

QALY loss due to clinical influenza were taken from EuroQol EQ-5D-3L surveys conducted in the United Kingdom during the 2009 H1N1v pandemic [18, 35]. Life expectancy data were taken from quality-adjusted life expectancy tables.

We used the same cost items as Baguelin et al. (2010) [21], but updated sources to reflect 2013 costs where possible. Costs for GP surgery consultations, hospitalisations and intensive care stays were taken from published sources. Costs relating to vaccinations were taken as the unit cost of the Fluenz vaccination [39] plus 10 minutes of a Band 7 nurse's time [40].

The cost-effectiveness of each vaccination scenario was estimated using the net incremental cost per quality-adjusted life year saved (ICER), comparing each modelled vaccination uptake level to the next best non-dominated uptake level. We calculated an ICER for each vaccination policy by adjusting the vaccination coverage level by increments of 1%. The optimally cost-effective level of uptake was deemed to be the highest uptake possible with an ICER of less than £20,000 per QALY gained, the threshold at which an intervention is considered cost-effective according to NICE [3].

## **SENSITIVITY ANALYSIS**

A multivariate parametric sensitivity analysis was performed to assess the sensitivity of the model to different parameters:  $R_0$ , the proportion of each age group susceptible, vaccine efficacy in school children, risk of hospitalisation in school children, QALY loss for hospitalised and non-hospitalised school children, the cost of a GP consultation, the cost of a non-elective hospital admission, the cost of admission to intensive care and the total cost of the vaccine per dose. Ranges for parameters were defined as a uniformly distributed  $\pm 5\%$  of the parameter value used in the model, or according to the distributions from previous studies as shown in Table 5.2 and Table 5.3 (marked with †). We ran 5,000 simulations of the most cost-effective coverage levels for each vaccination policy to plot cost-effectiveness estimates compared to no JCVI programme extension.

In addition to the multivariate parametric sensitivity analysis we used the best-fitting 1% and 5% of realisations from the calibration exercise to check how sensitive the model results are to the proportion of each age group with prior immunity to influenza by reporting the proportion of the best-fitting parameters that confirmed the dominance of the most cost-effective vaccination policy.

## **RESULTS**

### **MODEL CALIBRATION**

Figure 5.2 shows the epidemic curves from the best-fitting realisations of the model. We used the set of parameters that minimised the binomial log-likelihood but we kept the best-fitting 5% of realisations for sensitivity analyses.

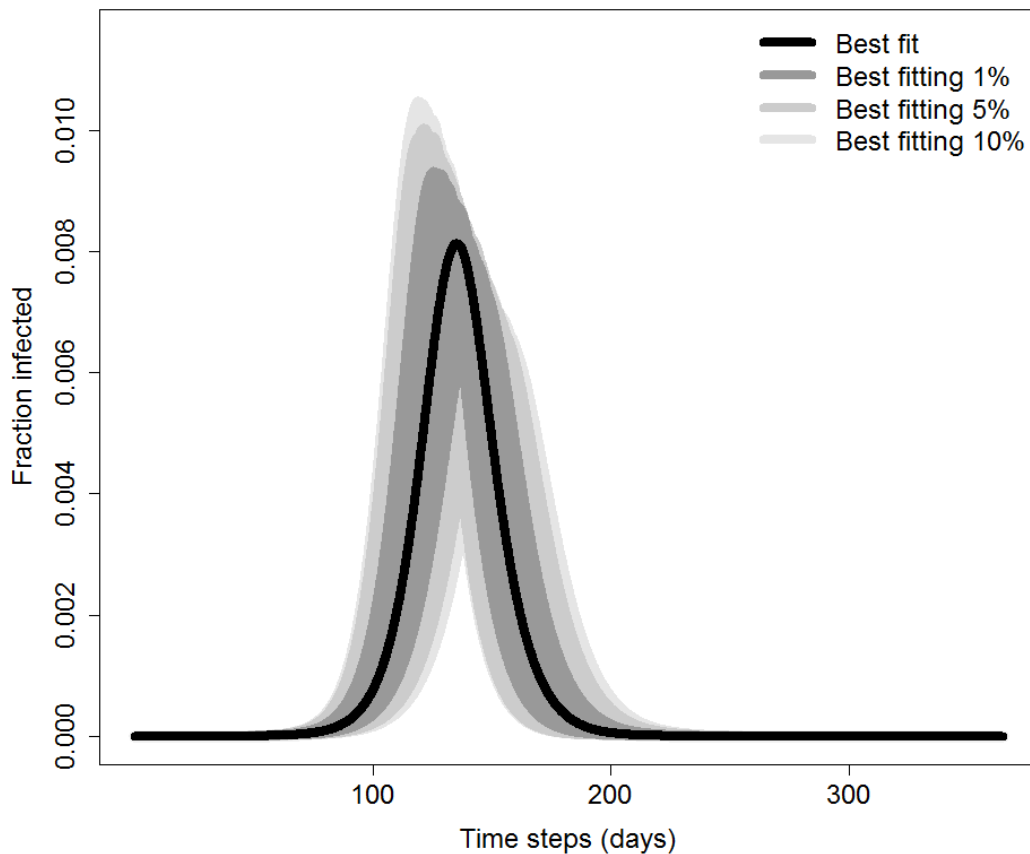


Figure 5.2 - The epidemic curves of the best fitting models from 25,000 parameter sets sampled using uniform Latin Hypercube sampling

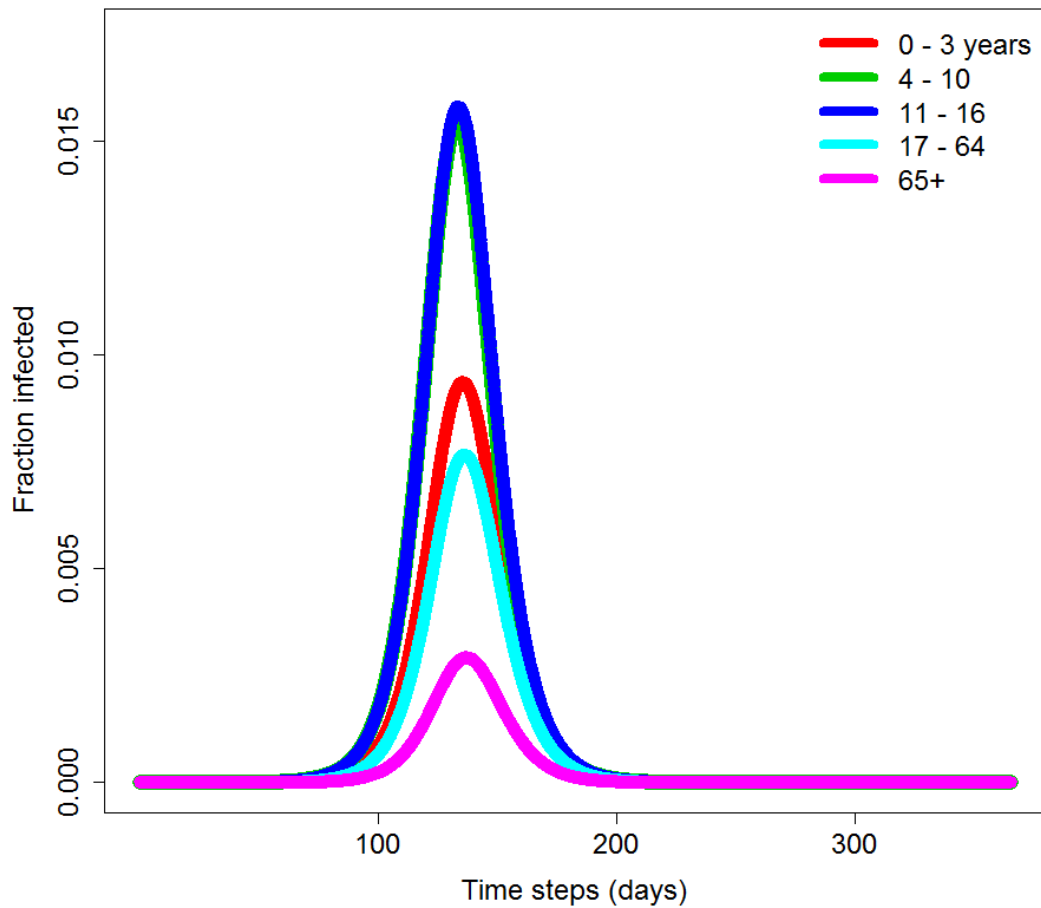
#### NO EXTENSION TO THE SEASONAL INFLUENZA VACCINATION PROGRAMME

##### BURDEN OF DISEASE

The proportion of the total population infected over a season prior to the extension of vaccination to low-risk children is 25.0% (13.3m), of which 4.7m are clinical influenza cases (Figure 5.3). 4,309 deaths occur due to influenza and 35.8% of those are deaths in the 65+ years age group. Baguelin et al. (2012) estimated 370-4,700 seasonal influenza-attributable deaths per year in a low-severity scenario, a range that includes the estimates from our model [18].

##### COST-EFFECTIVENESS

The outbreak costs £188m from the perspective of the health care provider with 38,600 QALYs lost due to infection.



*Figure 5.3 - Epidemic curve plotting the fraction of each age group infected for the baseline scenario, in which there are no vaccination programme extensions beyond those in at-risk groups and adults of age 65+ years*

#### **HOMOGENEOUS VACCINATION PROGRAMME EXTENSION**

##### **BURDEN OF DISEASE**

Vaccination of school children, in addition to the current regime of vaccination, can eliminate influenza transmission. The model predicts fewer than 10 cases of clinical influenza at 66% vaccine coverage.

## COST-EFFECTIVENESS

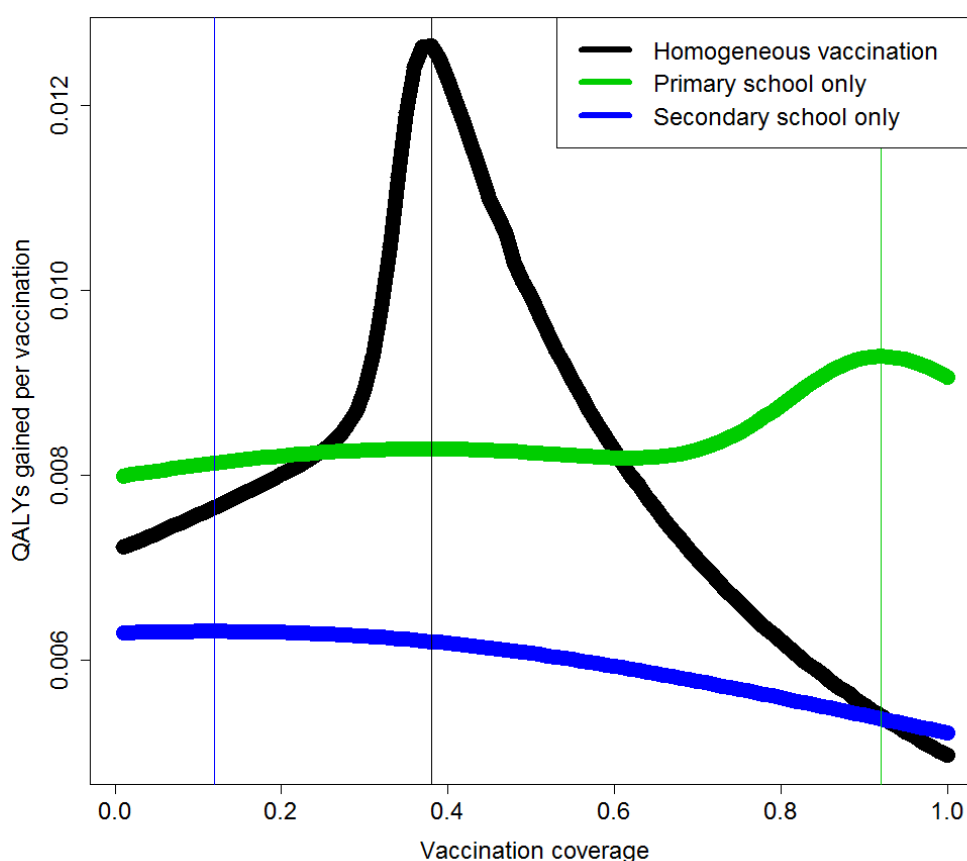


Figure 5.4 - QALYs gained per vaccination administered for each vaccination policy. Homogeneous vaccination efficiency across both primary and secondary schools (black) peaks when coverage reaches 32%. QALYs gained per vaccination in primary schools (green) peaks

The most cost-effective level of vaccine coverage is 42% (ICER of £14,394 per QALY saved). At this level the policy costs £210.7m and saves 38,505 QALYs over baseline. The number of QALYs gained per vaccination administered is maximised when vaccination coverage reaches 38%, where each vaccination dose administered saves 0.0126 QALYs, equivalent to 4.62 QALDs (Figure 5.4). Between 30% and 38% coverage the number of QALYs gained per vaccination administered increases faster than for lower vaccination coverage levels, highlighting the indirect benefit to the whole population of vaccinating school-age children for seasonal influenza.

### TARGETED VACCINATION IN PRIMARY SCHOOLS

#### BURDEN OF DISEASE

Primary school vaccination alone cannot eliminate influenza transmission. Even at 100% coverage the model predicts a total of 149 influenza-attributable deaths.

## COST-EFFECTIVENESS

The optimal cost-effectiveness occurs when coverage reaches 100% (ICER of £3,117 per QALY, Figure 5.5). At this level of coverage the targeted policy costs £226.1m and saves 37,244 QALYs over baseline (Table 5.4).

The number of QALYs gained per vaccination administered is maximised when coverage reaches 92% and each vaccination administered saves 0.0093 QALYs, equivalent to 3.39 QALDs (Figure 5.4). The mean number of pupils in a state-funded primary school in England is 263 [42] so achieving 92% coverage in each primary school saves 2.25 QALYs or 820 QALDs per school over the course of an influenza season.

The number of QALYs gained per vaccination administered increases to the maximum value from 60%. This sharp increase in programme effectiveness is due to herd immunity and the indirect impact on the wider population of vaccinating a large percentage of the primary school children.

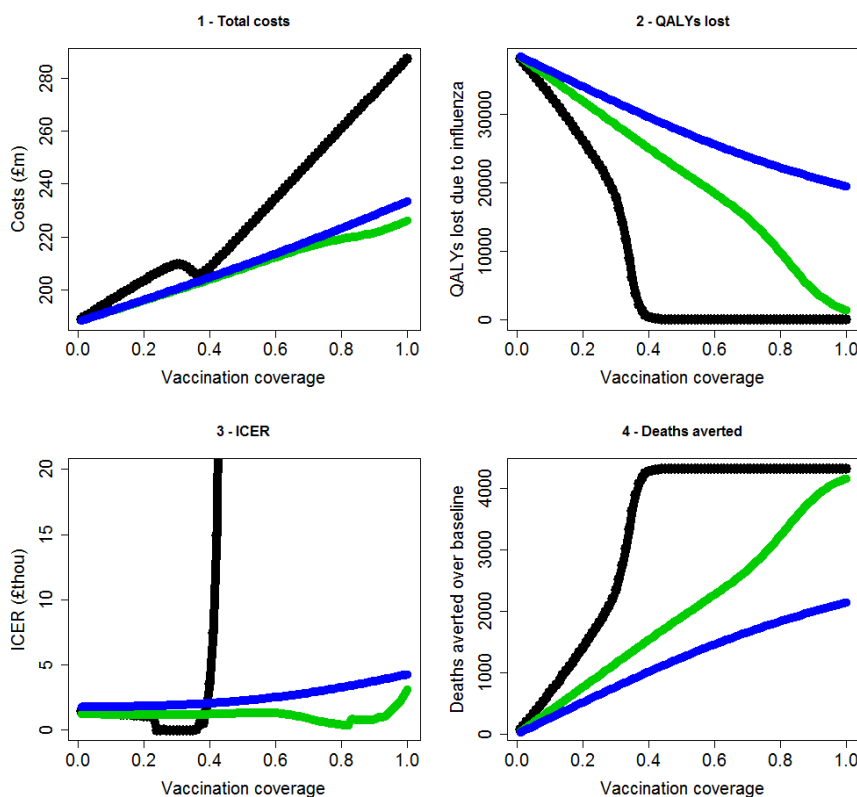


Figure 5.5 - (1) The total costs of the vaccination policies plus healthcare and treatment costs, (2) the QALYs lost due to influenza, (3) the incremental cost-effectiveness ratio and (4) the number of deaths averted over baseline. Homogenous vaccination (black), targeted vaccination in primary schools (green) and targeted vaccination in secondary schools (blue)

## **TARGETED VACCINATION IN SECONDARY SCHOOLS**

### **BURDEN OF DISEASE**

Secondary school vaccination alone cannot eliminate influenza transmission and reduces transmission to a lesser degree than at the same level of coverage for primary school vaccination - at vaccination coverage of 100% in secondary schools the overall final size of an outbreak is 11.89% (6.31m total infections of which 2.21m would be clinical influenza).

### **COST-EFFECTIVENESS**

The optimal cost-effectiveness occurs threshold when coverage reaches 100% (£4,280 per QALY saved, Figure 5.5). The number of QALYs saved per vaccination administered in secondary schools peaks at 0.0063 QALYs or 2.30 QALDs at 12% coverage.

## **HETEROGENEOUS COVERAGE ACROSS PRIMARY AND SECONDARY SCHOOLS**

### **BURDEN OF DISEASE**

The minimum coverage required to eliminate influenza transmission is 79% in primary schools and 48% in secondary schools. The model predicts fewer than 10 cases of clinical influenza with this vaccine coverage.

### **COST-EFFECTIVENESS**

The optimal cost-effectiveness occurs at a coverage level of 48% in primary schools and 34% in secondary schools (£16,152 per QALY saved, Figure 5.6). At this level of coverage the total cost of the policy is £210.0m and saves 38,496 QALYs over baseline. The next most costly vaccination coverage was to achieve 48% in primary schools and 35% in secondary schools, with incremental costs of £603,108 and 26.8 additional QALYs saved (ICER of £22,526/QALY, above the cost-effectiveness threshold of £20,000).

The number of QALYs gained per vaccination administered is maximised when coverage reaches 45% in primary schools and 28% in secondary schools. Each vaccination saves 0.0128 QALYs, equivalent to 4.67 QALDs. Using the mean number of pupils in a primary school and a secondary school (263 and 956 respectively [42]), implementing a policy of heterogeneous coverage to these coverage levels for one primary school and one secondary school saves 4.94 QALYs or 1,804 QALDs.



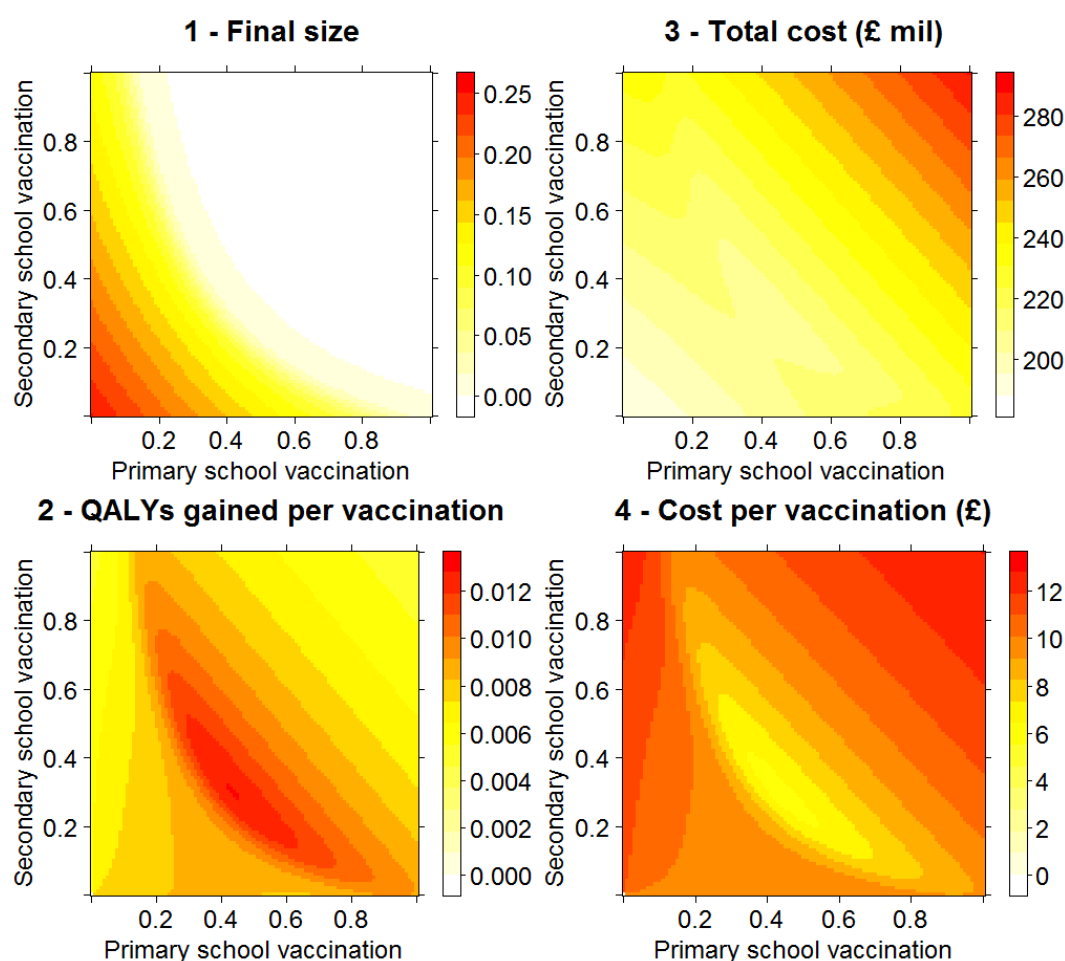


Figure 5.6 - Examining the impact of heterogeneous vaccination coverage. (1) final size of outbreak, (2) the QALYs gained per vaccination administered (3) the total cost of the vaccination policy (£ millions) and (4) the costs per vaccination administered (£). Horizontal axis shows the proportion of vaccination coverage in primary schools and the vertical axis shows the vaccination coverage in secondary schools

	Most cost-effective scenario	Maximum QALYs gained per vaccination	Minimum total costs per vaccination
<b>Targeted policy in primary schools</b>	100% (ICER = £3,117)	0.0093 (92% coverage)	£9.13 (92% coverage)
<b>Targeted policy in secondary schools</b>	100% (ICER = £4,280)	0.0063 (12% coverage)	£11.26 (1% coverage)
<b>Heterogeneous policy</b>	48% and 34% (ICER = £16,152)	0.0128 (45% and 28%)	£6.14 (44% and 29%)

Table 5.4 - Comparing three new vaccination policies

## Sensitivity analysis

### PROBABILISTIC SENSITIVITY ANALYSIS

Figure 5.7 shows that the uncertainty in the parameters used to calculate the cost-effectiveness ratios does not impact on probability that each vaccination strategy could be cost-effective at the willingness-to-pay threshold of £20,000 per QALY, when compared to no extension of the seasonal vaccination policy. There is more uncertainty in the total number of QALYs saved than in the total cost of the new vaccination policies.

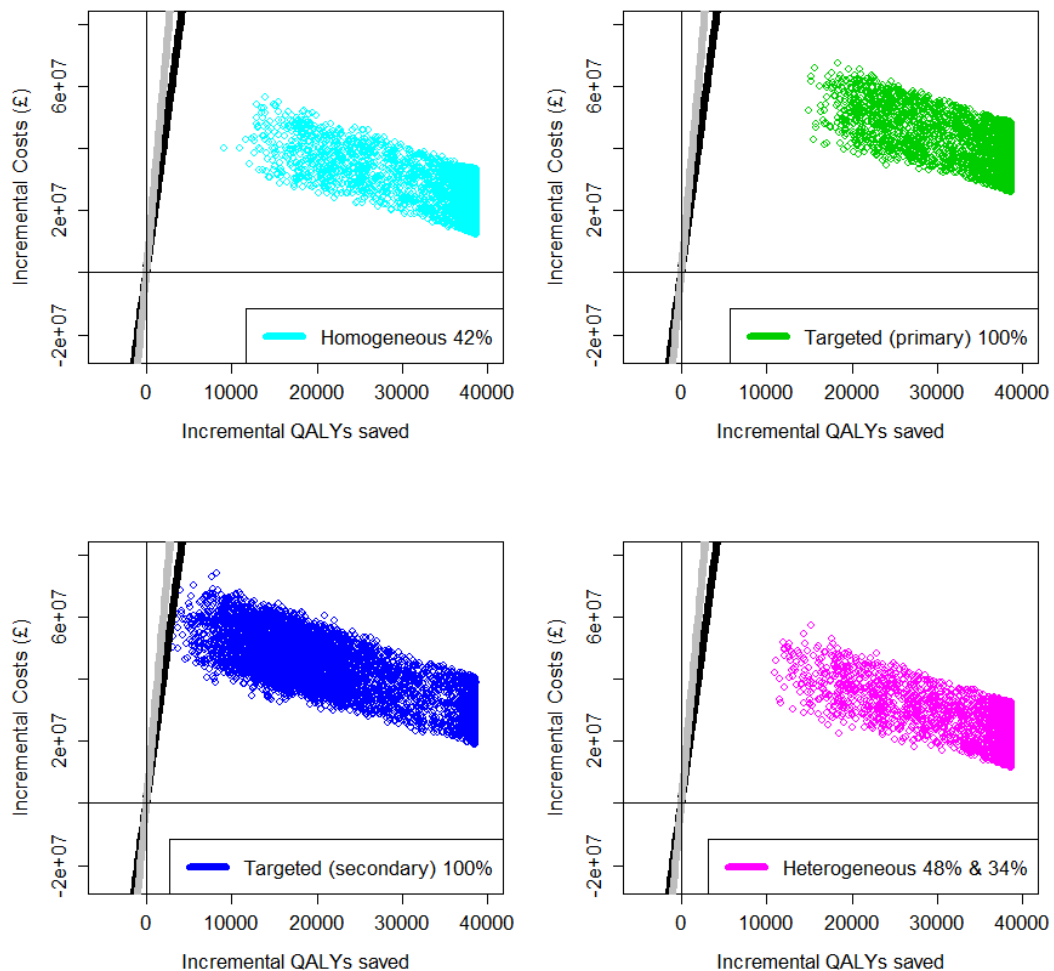


Figure 5.7 - Sensitivity analysis of the most cost-effective strategies of each of the four different vaccination policies when compared with no implementation of the new JCVI-recommended programme. Grey and black lines denote the £30,000 per QALY and £20,000 per QALY ratios respectively

In addition, in 208 (83.2%) of the best-fitting 1% of model realisations, the heterogeneous vaccination policy was the dominant option, with a targeted vaccination policy in primary schools dominant just 42 (16.8%) times. When extending to the best-fitting 5% of model realisations, the heterogeneous vaccination policy dominated other options 793 (63.4%) times.

## DISCUSSION

We investigated the optimal influenza LAIV coverage levels in primary schools and secondary schools to examine potential modifications to the JCVI influenza vaccination programme. We varied coverage levels in both primary and secondary schools between 0 – 100% and calculated the ICERs for each coverage level for four different vaccination strategies.

Overall, the optimum coverage level is 48% in primary schools and 34% in secondary schools in a heterogeneous vaccination strategy with an ICER of £16,152 per QALY saved. As the two targeted strategies and one homogenous coverage strategy are subgroups of the heterogeneous strategy we conclude that a policy of heterogeneous coverage should be pursued by the UK.

We examined the impact of the uncertainty of all parameters in the model and concluded that the cost-effectiveness estimates are not affected by these uncertainties. The heterogeneous vaccination policy was the dominant policy for the majority of model realisations.

## STUDY LIMITATIONS

### UNCERTAINTY IN PARAMETER ESTIMATES

Our sensitivity analysis explored the uncertainty in the model results using a range of values  $\pm 5\%$  of the parameter value used in the model. This range may not have captured the full uncertainty of some parameters in the model and therefore our sensitivity analysis may not have fully assessed the robustness of our estimates.

The accurate estimation of the duration of both the latent and infectious periods for influenza is difficult, therefore it is likely that the fixed values for both parameters used in our model do not capture the uncertainty for these parameters. Similarly, the value used for the proportion of cases with clinical influenza as well as rates of hospitalisation and mortality do not capture uncertainty in these parameters. All of these values are very difficult to measure so not incorporating the appropriate parameter distributions limited our ability to properly evaluate the uncertainty in our results.

### MODELLING A SINGLE INFLUENZA SEASON

For simplicity, we have only modelled a single influenza season and did not model immunity between seasons (other than to assume that an age-dependent proportion of individuals are immune at the start of the season). Immunity from influenza will wane, whether acquired through influenza infection or through vaccination. This may impact the cost-effectiveness estimates in our model but is likely to improve cost-effectiveness if acquired immunity lasts longer than one influenza season. Modelling influenza outbreaks over a longer time horizon is more complex as many other ideas such as cross-immunity, antigenic drift and competing strains could be incorporated into the model. It is possible

that primary school children have less time than secondary school children to acquire immunity for different influenza viruses from past infection and this can impact on the number of susceptible individuals in the model. Indeed, our model already sees that more primary school children are susceptible to the single pathogen assumed to cause this single outbreak, but additional circulating strains could change our results.

#### CONTACT PATTERNS ON TERM-TIME CONTACTS ONLY

We used data on contact patterns only during term-time at school and did not include changes in these contact patterns during school holidays or weekends for simplicity. Studies have shown that the daily number of age-dependent contacts for children can vary between term-time and holidays or weekends [43-45]. The inclusion of additional contact matrices in the model would improve the accuracy of the mathematical model in estimating the daily number of contacts sufficient for influenza transmission between children and their contacts. The simplest adaption of the model to include dynamic contact patterns is to reduce the daily number of contacts that school children have with other school children whilst increasing the daily number of contacts that school children have with adults during school holiday periods, as reported by Eames et al. (2011) [43]. Further adjustments could be made to include typical weekend contact patterns by assuming that school holiday contact patterns and weekend contact patterns are similar in nature.

In addition, we divided the school population into two age groups that saw children aged 4-10 years in primary school with those aged 11-16 years in secondary school. This broad distinction isn't reflective of school age distributions and a more detailed age-structured model could account for a proportion of those children aged 11 years attending primary school with the complement attending secondary school.

#### CONTACT PATTERNS FOR INDIVIDUALS WITH INFECTIOUS DISEASES

Including contact patterns from the European contact surveys conducted by Mossong et al. (2008) [12] makes an assumption that individuals with infectious diseases maintain daily contact patterns throughout their period of infection, consistent with their regular contact patterns when healthy. This assumption can be challenged using data from our studies on the impact of influenza and measles, as large proportions of those infected with each disease reported several days at home from school or work. Their typical contact patterns during periods of good health - assumed to approximate to the POLYMOD contact matrices – would be the daily contact patterns experienced whilst at school or work, therefore their infection and subsequent change in their daily routine would dramatically change their daily contact patterns. This is not reflected in our mathematical modelling and such a change in daily contact patterns is likely to change an individual's potential for transmission in the community.

Recording contact patterns for individuals with infectious disease would require further contact studies utilising diaries for reporting contacts before, during and after infection. Recruiting a sufficient sample size to be comparable to Mossong et al. (2008) would involve challenges in identifying enough individuals in a large population that would subsequently acquire influenza during the influenza season. Self-selecting online surveys such as the UK Flusurvey [46] record contact patterns for those reporting symptoms consistent with ILI, which would assist in adapting mathematical models of influenza and ILI transmission.

#### HOMOGENOUS AGE-SPECIFIC VACCINATION UPTAKE

We assumed that age-specific vaccination uptake would be homogenous in England. The recent pilot of seven models for vaccine delivery for children attending primary schools showed variation in the coverage levels, even in those six geographical areas using school-based vaccine delivery [47]. In reality, community-level vaccination coverage is likely to be patchy, so an improved mathematical model would account for this community-level heterogeneity even if a policy aims for homogeneous age-specific uptake as we recommended.

#### MODELLING VACCINATION UPTAKE IN 2-3 YEAR OLDS

The new seasonal influenza vaccination policy includes the vaccination of 2-3 year olds in addition to children attending primary and secondary schools [6]. Uptake in these age groups was 42.6% and 39.6% respectively [48]. Our model includes vaccination in these age groups but only for those individuals in a clinically at-risk group, where we assumed 2.67% uptake in all individuals aged 0-3 years.

Vaccinating healthy children in the 2-3 years age group in addition to vaccinating those children in a clinical at-risk group is likely to provide some indirect protection to members of households with young children. The impact of this indirect protection on any vaccination policy in health school-age children should not therefore be considered negligible.

#### ESTIMATION OF PREVIOUS-ACQUIRED IMMUNITY THROUGH MODEL CALIBRATION

Data for previous-acquired immunity from influenza were not available, so we estimated this in the model calibration process. The sensitivity analysis demonstrated that the cost-effectiveness estimates for each scenario are robust when compared to no policy extension, though there was more uncertainty in the total QALYs saved than in the total cost of the modelled programmes. There are some years where acquired immunity is less protective against the seasonal strain, which leads to larger outbreaks of influenza and hence less proportional effect from the same level of vaccine coverage.

Our parameter calibration process used binomial maximum likelihood to fit the expected final size from the model to the observed final size of a single epidemic period. The model may be further

improved by using different values for parameters in the economic evaluation (e.g. proportion of GP visits subsequently requiring hospitalisation) for those individuals in clinical at-risk groups.

#### CALIBRATED TO THE FINAL SIZE OF A MILD INFLUENZA SEASON

Finally, the model was calibrated to 2006-07 data which was a year of low incidence (as have been recent years [49, 50]), so we may have underestimated the cost-effectiveness of vaccination (but also the potential of vaccination to eliminate influenza for that year). We used recently-published data on health care resource use that have been used in scenarios of high severity influenza. We examined the possibility of high incidence years by varying  $R_0$  in the multivariate parametric sensitivity analysis and concluded that our cost-effectiveness estimates were not affected by uncertainty in the incidence of future influenza seasons.

Despite these limitations, our conclusion that primary school vaccination alone is not able to eliminate influenza in the UK appears to be robust, even in a season of low influenza activity. Further work using a model calibrated to data from multiple influenza seasons and taking into account long-term natural and acquired immunity may allow a more precise estimate of the level of coverage to aim to achieve in order to optimise cost-effectiveness.

#### FUNDING

This work was funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

#### ACKNOWLEDGEMENTS

We would like to thank colleagues at both the London School of Hygiene & Tropical Medicine and Public Health England for helpful discussions on the disease transmission model and the decision analytic model.

The research was part funded by the National Institute for Health Research Health Protection Research Unit in Immunisation at the London School of Hygiene & Tropical Medicine in partnership with Public Health England, and part funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health, or Public Health England.

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## **Chapter 6 - Modelling seasonal influenza vaccination programmes, part II: heterogeneous vaccination coverage between schools in a theoretical representative metapopulation framework**

Portions of this section were presented at the Epidemics 5 conference in Tampa, FL USA in December 2015.

### **ABSTRACT**

#### **BACKGROUND**

Mathematical models show the new seasonal influenza vaccination programme in healthy children will be both highly effective at reducing the burden of disease as well as cost-effective, but such models do not explore the potential for heterogeneous uptake between schools where the vaccination programme is implemented.

#### **OBJECTIVE**

We investigated the potential impact of heterogeneities in vaccination uptake on a theoretical population, representative of a small administrative district in England. We investigated the problem of unintended heterogeneity in coverage (i.e. one or more schools reporting lower vaccination uptake than other schools in the area), then we considered the possible impact of intended heterogeneity in vaccination coverage (i.e. concentrating vaccination delivery in specific schools, maintaining a mean target coverage level across the area).

#### **METHODS AND FINDINGS**

An age-structured stochastic transmission dynamic SEIR-type mathematical model with a patch-structured metapopulation of  $\approx 78,000$  individuals were used to simulate influenza epidemics. Vaccination programmes targeting different age groups were simulated in order to assess their impact on the total burden of disease for the community. Heterogeneity in vaccination coverage was managed by assigning each school with its own level of coverage. Targeted vaccination in only primary or secondary schools is insufficient to stop sustained transmission, even at very high coverage. 44.5% homogeneous coverage stopped the outbreak from spreading across all metapopulation patches whilst 47.8% coverage stopped influenza epidemics from occurring at all.

## CONCLUSION

Unintended heterogeneity through schools failing to achieve the target level of coverage in either primary or secondary schools increases the expected mean final size of epidemics. For low levels of coverage, one under-achieving secondary school increased the final size of epidemics but one under-achieving primary cannot. Intended heterogeneity in vaccination programmes that target either one or both school groups through the concentration of coverage in selected schools consistently increases the mean final size of epidemics. Heterogeneity in vaccination coverage between schools is unlikely to be beneficial to public health officials designing vaccination programmes.

## INTRODUCTION

The previous chapter considered the impact of modifications to the new national influenza vaccination programme. The investigation proposed the division of the sub-population group of school children into two groups: primary school children and secondary school children and heterogeneity in the uptake of the vaccine is considered between these two groups. This plan, however, treats each age group as a homogenous group with homogenous vaccination uptake in all schools. Whilst this is a sensible assumption for modelling and economic analyses for national vaccination programmes, it is unlikely to reflect reality at a smaller level as schools in each district of the country may report different coverage levels for many reasons.

In this section we discuss a mathematical modelling analysis to determine the impact of heterogeneous vaccine coverage between schools, in a theoretical district of England using a representative study population.

## BACKGROUND

### INTRODUCING HETEROGENEOUS VACCINATION COVERAGE

Vaccination programmes aim for high levels of coverage to minimise the possibility of sustained community-wide infectious disease transmission caused by the introduction of a pathogen. However, reporting high levels of coverage over a large population and geographic area can hide low levels of coverage in small communities in that area [1]. The existence of these pockets of low vaccination coverage expose those communities to an increased risk of disease transmission, triggering minor outbreaks in the larger population [2]. This type of heterogeneity in vaccination coverage is a result of the vaccination programme not reaching as many individuals as it was designed to do, and can therefore be described as *Unintended Heterogeneity*. Increasing the vaccination coverage in the small pockets of lower levels of vaccination coverage to decrease this type of heterogeneity has associated costs but may reduce the likelihood of further minor outbreaks in the population [3].

Another source of heterogeneity in vaccination coverage is how a mean coverage level is spread over all patches of a metapopulation. Achieving a mean vaccination coverage level of  $v$  across the metapopulation can be achieved by:

1. Vaccinating a proportion  $v$  inhabitants of each metapopulation patch, or
2. Vaccination of all inhabitants of a proportion  $v$  of the number of equally-sized metapopulation patches, or
3. Vaccination a proportion  $v_1$  of inhabitants of one group of equally-sized metapopulation patches, and a proportion  $v_2$  of inhabitants of inhabitants of another group of equally-sized metapopulation patches, with an overall vaccination coverage of  $v$

This form of heterogeneity in vaccination coverage is a result of the design of a targeted vaccination programme, and can therefore be labelled *Intended Heterogeneity*.

#### SUSCEPTIBILITY CLUSTERING AND CONSEQUENCES

An outbreak of measles ensued in San Diego, California, in January 2008 after an intentionally unvaccinated boy returned home from Switzerland with measles [4]. The boy exposed 839 persons to measles infection and infected 11 more unvaccinated persons. Nine of the 12 unvaccinated individuals with measles had parents who had deliberately rejected vaccination, with the remaining three too young to receive their vaccinations. The authors of the indicated that the outbreak was fuelled by intentionally unvaccinated individuals [4].

Choi et al. (2008) reported on the potential for measles transmission in England, even though at the time measles had been eliminated from both England and Wales for more than 10 years [5]. The increased risk of community-wide transmission was due to several district health authorities reporting declining MMR coverage [1]. 14 of the 99 district health authorities contained enough susceptible individuals to have an effective reproduction number greater than one, facilitating the reestablishment of measles within the community should the pathogen be introduced. Indeed, in 2009 the Health Protection Agency reported 876 laboratory-confirmed cases of measles in England and Wales with a significant number of additional confirmed cases in all subsequent years [6].

An example of an under-vaccinated community fuelling an outbreak of a vaccine-preventable disease when the general population had very high vaccination coverage is the 1999-00 measles outbreaks in the Netherlands [7]. In 1999 national MMR coverage was 96% but 34 of the 539 municipalities of the country reported coverage below 90%. The outbreak started in an orthodox reform elementary school with MMR coverage of just 7%. By May 2000 3,292 confirmed cases of measles had been reported with 72 hospitalisations and three measles-related deaths in the Netherlands.

#### PREVIOUS MODELS CONSIDERING UNINTENDED HETEROGENEOUS VACCINATION COVERAGE

A metapopulation framework divides the study population into distinct spatial domains, allowing individuals from different domains to interact whilst maintaining their grouping based on demographic factors. Given a suitably large population, one can divide the large geographical area it inhabits into smaller regions along lines of population density (e.g. cities, counties), recognised boundaries (e.g. countries, continents), or population centres (e.g. schools, workplaces).

Glass et al. (2004) considered heterogeneous vaccination coverage for measles in the Netherlands by dividing a population of 1 million persons into 1,000 patches, each of 1,000 people [8]. Population-mixing was determined by three parameters that summed to one and are defined in Table 6.1.

$\epsilon_1$	Coefficient of mixing between metapopulation and the external population
$\epsilon_2$	Coefficient of between-patch mixing
$\epsilon_3$	Coefficient of within-patch mixing

*Table 6.1 - Population-mixing parameters as defined by Glass et al. (2004)*

This metapopulation framework facilitated the study of the effect of metapopulation dynamics on infectious disease transmission by using an SIR-type transmission model. The overall vaccination coverage level was split between 350 high-coverage patches and 650 low-coverage patches. Increased heterogeneity in the vaccination coverage led to an overall increased risk of infection, but particularly in the patches of low-coverage. An increase in the overall risk of infection also led to a decrease in the mean age of infection during simulated outbreaks.

#### THE CHILDHOOD SEASONAL INFLUENZA VACCINATION PROGRAMME AND THE ROLE OF UNINTENDED VACCINE COVERAGE HETEROGENEITY

As discussed in previous sections, in 2012 the Joint Committee on Vaccination and Immunisation (JCVI) recommended extending the seasonal influenza vaccination programme of England and Wales to include all school children [9]. Modelling analyses demonstrating the cost-effectiveness of vaccinating healthy children have consistently assumed that children in both primary schools (aged 4 – 11 years) and secondary schools (11 – 16 years) must be simultaneously vaccinated [10, 11], achieving homogenous coverage across the study population. However, other studies [1, 4, 7, 12] have highlighted the potential problems caused by vaccine coverage heterogeneity. Indeed, the pilot study to test different administration methods for the new programme extension displays some heterogeneity in coverage, with uptake varying from 35.8% in Cumbria to 71.5% in South East Essex [13]. This pattern may be repeated at the local level, with individual schools within a district reporting differing vaccination coverage levels as per Omer et al. (2008) [12], affecting the possible disease transmission dynamics.

## RESEARCH QUESTIONS

1. Within a theoretical metapopulation framework, what impact would a targeted vaccination policy focused on either primary schools or secondary schools have on the potential for community-wide seasonal influenza epidemics? How does a targeted vaccination policy in one school group compare to homogeneous vaccination across both groups?
2. What is the impact on the potential burden of disease of one low-coverage school in the metapopulation within different vaccination strategies? How does increasing this unintended heterogeneity in uptake affect the potential for influenza epidemics?
3. Can intended heterogeneity in a vaccination programme be advantageous in reducing the potential burden of disease over the same number of vaccinations administered homogeneously in the metapopulation?

## METHODS

### MODELLING BOTH UNINTENDED AND INTENDED HETEROGENEOUS VACCINATION COVERAGE

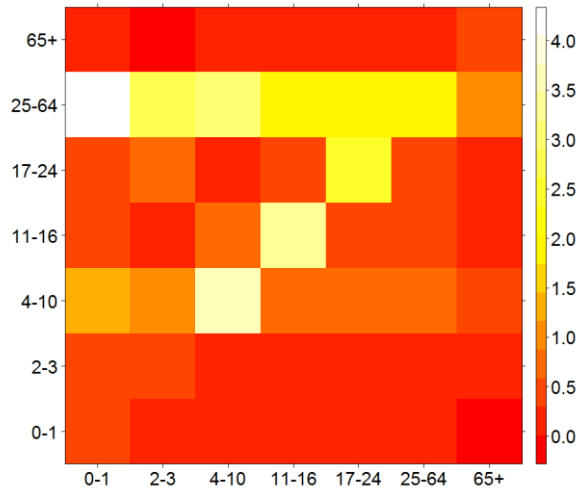
To describe the effect of heterogeneous vaccination coverage we used a mathematical model of infectious disease coupled with a metapopulation framework that divides the study population into  $n$  patches, with each patch assigned a level of vaccination coverage. The level of coverage was defined as high- or low-coverage, with the difference between the two a measure of heterogeneity in the study population.

Using methods similar to Glass et al. (2004) [8], the metapopulation was not spatially explicit and assumed that mixing patterns in the framework occurred on three levels:

- i. Within-patch mixing
- ii. Between-patch mixing
- iii. Mixing with the external population

### SOCIAL CONTACT PATTERNS

Mixing patterns at all levels described above were governed by a seven age group POLYMOD social contacts matrix for Great Britain (Figure 6.1) [14].



*Figure 6.1 - Social contact matrix for Great Britain based on close contacts weighted by sampling weights*

Age groups in the model were chosen to be able to model infectious disease dynamics by paying close attention to those individuals directly affected by the new seasonal influenza vaccination programme [9]. The metapopulation framework facilitated the modelling of the impact of an influenza outbreak in a community - we chose to model a community rather than utilise a metapopulation framework for a larger population both for computational reasons and to use a spatially explicit metapopulation model with a representative study population [15]. This framework provided a sufficiently large experimental space in which to test different vaccination strategies and the impact of heterogeneous vaccination coverage in English schools.

#### **METAPOPULATION FRAMEWORK**

Each patch within the metapopulation represented a small community unit with the collected patch framework representing a wider community. Modelling potential interventions for infectious disease epidemics using a small representative population has been successful in the past, notably with modelling childhood vaccination in the US [16] and social distancing measures in Australia [15]. In both cases the age distribution of the study populations approximate that of the wider populations for each respective country.

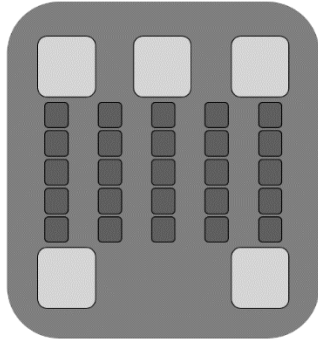
#### **THE NUMBER OF SCHOOLS**

We chose a metapopulation of 25 primary schools and 5 secondary schools to match the ratio of state-funded primary schools to secondary schools in England in 2014 [17]. Using a larger total number of schools would be computationally difficult. Each patch in the metapopulation represented one school.

In the same year 4.4m children attended state-funded primary schools and 3.2m children attended state-funded secondary schools [17]. For ease of computation in the infectious disease transmission

model this was rounded to an average of 250 children per state-funded primary school and 1,000 children per state-funded secondary school.

#### THE TOTAL NUMBER OF PATCHES



*Figure 6.2 - The metapopulation framework used to model heterogeneous influenza vaccination coverage in English schools*

In addition to modelling infectious disease transmission within schools we included an external population of those either too young or too old to attend primary or secondary schools. These individuals were assigned to a single patch and are subsequently referred to as the *external population*. Our metapopulation therefore consisted of 31 patches in total. Mid-year population estimates were used to complete the study population [18]. Figure 6.2 shows the metapopulation framework with large squares representing secondary schools, small squares representing primary schools and the large surrounding square representing the external population.

#### SOCIAL MIXING PATTERNS BETWEEN METAPOPOPULATION PATCHES

Social mixing was determined by a seven age group POLYMOD social contact matrix for close contacts,  $\mathbf{M}$  with elements  $m_{ij}$ . Social contacts occurred on three levels so the POLYMOD social contact matrix was adjusted to facilitate this mixing in the metapopulation:

Case 1: Individuals mixing with other individuals in their own metapopulation patch

Patches 1 to 25 contain individuals belonging to age group 3 only and patches 26 to 30 contain individuals belonging to age group 4 only, whilst patch 31 contains all other individuals. Applying the POLYMOD social contact matrix to an individual's social contacts within their own patch requires the introduction of a parameter  $\varepsilon_1$  on the interval  $[0,1]$  to define the proportion of that individual's social contacts within that age group within that patch.



$m_{1,1}$	$m_{1,2}$	0	0	$m_{1,5}$	$m_{1,6}$	$m_{1,7}$
$m_{2,1}$	$m_{2,2}$	0	0	$m_{2,5}$	$m_{2,6}$	$m_{2,7}$
0	0	$\varepsilon_1 m_{3,3}$	0	0	0	0
0	0	0	$\varepsilon_1 m_{4,4}$	0	0	0
$m_{5,1}$	$m_{5,2}$	0	0	$m_{5,5}$	$m_{5,6}$	$m_{5,7}$
$m_{6,1}$	$m_{6,2}$	0	0	$m_{6,5}$	$m_{6,6}$	$m_{6,7}$
$m_{7,1}$	$m_{7,2}$	0	0	$m_{7,5}$	$m_{7,6}$	$m_{7,7}$

Equation 6.1 - The POLYMOD social contact matrix for contacts made within an individual's own patch

An individual in age group 3 has  $m_{3,3}$  social contacts within that age group per day. As individuals in that age group are split across 25 primary schools a proportion  $\varepsilon_1$  of those contacts will be in the same patch with the remaining proportion  $1-\varepsilon_1$  split across all remaining patches. The same is true for individuals of age group 4 who have  $m_{4,4}$  social contacts with individuals in secondary schools.

Individuals in the external population (i.e. those individuals in age groups 1, 2, 5, 6 and 7) contact other individuals in these age groups according to the POLYMOD social contact matrix without the need for scaling parameters. Equation 6.1 shows the matrix used in the model.

Case 2: Individuals mixing with other individuals in a different metapopulation patch

0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	$(1-\varepsilon_1)m_{3,3}$	0	0	0	0
0	0	0	$(1-\varepsilon_1)m_{4,4}$	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0

Equation 6.2 - The POLYMOD social contact matrix for contacts made by an individual and another from a different metapopulation patch

To complement the social contact matrix for contacts within an individual's patch, the proportion of contacts within their age group but not in the same patch is  $1-\varepsilon_1$ . These contacts are divided over the number of patches remaining that contain individuals of that age group. Equation 6.2 shows the matrix used in the model.

Case 3: Individuals mixing between the school patches and the external population

For those individuals in age groups 3 and 4, their contacts with the external population are described by the elements of the original POLYMOD social contact matrix. Equation 6.3 shows the matrix used in the model.

0	0	$m_{1,3}$	$m_{1,4}$	0	0	0
0	0	$m_{2,3}$	$m_{2,4}$	0	0	0
$m_{3,1}$	$m_{3,2}$	0	0	$m_{3,5}$	$m_{3,6}$	$m_{3,7}$
$m_{4,1}$	$m_{4,2}$	0	0	$m_{4,5}$	$m_{4,6}$	$m_{4,7}$
0	0	$m_{5,3}$	$m_{5,4}$	0	0	0
0	0	$m_{6,3}$	$m_{6,4}$	0	0	0
0	0	$m_{7,3}$	$m_{7,4}$	0	0	0

*Equation 6.3 - The POLYMOD social contact matrix for contacts made by an individual and individuals in the external population*

The sum of all three contact matrices is the original POLYMOD social contact matrix for seven age groups in Great Britain. This meant that individuals in the metapopulation framework would have as many age-specific daily contacts as if we used a modelling framework without the metapopulation. For those individuals of school-attending age, their daily contacts with other individuals of the same age group were split using the  $\epsilon_1$  factor.

#### **MATHEMATICAL MODEL OF THE BURDEN OF DISEASE**

##### **STOCHASTIC COMPARTMENTAL SEIR MODEL**

Compartment	Meaning
S	Susceptible individuals
E	Exposed individuals
I	Infectious individuals
R	Removed individuals
W	Total vaccinated individuals
V	Successfully vaccinated individuals
A	Individuals with prior immunity

*Table 6.2 - Compartments of the mathematical model*

The infectious disease transmission model used was an age-structured stochastic SEIR-type model. The total population  $N$  was divided into seven age groups. The compartments for the model are listed in Table 6.2. An SEIR-type framework was chosen to follow the natural progression of influenza infection.

Susceptible individuals (S) move to the compartment for exposed individuals (E) after contact with an infectious individual sufficient for disease transmission. Once infectious the individuals transfer to the infectious compartment (I) before removal and finishing in the last compartment (R). Some individuals are vaccinated before the outbreak (W) but not all acquire immunity; those that do remain immune (V) for the duration of the epidemic. Some individuals have already immune from infection remain in their own compartment (A) for the duration of the epidemic

Movement from the susceptible compartment to the exposed compartment was governed by a probabilistic process based on a binomial distribution with parameters  $B(S_{pa}, \epsilon \lambda_{pa})$ , where  $\lambda_{pa}$  is the patch- and age-specific force of infection and  $\epsilon$  is the time step set to 1 day, ensuring high precision in

calculation without reducing feasibility in computational requirements. The force of infection is defined in Equation 6.4:

$$\lambda_{pa} = \sum_{\hat{p}=p \in [1,31]} \sum_{\hat{a}=1}^7 \beta m_{a\hat{a}} \frac{I_{\hat{p}\hat{a}}}{N_{\hat{p}\hat{a}}} + \sum_{\hat{p} \neq p \in [1,30]} \sum_{\hat{a}=1}^7 \beta m_{a\hat{a}} \frac{I_{\hat{p}\hat{a}}}{N_{\hat{p}\hat{a}}} + \sum_{\substack{p \in [1,30] \Rightarrow \hat{p}=31 \\ p=31 \Rightarrow \hat{p} \in [1,30]}} \sum_{\hat{a}=1}^7 \beta m_{a\hat{a}} \frac{I_{\hat{p}\hat{a}}}{N_{\hat{p}\hat{a}}}$$

*Equation 6.4 - The force of infection for the stochastic compartmental SEIR model*

Equation 6.4 consists of three expressions; the force of infection for within-patch transmission, the force of infection for between-patch transmission and the force of infection for two-way transmission between schools and the external population. The parameter  $m_{ij}$  is the social contact matrix as previously described.

$\beta$  is reverse-engineered from Equation 6.5, dividing the product of the basic reproduction number  $R_0$  and the reciprocal of the infectious period  $\gamma$  by the maximum eigenvalue of the social contact matrix.

$$\beta = \frac{R_0 \gamma}{\text{Eig}_{\max}(M)}$$

*Equation 6.5 - Calculating  $\beta$*

Individuals in the exposed compartment (E) become infectious at a rate  $\delta^{-1}$ , recovering at a rate  $\gamma^{-1}$ . For consistency, we used parameters from the model described in Chapter 6. All model parameters are shown in Table 6.3.

The model was seeded with one infectious individual in a randomly chosen primary school. The model was executed in R version 3.0.2 [19].

Parameter	Explanation	Value
$R_0$	Basic reproduction number	1.46
$\epsilon_1$	Proportion of contacts within patch	0 to 1
$\gamma$	Infectious period (days) <sup>-1</sup>	0.7813
$\delta$	Latent period (days) <sup>-1</sup>	0.6849
$v_p$	High-vaccination coverage in primary schools	0 to 1
$v_s$	High-vaccination coverage in secondary schools	0 to 1
$\tau$	Proportional reduction in vaccination coverage between high- and low-vaccination schools	$0.5 v_{p/s}$
$initial\_sus_i$	Proportion of age group initially susceptible	0.7837 (0-1 years) 0.7837 (2-3) 0.8943 (4-10) 0.9819 (11-16) 0.9496 (17-24) 0.9496 (25-64) 0.9736 (65+)
$risk\_groups_i$	Proportion of age group in at-risk group	0.0517 (0-1 years) 0.0517 (2-3) 0.0517 (4-10) 0.0517 (11-16) 0.1356 (17-24) 0.1356 (25-64) 1.0000 (65+)
$uptake\_risk_i$	Vaccination uptake for at-risk groups	0.516 (0-1 years) 0.516 (2-3) 0.516 (4-10) 0.516 (11-16) 0.516 (17-24) 0.516 (25-64) 0.740 (65+)
$vac\_efficacy_i$	Vaccine efficacy	0.70 (0-1 years) 0.70 (2-3) 0.70 (4-10) 0.70 (11-16) 0.70 (17-24) 0.70 (25-64) 0.46 (65+)
$ageSize_i$	Population	2,000 (0-1 years) 2,000 (2-3) 6,250 (4-10) 5,000 (11-16) 8,300 (17-24) 41,500 (25-64) 13,000 (65+)

Table 6.3 - Parameters used in the mathematical model of infectious disease transmission

#### MODELLING INFLUENZA VACCINATION: UNINTENDED HETEROGENEITY THROUGH LOW-COVERAGE METAPOPOPULATION PATCHES

$v_p$  and  $v_s$  are the parameters that represent high-vaccination coverage levels in primary and secondary schools respectively. Vaccination coverage levels of 0%, 20%, 40%, 60%, 80% and 100% were chosen for each vaccination policy for ease of implementation due to the metapopulation configuration. In addition to this, the parameter  $\tau$  represents the reduction in vaccination coverage for low-vaccination

patches.  $\tau$  is defined as 0.5 times the value of  $v_p$  or  $v_s$ , meaning that low-coverage patches in the metapopulation have half the vaccination coverage of high-coverage patches.

Before the recommendation for a school-based influenza vaccination programme many individuals in at-risk groups received the trivalent seasonal influenza vaccination from their GP or another local health care provider. Coverage figures and the number of at-risk individuals were obtained from Public Health England [20] and Baguelin et al. (2010) [21]. We assumed an age-specific proportion of the population belonged to an at-risk group and an age-specific proportion of those individuals accepted the offer of seasonal influenza vaccination. We used age-specific vaccine efficacy data from Fleming et al. (2010) [22].

To model unintended heterogeneity in the vaccination uptake we sequentially assigned different schools to be low-vaccination coverage, with all other schools assigned to be high-vaccination coverage. The vaccination of those individuals outside of the school system was not changed.

#### MODELLING INFLUENZA VACCINATION: INTENDED HETEROGENEITY THROUGH FIXED COVERAGE SPREAD UNEVENLY

Rather than vaccinating metapopulation patches to  $v_p$  and  $v_s$  coverage levels, we modelled a mean coverage level of  $v$  across the target population using different metapopulation configurations to achieve this coverage level.

Vaccination coverage levels of 20%, 40%, 60% and 80% were chosen for each vaccination policy for ease of implementation due to the metapopulation configuration. For example, vaccinating 20% of primary school children can be achieved by administering vaccination to 20% of all children attending the 25 primary schools, or by achieving 100% coverage in 5 of the 25 primary schools. It can also be achieved by vaccinating 4% of all primary school children and 40% of all secondary school children, as well as many other combinations of coverage levels.

For targeted vaccination policies in primary and secondary schools we varied vaccination coverage  $v$  by:

1. Vaccinating a proportion  $v$  children of each school in the targeted population, and
2. Vaccination of all children of a proportion  $v$  of the number of school in the targeted population, and
3. Vaccination in all schools in a targeted population to two different coverage levels, with mean overall vaccination coverage  $v$

For homogenous vaccination coverage  $v \in (20\%, 40\%, 60\%, 80\%)$ , an equivalent overall vaccination coverage can be achieved by vaccinating to different levels in the primary schools and secondary

schools. The coverage levels in each age group for concentrated coverage are listed below in Table 6.4.

Homogeneous vaccination coverage, $v$	Number of primary schools with 100% coverage, $p$	Number of secondary schools with 100% coverage, $s$
20%	9	0
	5	1
	1	2
40%	18	0
	14	1
	10	2
	6	3
	2	4
60%	19	2
	15	3
	11	4
	7	5
80%	24	3
	20	4
	16	5

*Table 6.4 - The number of primary and secondary schools required to achieve the same level of vaccination coverage as a homogeneous vaccination policy in all schools*

The concentration of vaccination coverage in both primary and secondary schools could be used by Public Health officials in the design of vaccination programmes. For example, to achieve the same number of vaccinations administered for 20% coverage in the metapopulation, Public Health officials could concentrate this coverage in primary schools by vaccinating 100% of the children in 9 primary schools. Alternatively, by vaccinating 100% of the children in 2 secondary schools and supplementing this with 100% coverage in a primary school, the vaccination programme is concentrated in secondary schools.

However, these scenarios require several metapopulation patches to be completely unvaccinated. Another option to achieve homogeneous coverage  $v \in (20\%, 40\%, 60\%, 80\%)$  is to vaccinate in all metapopulation patches of the target population, with some patches reporting lower coverage than others. Details of these coverage levels are listed in Table 6.5.

<b>Targeting primary schools</b>				
Coverage in target group 1	Number of patches in group 1	Coverage in target group 2	Number of patches in group 2	Overall coverage for population
80%	5	5%	20	20%
60%	5	10%	20	20%
40%	5	15%	20	20%
80%	5	30%	20	40%
60%	5	35%	20	40%
20%	5	45%	20	40%
80%	5	55%	20	60%
40%	5	65%	20	60%
20%	5	70%	20	60%
60%	5	85%	20	80%
40%	5	90%	20	80%
20%	5	95%	20	80%
<b>Targeting secondary schools</b>				
Coverage in target group 1	Number of patches in group 1	Coverage in target group 2	Number of patches in group 2	Overall coverage for population
80%	1	5%	4	20%
60%	1	10%	4	20%
40%	1	15%	4	20%
80%	1	30%	4	40%
60%	1	35%	4	40%
20%	1	45%	4	40%
80%	1	55%	4	60%
40%	1	65%	4	60%
20%	1	70%	4	60%
60%	1	85%	4	80%
40%	1	90%	4	80%
20%	1	95%	4	80%

*Table 6.5 - Targeted vaccination strategies in primary schools and secondary schools with heterogeneous uptake, ensuring all patches in the targeted population receive some coverage*

Finally, vaccinating in both age groups to achieve a mean overall vaccination coverage  $v \in (20\%, 40\%, 60\%, 80\%)$  can be achieved by vaccinating all primary schools with coverage level  $v_p$  and all secondary schools with coverage level  $v_s$ , ensuring that no school patch goes unvaccinated. Details of each vaccination strategy to achieve coverage level  $v$  are listed in Table 6.6.

Primary school coverage, $v_p$	Secondary school coverage, $v_s$	Mean overall coverage, $v$
4%	40%	20%
60%	15%	40%
20%	65%	40%
8%	80%	40%
24%	60%	40%
56%	20%	40%
80%	35%	60%
40%	85%	60%
100%	10%	60%
92%	20%	60%
76%	40%	60%
44%	80%	60%
28%	100%	60%
100%	55%	80%
96%	60%	80%
64%	100%	80%

*Table 6.6 - Heterogeneous vaccination strategies in the metapopulation to achieve an overall vaccination coverage  $v$*

Methods to calculate the epidemic duration, final size and other metrics are displayed in the appendix.

#### **MODELLING THEORETICAL SEASONAL INFLUENZA VACCINATION STRATEGIES**

In implementing a new vaccination programme in the theoretical metapopulation, Public Health officials would have a choice from four different programmes:

I. No extended vaccination policy

Included as an option in this study for the purpose of providing a baseline measurement of effectiveness, this option sees the continuation of the previous seasonal influenza vaccination programme without offering additional seasonal vaccinations to healthy school children.

II. Targeted vaccination in primary schools only

Seasonal vaccination is offered only to those children attending primary schools in the metapopulation.

III. Targeted vaccination in secondary schools only

Seasonal vaccination is offered only to those children attending secondary schools in the metapopulation.

IV. Vaccination across both primary schools and secondary schools



Seasonal vaccination is offered to all children attending primary schools or secondary schools in the metapopulation. The programme is implemented with a target of either homogeneous coverage across the two school groups or heterogeneous coverage between them.

Four possible heterogeneities in vaccination coverage were explored in theoretical vaccination programmes II-IV:

1. Variation in the vaccination coverage.

$v_p$  and/or  $v_s$  were varied to examine the impact of increasing vaccination coverage in the metapopulation.

2. Variation in the number of high-coverage primary schools, from 1-25.

By default, the model simulates epidemics with 25 high-coverage primary schools. This can be reduced incrementally to one high-coverage primary school.

3. Variation in the number of high-coverage secondary schools, from 1-5.

By default, the model simulates epidemics with 5 high-coverage secondary schools. This can be reduced incrementally to one high-coverage secondary school.

4. Fixed number of vaccinations with variation within the schools included in the target population

Vaccination is heterogeneous within the specified target population, through the concentration of vaccination in some schools at the expense of others.

The different theoretical vaccination programmes and scenarios are described below.

#### NO EXTENDED VACCINATION POLICY (BASELINE)

$v_p$  and  $v_s$  were set to zero and the continuation of the previous seasonal influenza vaccination policy was executed, to act as a baseline against all subsequent vaccination strategies.

#### TARGETED VACCINATION IN PRIMARY SCHOOLS

$v_p$  varied,  $v_s = 0$ . Vaccination in secondary schools is ignored and the vaccination policy targets only primary schools in the metapopulation. Three heterogeneities are explored with this vaccination programme:

1. The vaccination coverage of high-coverage primary schools.
2. The number of low-coverage primary schools.

3. The difference between fixed vaccination coverage spread evenly across the population against the same coverage concentrated in a small number of primary schools.

#### TARGETED VACCINATION IN SECONDARY SCHOOLS

$v_s$  varied,  $v_p = 0$ . Vaccination in primary schools is ignored and the vaccination policy targets only secondary schools in the metapopulation. Three heterogeneities are explored with this vaccination programme:

1. The vaccination coverage of high-coverage secondary schools.
2. The number of low-coverage secondary schools.
3. The difference between fixed vaccination coverage spread evenly across the population against the same coverage concentrated in a small number of secondary schools.

#### VACCINATION IN BOTH PRIMARY AND SECONDARY SCHOOLS

As with (i), with  $v_p = v_s$  and varied. This strategy represents successfully achieving high homogeneous coverage in every primary school and secondary school in the metapopulation. Four heterogeneities are explored with this vaccination programme:

1. The homogeneous vaccination coverage of both high-coverage primary and secondary schools.
2. The number of low-coverage primary schools.
3. The number of low-coverage secondary schools.
4. The difference between fixed vaccination coverage spread evenly across the population against the same coverage concentrated in a small number of primary and secondary schools.

For each vaccination strategy the model was executed 5,000 times. Data were output to a .csv file and analysed with R version 3.0.2 [19]. To remove those simulations with rapid stochastic fadeout we present the results from simulations with a final size of ILI epidemics above 0.5% of the population, assuming these simulations were the results of quick stochastic fadeouts.

All 95% confidence intervals of the mean for each presented metric were calculated using 1,000 bootstrap replications and the strength of evidence for a difference between two metrics was examined using the Wilcoxon rank sum test statistic.

## RESULTS

### NO EXTENSION TO THE SEASONAL INFLUENZA VACCINATION PROGRAMME

To provide a baseline against which other results would be compared, the model was executed with the assumption that healthy school children would not be offered to participate in the seasonal influenza vaccination programme.

#### BASELINE RESULTS

62.9% of simulated epidemics resulted in an overall ILI final size less than 0.5% of the total population. From the remaining simulated epidemics the mean overall ILI final size was 16.40% (95% CI: 16.36 – 16.44%) (Figure 6.3). Further results are reported in Table 6.7.

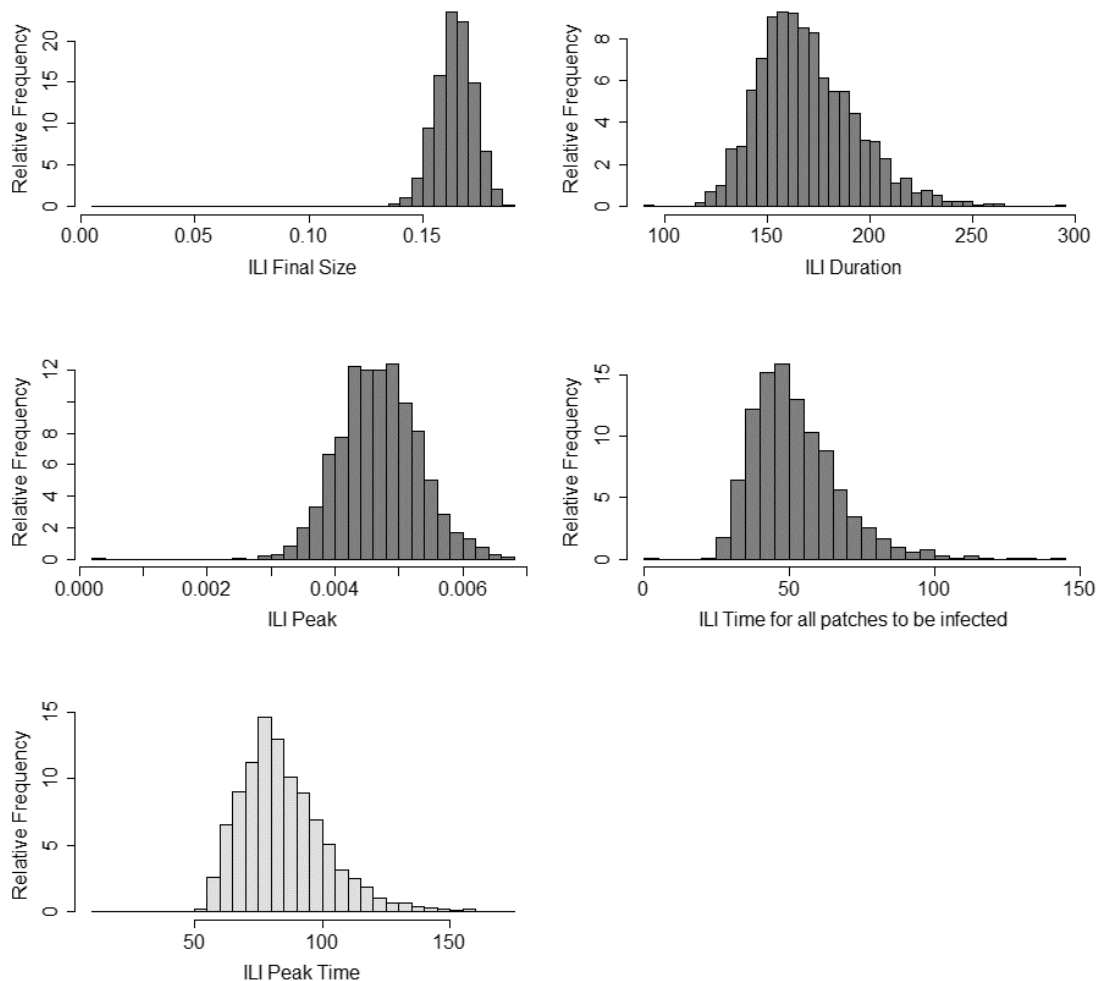


Figure 6.3 - Results from 5,000 simulations of the metapopulation model with stochastic fadeouts excluded

	Mean	95% CI of the mean
ILI Final Size	16.40%	16.36 – 16.44%
ILI Duration	169.90 days	168.81 – 171.04 days
ILI Peak	0.468%	0.466 – 0.471%
ILI time for all patches to be infected	52.74 days	52.06 – 53.43 days
ILI Peak Time	85.32 days	84.59 – 86.16 days

*Table 6.7 - Results from 5,000 simulations of the metapopulation model with stochastic fadeouts excluded*

Table 6.8 shows the age-specific results from the 5,000 simulations for each age group with the stochastic fadeouts excluded. The mean greatest burden of disease was in the primary school and secondary school age groups with final sizes of 37.99% (95% CI: 37.90-38.87%) and 39.99% (95% CI: 39.88-40.10%) respectively. Mean duration of the ILI epidemics ranged from 134.70 days (95% CI: 133.61-135.87 days) in the 2 – 3 year age group to 165.42 days (95% CI: 164.38-166.50 days) in the 25 – 64 years age group.

Age	ILI Final Size	ILI Duration (days)	ILI Peak
0-1	12.55% (12.50-12.60%)	138.04 (136.90-139.17)	0.584% (0.580-0.589%)
2-3	10.30% (10.25-10.34%)	134.70 (133.61-135.87)	0.504% (0.500-0.508%)
4-10	37.99% (37.90-38.87%)	160.35 (159.32-161.45)	1.21% (1.20-1.21%)
11-16	39.99% (39.88-40.10%)	154.69 (153.63-155.70)	1.30% (1.29-1.31%)
17-24	19.32% (19.26-19.38%)	154.85 (153.78-155.86)	0.645% (0.641-0.649%)
25-64	14.22% (14.18-14.25%)	165.42 (164.38-166.50)	0.424% (0.422-0.427%)
65+	3.58% (3.57-3.59%)	146.14 (145.11-147.13)	0.145% (0.144-0.146%)

*Table 6.8 - Mean and 95% CIs of ILI Final Size, ILI Duration and ILI Peak for each age group in the model with stochastic fadeouts excluded*

Patch-specific results are shown in Table 6.9. The comparatively high vaccination coverage of the external population, due to coverage in the oldest age group of 65+ years, is a likely contributor to the lower mean final size of epidemics in the external population is much smaller than in the school patches. The mean durations of ILI epidemics in the primary and secondary school patches were shorter than in the external population; 108.84 days (95% CI: 108.61-109.07 days) for primary schools and 134.12 days (95% CI: 133.66-134.758 days) for secondary schools, with a mean duration in the external population of 165.85 days (95% CI: 164.81-167.01 days).

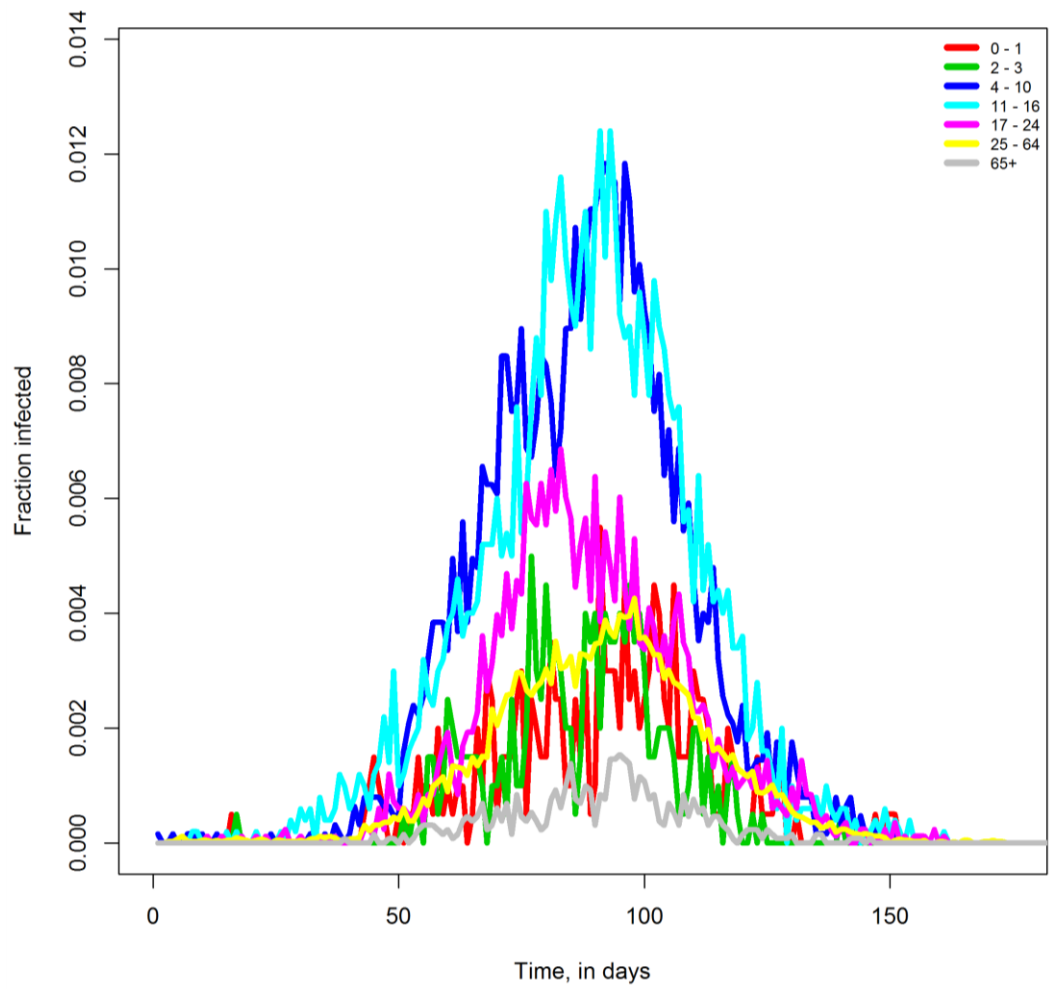
The mean duration in the school patches differs from the mean duration in their respective age groups (160.35 days (95% CI: 159.32-161.45 days) for all those attending primary schools compared to 108.84 days (95% CI: 108.61-109.07 days) for the mean duration of epidemics in primary schools, for example) because the latter result is the mean duration for each school. The mean duration of epidemics in a primary school according to this model was 108.84 days, but at the community level the infection existed in that age group for a mean time of 160.35 days.

	Median (min – max)	Mean (95% CI)
ILI Final Size (all primary schools)	38.00% (0.00-57.20%)	37.99% (37.90-38.87%)
ILI Final Size (all secondary schools)	40.10% (0.80-50.20%)	39.99% (39.88-40.10%)
ILI Final Size (external population)	12.63% (0.55-14.42%)	12.61% (12.58-12.65%)
ILI Duration in days (all primary schools)	106.00 (0.00-257.00)	108.84 (108.61-109.07)
ILI Duration in days (all secondary schools)	131.00 (44.00-269.00)	134.12 (133.66-134.58)
ILI Duration in days (external population)	163.00 (91.00-289.00)	165.85 (164.81-167.01)

*Table 6.9 - Results from 5,000 simulations of the metapopulation model with stochastic fadeouts excluded*

Figure 6.4 shows the epidemic curve for each age group during a typical simulated epidemic with no vaccination other than in the clinical at-risk groups. The stochastic model results agree with the deterministic model results from Chapter 6 that show the greatest burden of disease is seen in the primary and secondary school age groups.

Figure 6.5 shows patch-specific epidemic curves for the same epidemic. Dark blue curves represent the epidemics in each of the primary school patches; light blue curves for the secondary school epidemics and the single black curve for the external population. The single orange curve marks the primary school patch randomly chosen by the model to be seeded. The mean epidemic peak across primary schools varies from approximately 1.5% in one patch to 3% in another.



*Figure 6.4 - Age-specific epidemic curves for a typical epidemic simulated using the model*

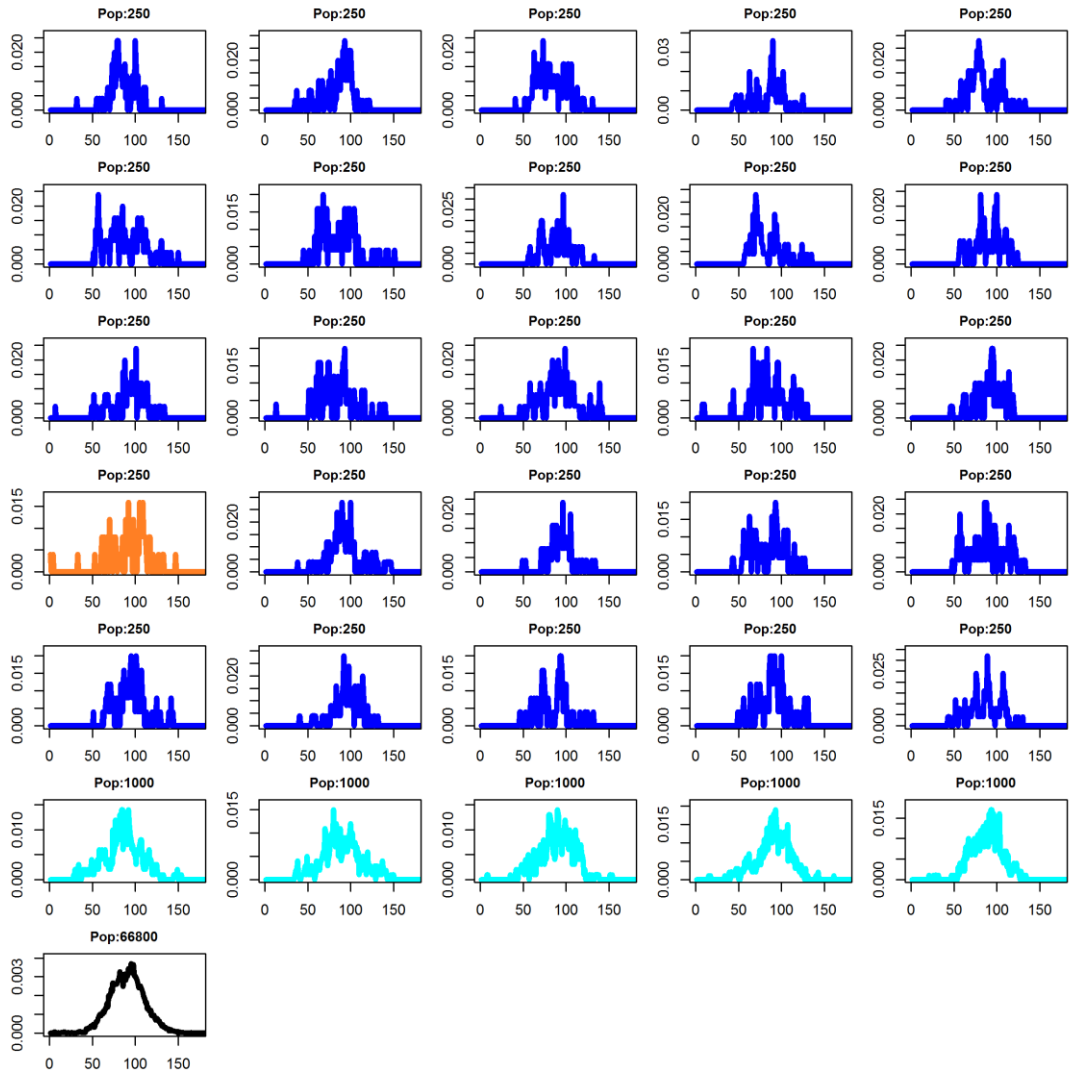


Figure 6.5 - Patch-specific epidemic curves for a typical epidemic simulated using the model. The final size of the epidemic is plotted on the vertical axis and the epidemic duration (in days) on the horizontal axis

#### VARYING THE $\epsilon_1$ PARAMETER

The mean final size of ILI epidemics in the metapopulation declines as  $\epsilon_1$  is increased from 0 to 1 (Table 6.10). That is, in a metapopulation where individuals of school-attending age have no contacts with those individuals in both the same age group and metapopulation patch the mean final size of ILI epidemics is at its maximum of 16.50% (95% CI: 16.47-16.54%) and a minimum of 16.28% (95% CI: 16.23-16.32%) when all contacts between school children occur in their own school with no mixing with other individuals in their age group from other schools.

	$\varepsilon_1 = 0.00$ Mean (95% CI)	$\varepsilon_1 = 0.25$ Mean (95% CI)	$\varepsilon_1 = 0.50$ Mean (95% CI)	$\varepsilon_1 = 0.75$ Mean (95% CI)	$\varepsilon_1 = 1.00$ Mean (95% CI)
ILI Final Size	16.50% (16.47- 16.54%)	16.49% (16.46- 16.53%)	16.46% (16.42- 16.50%)	16.40% (16.36- 16.44%)	16.28% (16.23- 16.32%)
ILI Duration (days)	168.03 (167.01- 169.07)	169.21 (168.09- 170.43)	169.32 (168.26- 170.42)	169.90 (168.81- 171.04)	173.95 (172.81- 175.10)
ILI Peak	0.479% (0.477- 0.483%)	0.476% (0.472- 0.479%)	0.475% (0.472- 0.478%)	0.468% (0.466- 0.471%)	0.454% (0.452- 0.457%)
ILI time for all patches to be infected (days)	43.04 (42.43- 43.67)	45.88 (45.19- 46.60)	48.75 (48.10- 49.47)	52.74 (52.06- 53.43)	60.09 (59.36- 60.85)
ILI Peak Time (days)	84.10 (83.32- 84.89)	84.60 (83.80- 85.48)	84.55 (83.72- 85.33)	85.32 (84.59- 86.16)	87.42 (86.63- 88.18)

*Table 6.10 - Model results after varying the  $\varepsilon_1$  parameter*

The scenario with  $\varepsilon_1 = 0$  is unlikely to occur as this would require all school-age children attending their respective schools to avoid contact with all other children attending their school. If  $\varepsilon_1 = 1$  then all mixing in a school child's age group takes place in their own school, which is also an unrealistic assumption. In the context of this metapopulation, the variation in  $\varepsilon_1$  results in an absolute difference in the mean final size of epidemics of 172 infections for the community.

There was strong evidence for a difference in the mean final size when  $\varepsilon_1 = 0.25$  and  $\varepsilon_1 = 0.75$  ( $W=1,751,612$ ,  $p=0.00076$ ), and when  $\varepsilon_1 = 0.50$  and  $\varepsilon_1 = 0.75$  ( $W=1,645,503$ ,  $p=0.03284$ ), but not between  $\varepsilon_1 = 0.25$  and  $\varepsilon_1 = 0.50$  ( $W=1,678,938$ ,  $p=0.2168$ ). However, in absolute terms the difference between the mean final size of epidemics when  $\varepsilon_1 = 0.25$  and  $\varepsilon_1 = 0.75$  is just 70 infections for the community. Both the mean duration of ILI epidemics and the mean epidemic peak time of ILI epidemics show minor variation with  $\varepsilon_1$  between 0 and 0.75, but  $\varepsilon_1 = 1$  increases both metrics.

As  $\varepsilon_1$  increases from 0 to 1 the mean time for infection to reach all 31 metapopulation patches increases exponentially from 43.04 days (95% CI: 42.43-43.67) to 60.09 days (95% CI: 59.36-60.85). Intuitively, as the proportion of an individual's daily contacts within their own patch increases, fewer contacts with individuals in other patches take place, therefore the epidemic will spread across the metapopulation at a slower rate.

It is important to note that  $\varepsilon_1 = 1$  does not mean that the 31 metapopulation patches are disconnected from one another, as contacts between individuals of different age groups do not depend on the  $\varepsilon_1$  parameter.



# TARGETED VACCINATION IN PRIMARY SCHOOLS ONLY

## TARGETED HOMOGENEOUS VACCINATION IN PRIMARY SCHOOLS

A vaccination programme of targeted coverage in primary schools alone reduces the mean final size and the mean peak of ILI epidemics (Figure 6.6) as vaccination coverage increases, though with 100% coverage in this age group the mean final size of epidemics in the metapopulation still reached 1.84% (95% CI: 1.49-2.22%). Mean duration and mean peak time also reduce.

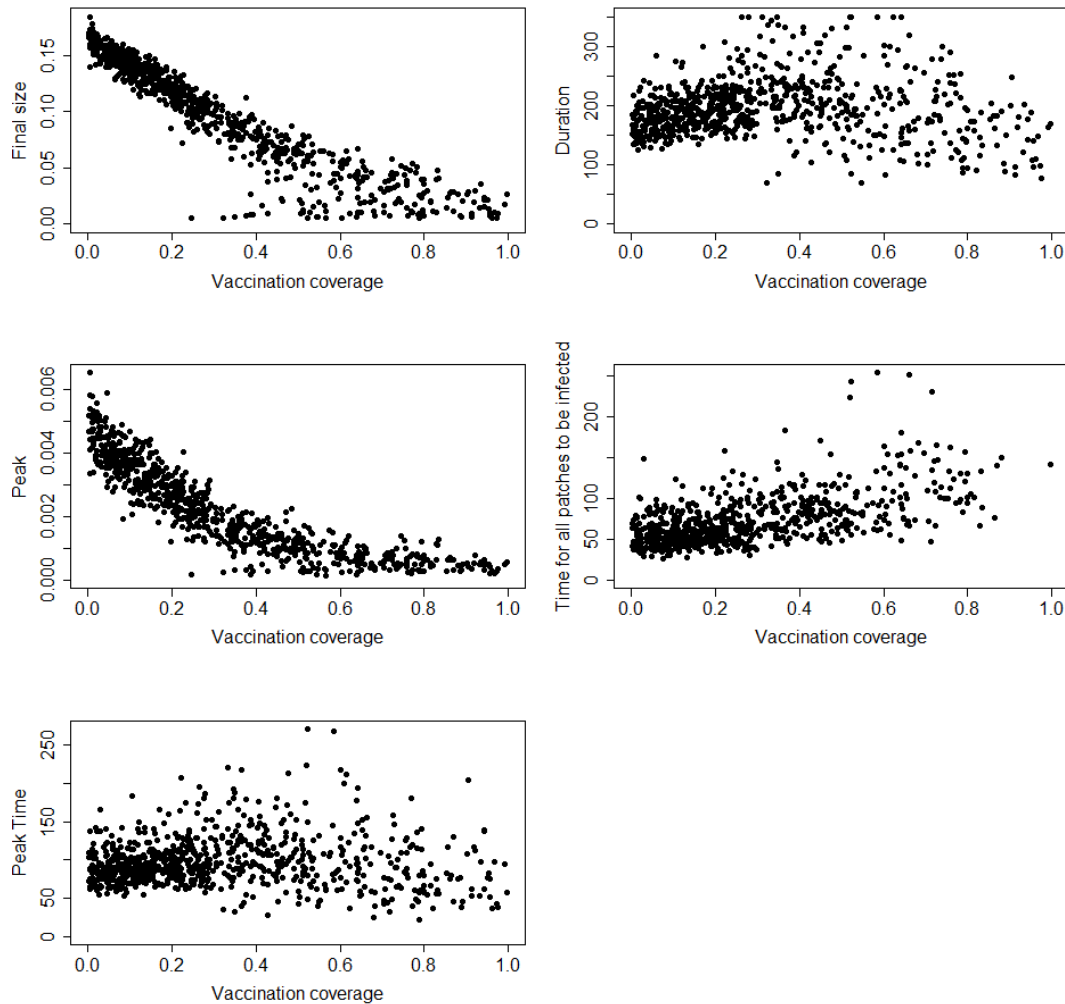


Figure 6.6 - Results from 5,000 simulations of the metapopulation model with targeted homogeneous vaccination coverage in primary schools only

Table 6.11 shows that the time for all patches to be infected with ILI increased as vaccination coverage increased, demonstrating that it became more difficult for the epidemic to spread through all metapopulation patches quickly at increasing coverage levels. However, even at full vaccination coverage for this programme it was still possible for the epidemic to reach all 31 metapopulation patches because the efficacy of the vaccine was less than 100% [22].

	Vaccination coverage				
	Mean (95% CI)				
	20%	40%	60%	80%	100%
ILI Final Size	11.86% (11.72-12.00%)	7.27% (6.96-7.55%)	3.76% (3.38-4.15%)	2.38% (2.01-2.78%)	1.84% (1.49-2.22%)
ILI Duration (days)	202.90 (198.60-207.15)	222.70 (214.77-230.16)	191.89 (179.87-203.56)	155.90 (141.45-169.75)	149.58 (133.46-166.13)
ILI Peak	0.266% (0.259-0.273%)	0.137% (0.130-0.144%)	0.076% (0.068-0.084%)	0.059% (0.051-0.068%)	0.048% (0.039-0.057%)
ILI time for all patches to be infected (days)	65.02 (62.69-67.51)	82.55 (78.43-87.06)	105.66 (97.71-114.24)	102.28 (89.50-117.11)	125.16 (77.0-174.0)
ILI Peak Time (days)	101.81 (98.95-104.74)	111.70 (106.09-117.68)	95.19 (87.19-104.01)	76.60 (67.81-86.34)	68.82 (55.95-83.04)

*Table 6.11 - Results from 5,000 simulations of the metapopulation model with targeted homogeneous vaccination coverage in primary schools only*

A targeted vaccination policy in primary schools would not eliminate the spread of seasonal influenza at the community level, similar to results from Chapter 5 showing that such a vaccination programme cannot eliminate nationwide influenza transmission.

#### VARYING THE $\epsilon_1$ PARAMETER

Figure 6.7 shows the effect of varying the  $\epsilon_1$  parameter in the model. As with previous results, increasing  $\epsilon_1$  to 1 marginally reduced the mean final size of epidemics. The mean duration of epidemics in the metapopulation also did not vary greatly with increasing  $\epsilon_1$ , nor did the mean peak of those epidemics and the timing of the peak. The mean time for all metapopulation patches to be infected increased as  $\epsilon_1$  increased, though as previously discussed the maximum time for complete epidemic spread across the metapopulation was seen when simulating epidemics with the unlikely scenario of  $\epsilon_1 = 1$ .

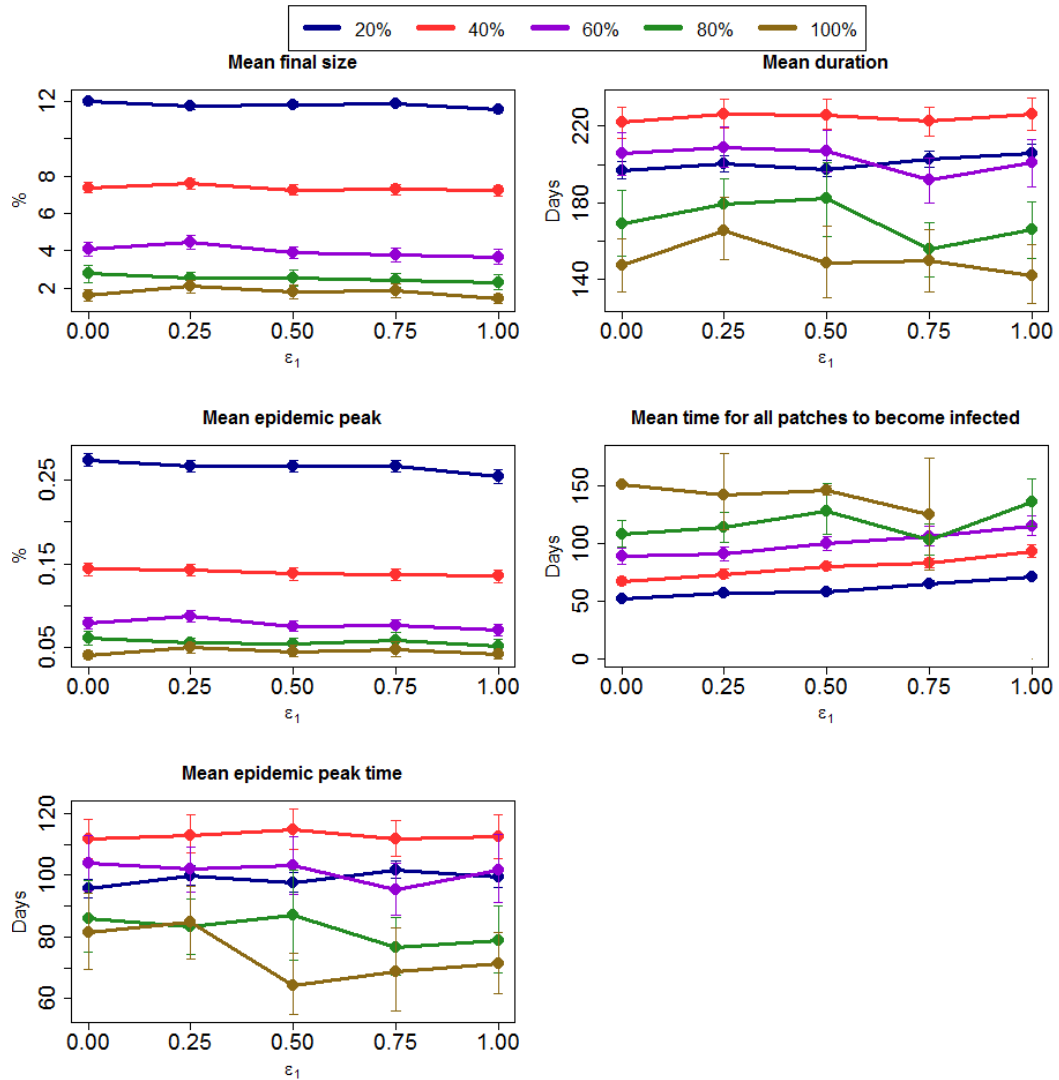


Figure 6.7 - Epidemic results with targeted homogeneous primary school vaccination and varying  $\varepsilon_1$  parameter

#### TARGETED HETEROGENEOUS VACCINATION IN PRIMARY SCHOOLS ONLY

With a vaccination policy that administers vaccines to those children attending primary schools only but sees unintended heterogeneous uptake in those primary schools (i.e. some schools to achieve only half the targeted coverage), there is little variation in the mean final size of the ILI epidemics with the number of low-coverage primary schools for low coverage levels of 20% (Figure 6.8).

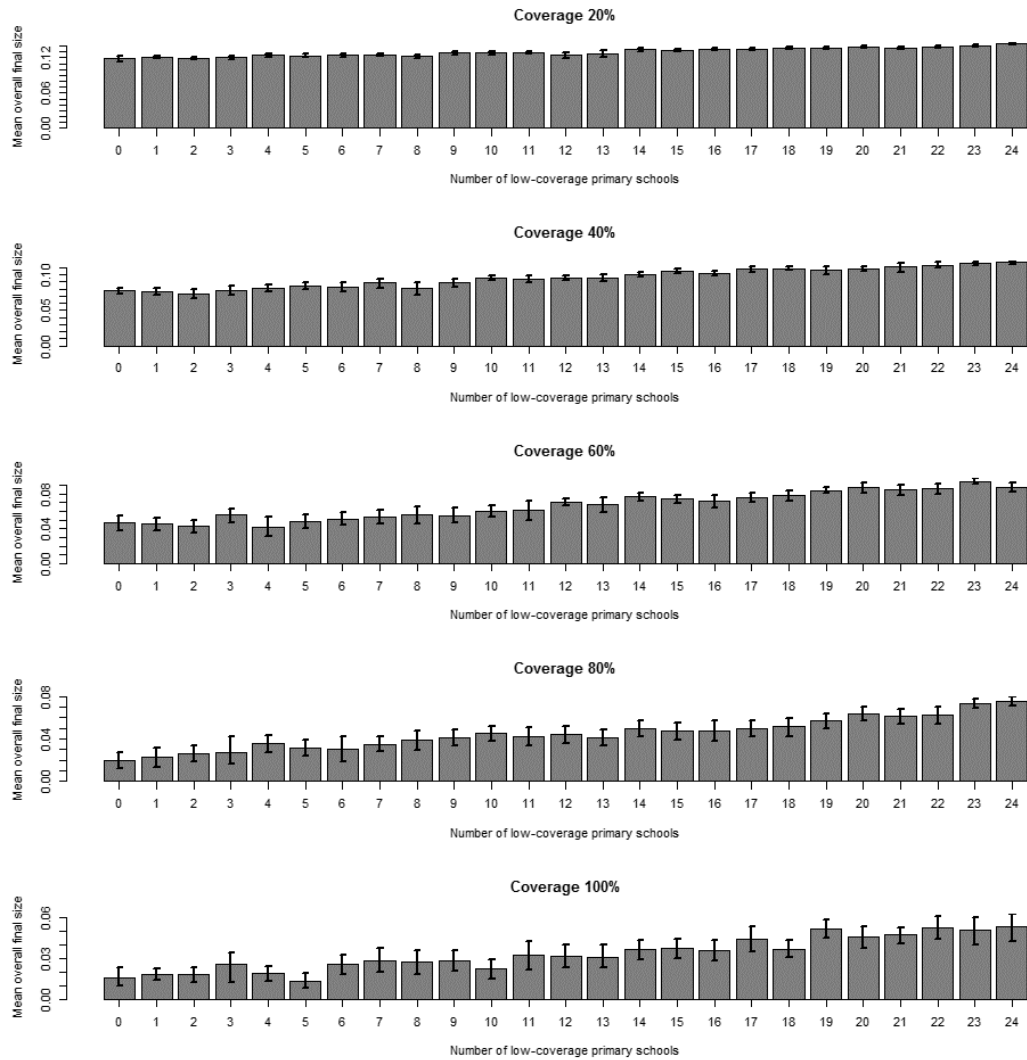


Figure 6.8 - Mean ILI final size for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in primary schools only

For increased coverage levels there is a clear trend with increasing mean final size and the increasing number of low-coverage primary schools – increasing the number of low-coverage primary schools will increase the mean final size of epidemics in the metapopulation, with these effects enhanced at higher vaccination levels.

Results for the mean duration, the mean peak, the mean time for all patches to become infected and the mean peak time are displayed in the appendix.

THE IMPACT OF A SINGLE LOW-COVERAGE PRIMARY SCHOOL IN THE METAPOPOPULATION WITH TARGETED VACCINATION IN PRIMARY SCHOOLS

Vaccination coverage 20%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
11.80% (11.50-12.07%)	12.06% (11.90-12.22%)	W=8,087.5, p=0.7151
Vaccination coverage 40%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
7.51% (7.07-7.90%)	7.57% (7.28-7.84%)	W=4,118, p=0.714
Vaccination coverage 60%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
3.95% (3.47-4.39%)	4.33% (3.76-4.85%)	W=1,084, p=0.2552
Vaccination coverage 80%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
2.34% (1.93-2.77%)	2.40% (1.97-2.85%)	W=459.5, p=0.7941
Vaccination coverage 100%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
1.25% (0.87-1.76%)	1.22% (0.95-1.51%)	W=139.5, p=0.5243

Table 6.12 - Comparing the final size of ILI epidemics with targeted heterogeneous vaccination in primary schools only

To examine the impact of a single low-coverage primary school in a scenario with targeted vaccination in primary schools we executed an additional 5,000 simulations with 0 or 1 low-coverage primary schools. In each case the vaccination coverage for high-coverage schools was varied, with  $\tau$  equal to half the target vaccination level.

Table 6.12 shows that there is little evidence that a single low-coverage primary school in the community has an impact on the mean final size of ILI epidemics. At all vaccination coverage levels in the high-coverage primary schools, there was no difference when increasing the number of low-coverage primary schools from 0 to 1.

#### VARYING THE $\tau$ PARAMETER

The parameter denoting the level of heterogeneity between high-coverage patches and low-coverage patches was set to  $\tau = 0.50$  in scenarios reported above. Here we executed additional simulations of the model for targeted heterogeneous vaccination primary schools for both  $\tau = 0.25$  and  $\tau = 0.75$ .

Figure 6.9 shows that increasing the  $\tau$  parameter from 0.25 to 0.75 consistently increases the mean final size of epidemics in the metapopulation at all vaccination coverage levels. With the maximum number of low-coverage primary schools in the metapopulation, the mean final size of epidemics with

$\tau = 0.25$  was 13.00% (95% CI: 12.76-13.24%) and 15.28% (95% CI: 15.07-15.48%) with  $\tau = 0.75$  with targeted coverage of 20%. With vaccination coverage reaching 100% the mean final size of epidemics in the same metapopulation configuration are 2.39% (95% CI: 1.55-3.21%) for  $\tau = 0.25$  and 10.75% (95% CI: 10.49-10.99%) for  $\tau = 0.75$ .

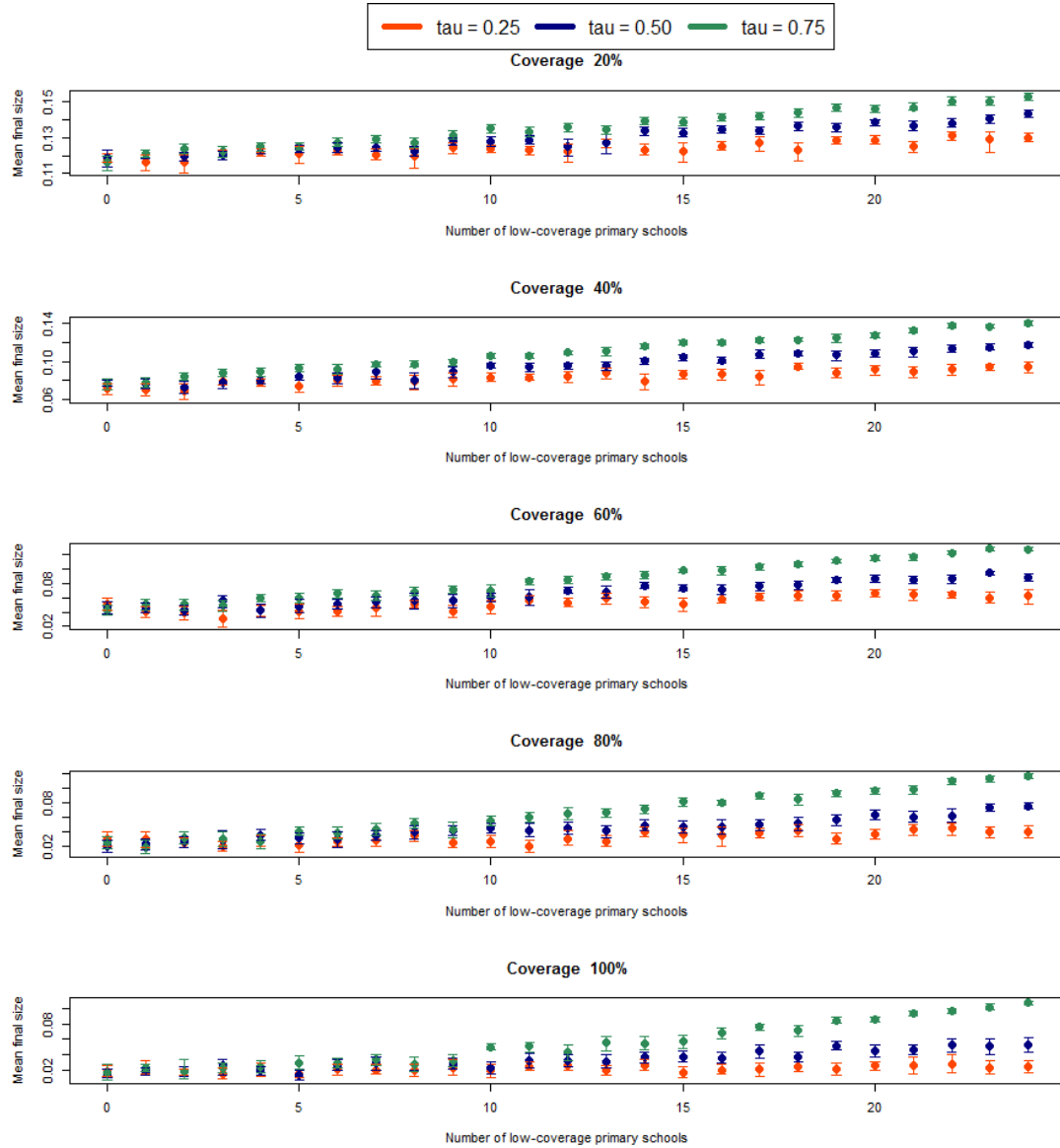


Figure 6.9 - Examining variation in the  $\tau$  parameter on the mean final size

Further results describing the impact of variation in the  $\tau$  parameter are displayed in the appendix.

INTENDED HETEROGENEITY THROUGH FIXED, CONCENTRATED VACCINATION COVERAGE

	Homogeneous coverage Mean (95% CI)	Concentrated coverage Mean (95% CI)
Results for the mean final size		
No vaccination	16.40% (16.36-16.44%)	N/A
20% coverage	11.41% (11.26-11.55%)	13.47% (13.38-13.55%)
40% coverage	7.05% (6.85-7.26%)	9.89% (9.74-10.04%)
60% coverage	3.96% (3.73-4.17%)	6.13% (5.92-6.35%)
80% coverage	2.51% (2.31-2.74%)	3.38% (3.15-3.61%)
Results for the mean duration		
No vaccination	169.9 days (168.8-171.0 days)	N/A
20% coverage	186.2 days (183.5-189.0 days)	173.5 days (171.7-175.2 days)
40% coverage	195.0 days (190.7-199.0 days)	187.5 days (184.6-190.7 days)
60% coverage	169.4 days (164.1-174.7 days)	183.5 days (178.9-188.2 days)
80% coverage	141.9 days (134.9-149.0 days)	160.4 days (153.8-166.9 days)
Results for the mean peak		
No vaccination	0.468% (0.466-0.471%)	N/A
20% coverage	0.272% (0.266-0.277%)	0.356% (0.352-0.360%)
40% coverage	0.150% (0.145-0.155%)	0.227% (0.223-0.232%)
60% coverage	0.095% (0.091-0.100%)	0.136% (0.131-0.141%)
80% coverage	0.070% (0.065-0.075%)	0.081% (0.076-0.086%)
Results for the mean time for all patches to become infected		
No vaccination	52.7 days (52.1-53.4 days)	N/A
20% coverage	55.7 days (54.5-56.9 days)	64.7 days (63.5-66.1 days)
40% coverage	70.7 days (68.5-73.0 days)	80.4 days (78.4-82.3 days)
60% coverage	87.3 days (83.3-91.3 days)	103.1 days (99.8-106.7 days)
80% coverage	101.5 days (93.8-110.2 days)	121.8 days (114.3-129.4 days)
Results for the mean peak time		
No vaccination	85.3 days (84.6-86.2 days)	N/A
20% coverage	90.1 days (88.2-92.0 days)	84.2 days (82.8-85.6 days)
40% coverage	96.0 days (92.9-99.2 days)	90.7 days (88.6-93.2 days)
60% coverage	85.9 days (82.4-89.8 days)	88.7 days (85.6-91.8 days)
80% coverage	67.0 days (62.6-71.6 days)	77.1 days (72.4-81.4 days)

*Table 6.13 - Targeted vaccination coverage in primary schools with both homogeneous coverage and concentrated coverage*

Homogeneous targeted coverage in primary schools reduces the mean final size of epidemics from 16.40% (95% CI: 16.36-16.44%) to 3.96% with 80% coverage (95% CI: 3.73-4.17%). A similar trend is seen when the same coverage levels are achieved by vaccinating a number of schools to 100%, leaving others without any coverage – the mean final size of epidemics decreased to 13.37% (95% CI: 13.38-13.55%) with 20% of primary schools fully vaccinated. However, this is greater than the final size with homogeneous 20% coverage and results in an additional 1,608 infections in the metapopulation. The trend of heterogeneous vaccination coverage resulting in a greater burden of disease continues for all vaccination coverage levels, even with the same number of vaccinations administered in both scenarios (Table 6.13). Concentrated coverage that results in heterogeneity between primary schools

would increase the mean final size of epidemics over the expected mean final size where homogenous vaccination is implemented.

Homogenous vaccination coverage increased the mean duration of epidemics to a maximum of 195.0 days (95% CI: 190.7-199.0) with 40% coverage, then reduced the duration to 141.9 days (95% CI: 134.9-149.0) at 80% coverage. The concentrated coverage levels decreased the mean duration for coverage of both 20% and 40% (173.5 days (95% CI: 171.7-175.2) and 187.5 days (95% CI: 184.6-190.7) respectively) but increased it with higher coverage of both 60% and 80% (183.5 days (95% CI: 179.9-188.2) and 160.4 days (95% CI: 153.8-166.9) respectively). If the primary aim of a vaccination programme is to reduce the mean final size of potential epidemics then heterogeneity in the vaccine uptake across the metapopulation will result in both a greater number of infected cases with longer epidemics for the highest levels of vaccination coverage.

Heterogeneity in the uptake of the vaccine across primary schools affects the mean epidemic peak in a similar manner to that of the mean final size, i.e. as vaccination coverage increases, the mean epidemic peak decreases but heterogeneity will result in greater epidemic peaks than with homogeneity. The mean epidemic peak reduced from 0.469% (95% CI: 0.463-0.472%) at baseline to 0.070% (95% CI: 0.065-0.075%) at 80% homogeneous coverage, but epidemics with 80% heterogeneous uptake had a mean epidemic peak of 0.081% (95% CI: 0.076-0.086%).

Heterogeneity in vaccination coverage consistently increased the mean time for all vaccination patches to become infected over that of a homogeneous policy. As previously mentioned, at baseline epidemics lasted a mean of 169.9 days (95% CI: 168.8-171.0), but they only took 52.7 days (95% CI: 52.1-53.4) to extend across all patches of the metapopulation. However, at 80% homogeneous coverage this increased to 101.5 days (95% CI: 93.8-110.2) to reach all 31 patches. By implementing a heterogeneous vaccination policy with coverage concentrated in several fully vaccinated schools, the mean time for all patches to be infected increased to 121.8 days (95% CI: 114.3-129.4) at 80% coverage. At this level of coverage, all attendees of 20 of the 25 primary schools would have been vaccinated. Infection still manages to reach these metapopulation patches because the vaccine efficacy was not 100%.

The timing of the epidemic peak behaves in the same manner as the mean epidemic duration, in that increasing coverage first increases the timing of the peak before the highest coverage levels reduce it below the baseline result. The mean time of the epidemic peak for 80% homogeneous coverage was 67.0 days (95% CI: 62.3-71.6), down from 85.3 days (95% CI: 84.6-86.2) at baseline. Heterogeneity at this level of coverage saw epidemics peaking on average after 77.1 days (95% CI: 72.4-81.4).



Heterogeneity in the target population whilst maintaining the same mean vaccination coverage does not reduce the expected final size of epidemics below the level expected with a homogeneous vaccination programme. For all four coverage levels modelled in the metapopulation (Figure 6.10 to Figure 6.13) the homogenous vaccination policy consistently resulted in the lowest mean final size of epidemics.

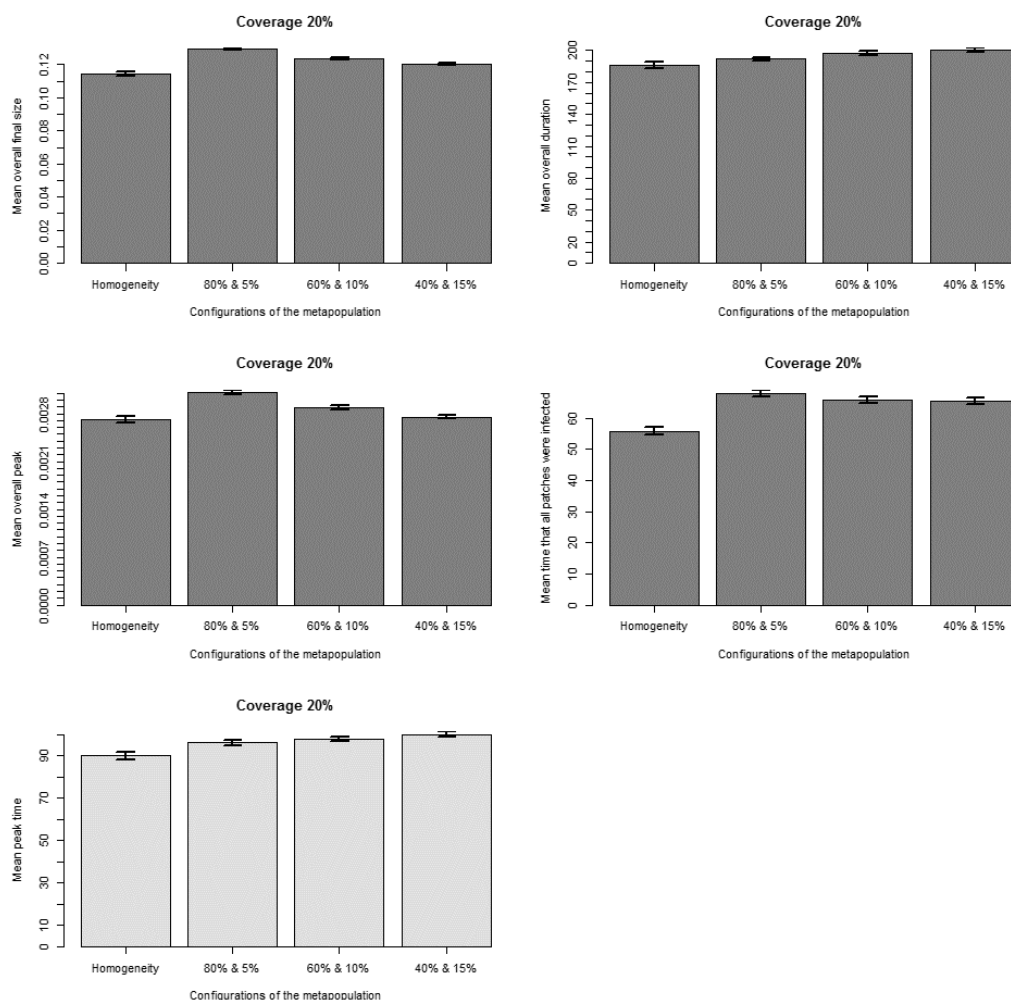
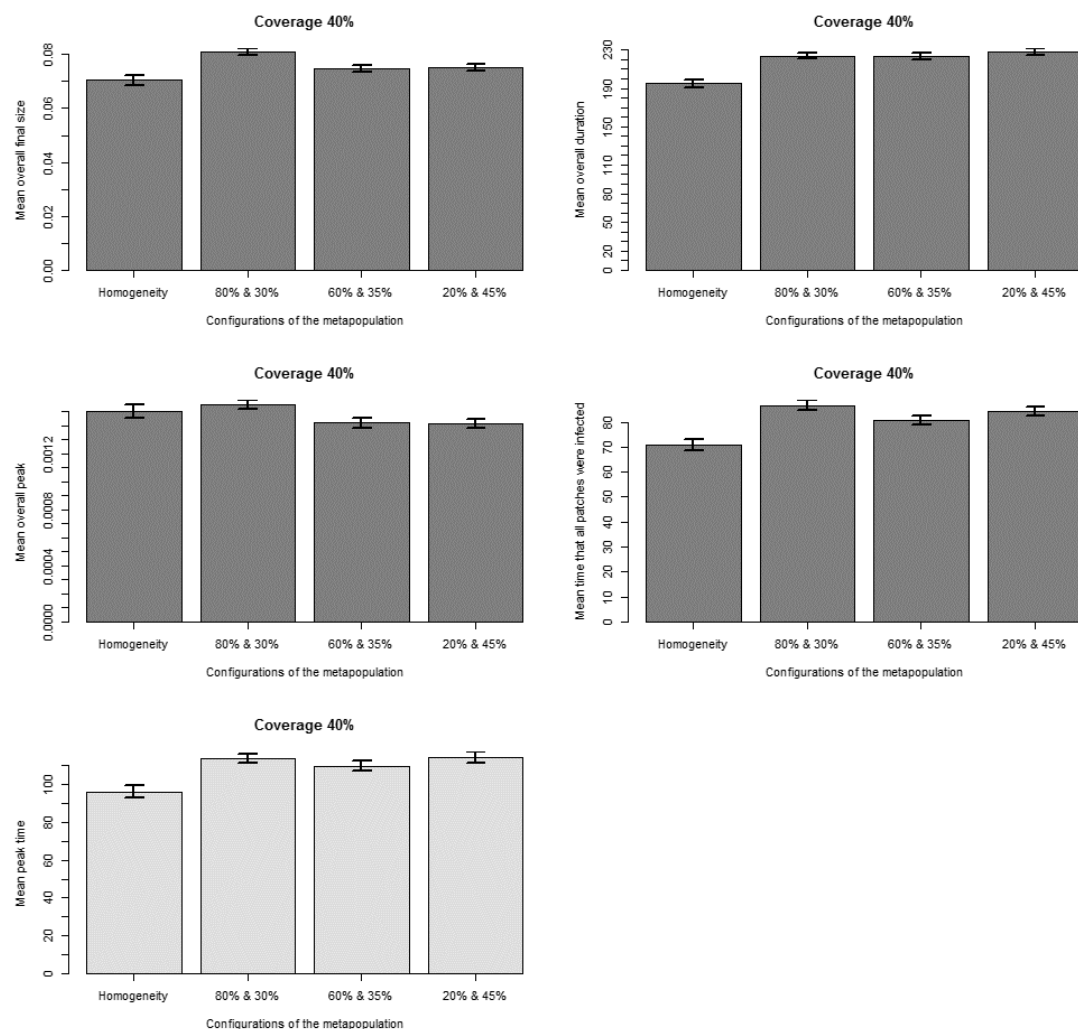


Figure 6.10 - Heterogeneity in a targeted vaccination programme for primary schools with mean overall coverage of 20%

With mean overall coverage of 20% in primary schools, the three alternative vaccination scenarios failed to reduce the mean final size of epidemics below that seen with a homogenous 20% coverage level (Figure 6.10). Homogeneous coverage results in a mean final size of 11.41% (95% CI: 11.28-11.55%), with the best-performing heterogeneous vaccination coverage achieving 12.03% (95% CI: 11.97-12.09%) with five schools increasing coverage to 40% and the remaining 20 schools decreasing coverage to 15%.

The mean duration of epidemics increased from 186.19 days (95% CI: 183.49-188.78) to a maximum of 200.24 days (95% CI: 198.49-201.99), again with five schools reporting coverage 40% and 20 schools reporting coverage of 15%. The mean time for all metapopulation patches to become infected increased above the mean time reported for homogeneous vaccination coverage (55.70 days (95% CI: 54.46-56.95)) to a maximum of 67.91 days (95% CI: 66.89-68.98) with five schools reporting 80% coverage and 20 schools reporting 5% coverage. The mean size of the epidemic peak followed the trend of the mean final size, and the mean time to reach the epidemic peak followed the trend of the mean duration of epidemics.



*Figure 6.11 - Heterogeneity in a targeted vaccination programme for primary schools with mean overall coverage of 40%*

Heterogeneous vaccination strategies with a mean overall coverage of 40% follow similar patterns to those discussed with 20% coverage. Figure 6.11 shows that the vaccination strategy resulting in the greatest mean final size was the strategy with the largest discrepancy between the two groups with different vaccination coverage. With five schools vaccinating to 80% coverage and 20 schools

vaccinating to 30% coverage, the mean final size of epidemics increased from 7.05% (95% CI: 6.84-7.24%) to 8.10% (95% CI: 7.99-8.21%). However, the heterogeneous strategy with the least heterogeneity in coverage between the two groups resulted in the longest mean epidemic duration, increasing the duration of epidemics from 194.87 days (95% CI: 190.39-199.07) at homogeneity to 227.42 days (95% CI: 224.02-230.89). Maximum heterogeneity in the vaccination coverage resulted in the longest mean time for the epidemic to reach all metapopulation patches, extending this time from 70.74 days (95% CI: 68.55-72.96) at homogeneity to 86.50 days (95% CI: 84.57-88.52).

Two heterogeneous vaccination strategies reduced the mean size of the epidemic peak, from 0.150% (95% CI: 0.146-0.155%) at homogeneity to 0.142% (95% CI: 0.138-0.145%) and 0.141% (95% CI: 0.138-0.145%) for strategies with five schools with 60%/20% coverage and 20 schools with 35%/45% coverage respectively.

With mean overall coverage of 60%, all three vaccination strategies with heterogeneity reduced the mean size of the epidemic peak from 0.095% (95% CI: 0.091-0.100%) at homogeneity to a minimum of 0.082% (95% CI: 0.078-0.085%) using a vaccination strategy consisting of five schools with 40% coverage and 20 schools with 65% coverage (Figure 6.12).

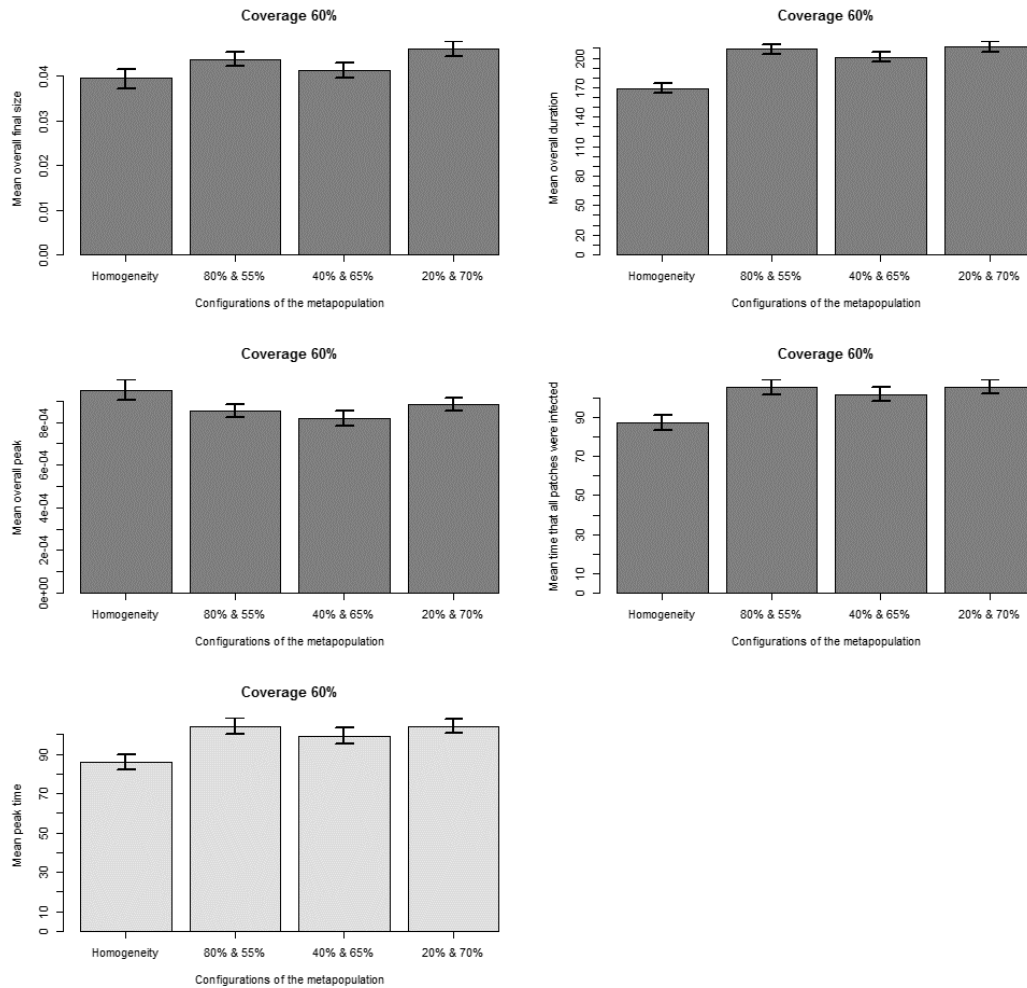


Figure 6.12 - Heterogeneity in a targeted vaccination programme for primary schools with mean overall coverage of 60%

All other metrics increased with heterogeneity in vaccination coverage introduced to the metapopulation. The vaccination strategy with the greatest level of heterogeneity (five schools with 20% coverage and 20 schools with 70% coverage) increased the mean final size to a maximum of 4.61% (95% CI: 4.45-4.76%). Heterogeneity also increased the mean duration of epidemics, delayed the mean time of the epidemic peak and increased the mean time for all patches to be infected.

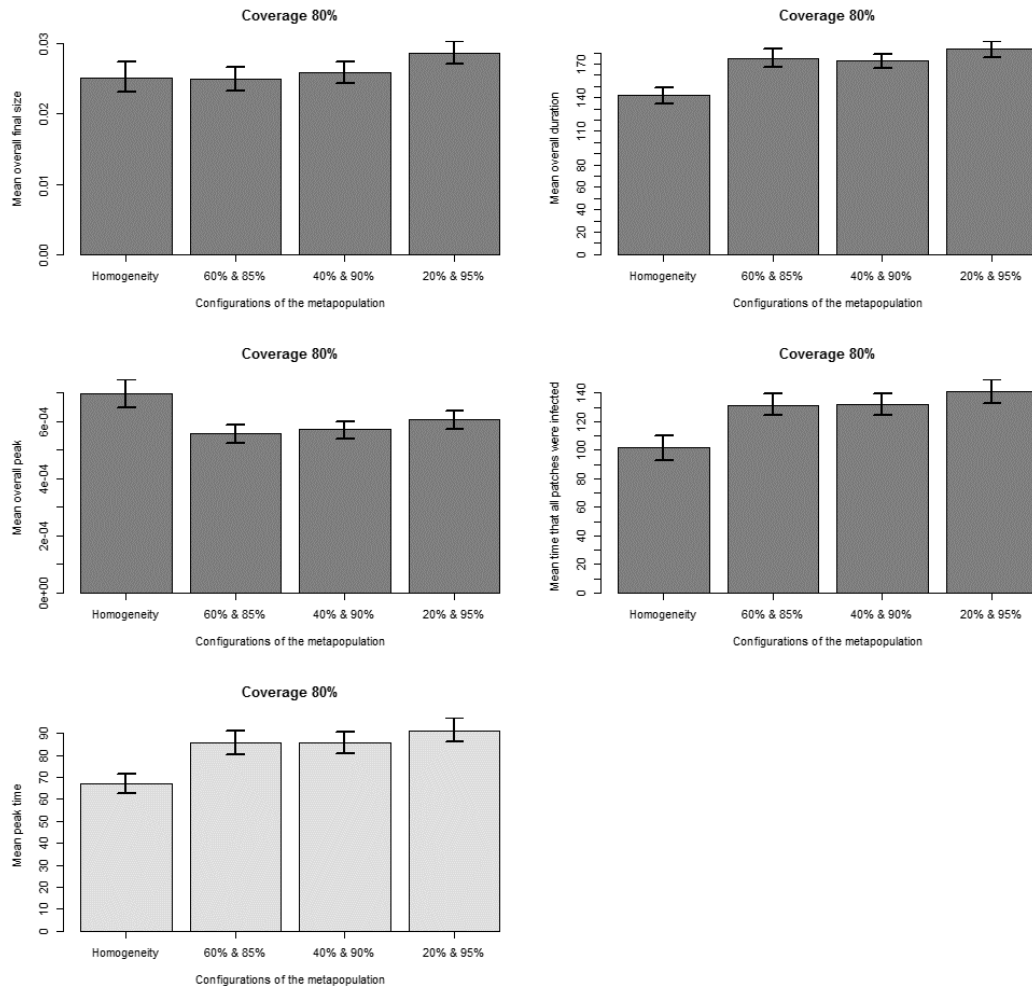


Figure 6.13 - Heterogeneity in a targeted vaccination programme for primary schools with mean overall coverage of 80%

For vaccination strategies with five schools with 60%/40% coverage and 20 schools with 85%/90% coverage respectively, the mean final size of epidemics were very similar to that with homogeneous 80% coverage – 2.50% (95% CI: 2.34-2.67%) and 2.58% (95% CI: 2.42-2.73%) respectively, compared to 2.51% (95% CI: 2.31-2.76%) with homogeneity. There was insufficient evidence to say that the strategy with 60% coverage in five schools and 85% in 20 schools reduced the mean final size of epidemics ( $W=21,014$ ,  $p=0.8949$ ), but very good evidence ( $W=23,890.5$ ,  $p=0.01673$ ) that a heterogeneous strategy of five schools with 20% coverage and 20 schools with 95% coverage resulted in an increase in the mean final size of epidemics to 2.85% (95% CI: 2.69-3.04%).

All three vaccination strategies with heterogeneity reduced the mean size of the epidemic peak from 0.070% (95% CI: 0.065-0.075%) with homogeneity to a minimum of 0.055% (95% CI: 0.053-0.059%) in a metapopulation with five schools with 60% coverage and 20 schools with 85% coverage. Heterogeneity in vaccination uptake increased the mean duration of epidemics, the mean time of the epidemic peak and the mean time for all patches to become infected.

Targeted vaccination in primary schools cannot eliminate the potential for epidemics to occur in the metapopulation - the mean final size of epidemics with 100% coverage was 1.84% (95% CI: 1.49-2.22%).

Uncertainty in the  $\varepsilon_1$  parameter provided marginal variation in the mean final size of epidemics for any level of targeted homogeneous coverage. However, increasing this parameter in the model resulted in a longer mean time for epidemics to spread to all metapopulation patches. With  $\varepsilon_1 = 1$  and vaccination coverage reaching 100% epidemics did not spread to all metapopulation patches.

Unintended heterogeneity through primary schools failing to achieve the targeted vaccination coverage consistently increased the expected mean final size of epidemics in the metapopulation. The increase in heterogeneity through additional low-coverage schools had the greatest impact on the mean final size when the targeted vaccination coverage was high – for vaccination programmes with 20% vaccination coverage the mean final size of epidemics for both 0 and 24 low-coverage primary schools was 11.89% (95% CI: 11.31-12.29%) and 14.34% (95% CI: 14.15-14.54%). With 100% targeted coverage the results were 1.55% (95% CI: 0.971-2.21%) and 5.31% (95% CI: 4.29-6.20%) respectively. However, the existence of a single low-coverage primary school in the metapopulation had no impact of the mean final size of epidemics for all simulated vaccination coverage levels. With 100% vaccination coverage it was possible for epidemics to spread to all metapopulation patches once 5 or more primary schools achieved only half the coverage of the remaining 20 primary schools.

Changing the level of heterogeneity between a low-coverage primary school and a high-coverage primary school changes the mean final size of epidemics for all levels of coverage. Increasing the heterogeneity between low- and high-coverage schools increases the mean final size of epidemics. Intended heterogeneity in the vaccination programme by concentrating coverage in primary schools consistently increased the mean final size of epidemics, the mean epidemic peak and the mean time for all patches to become infected. The impact on the duration of epidemics and the timing of the peak was dependent on the targeted vaccination coverage - that is epidemics were shorter with concentrated vaccination coverage of 20% and 40% than for homogeneous vaccination coverage, but longer for higher coverage of 60% and 80%. Vaccination strategies with intended heterogeneity that ensured all primary school patches were included in the vaccination programme consistently failed to reduce the mean final size of epidemics, and in many cases increased the total burden of disease by introducing heterogeneous uptake between the 25 primary schools.

# TARGETED VACCINATION IN SECONDARY SCHOOLS ONLY

## TARGETED HOMOGENEOUS VACCINATION IN SECONDARY SCHOOLS

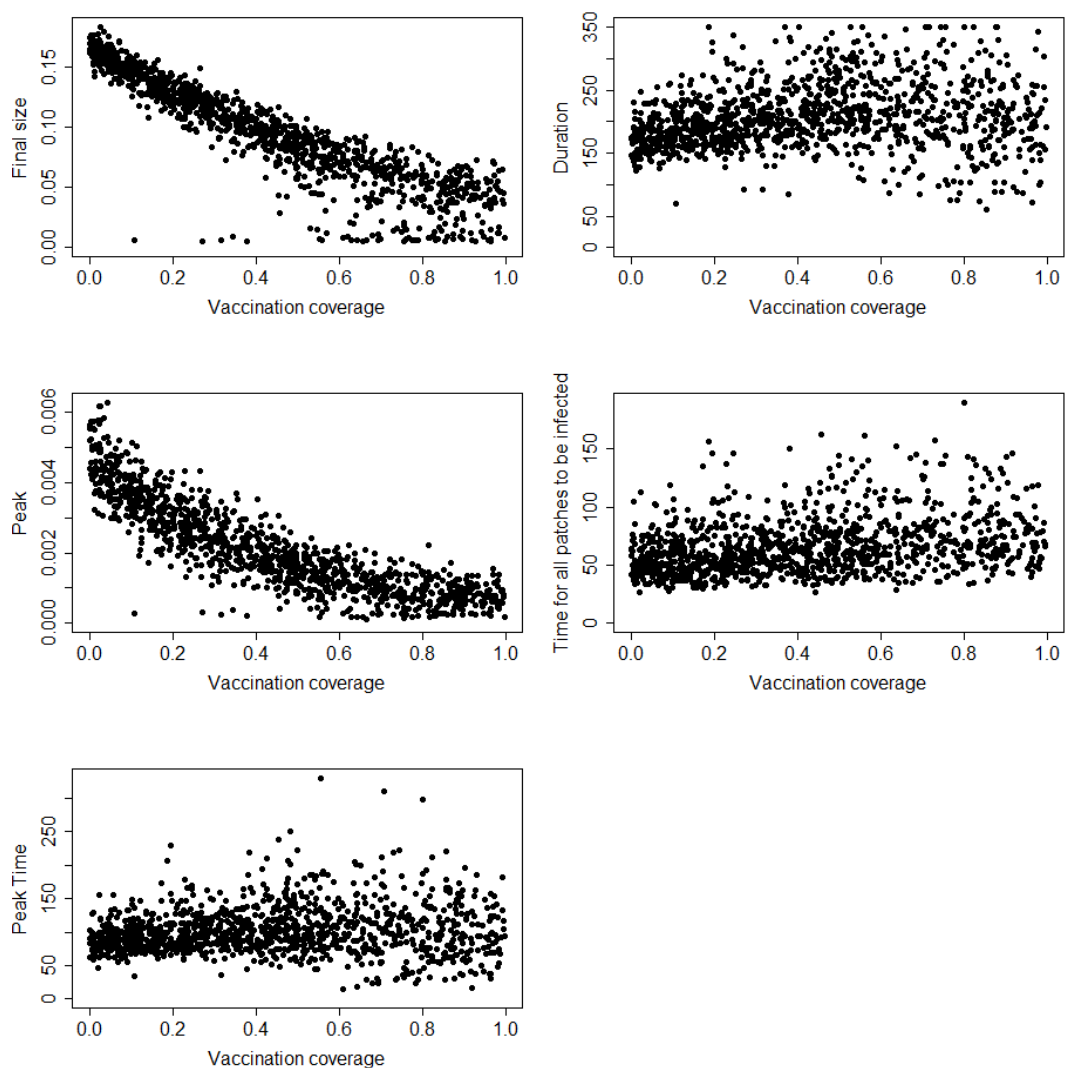


Figure 6.14 - Results from 5,000 simulations of the metapopulation model with targeted homogeneous vaccination coverage in secondary schools only

Figure 6.14 shows the results from the model for vaccinating secondary schools with a homogenous vaccination strategy. With results consistent with targeted homogenous vaccination in primary schools, sustained influenza transmission in the community cannot be eliminated even with 100% vaccination coverage.

Table 6.14 shows the reduction in the mean final size of ILI epidemics as vaccination coverage in secondary schools increases. The results expand on those shown in Figure 6.14, the maximum coverage in secondary schools reducing the mean final size of epidemics to 3.58% (95% CI: 3.32-3.86%).

	Vaccination coverage				
	Mean (95% CI)				
	20%	40%	60%	80%	100%
ILI Final Size	12.91% (12.79-13.02%)	9.53% (9.33-9.72%)	6.81% (6.56-7.03%)	4.69% (4.40-4.96%)	3.58% (3.32-3.86%)
ILI Duration (days)	198.58 (194.56-202.60)	219.59 (214.38-225.56)	230.63 (223.84-237.80)	209.60 (200.61-217.83)	191.47 (181.86-200.91)
ILI Peak	0.306% (0.300-0.312%)	0.188% (0.182-0.194%)	0.123% (0.118-0.128%)	0.088 (0.082-0.093%)	0.071% (0.066-0.075%)
ILI time for all patches to be infected (days)	62.04 (59.80-64.40)	65.72 (63.19-68.68)	73.41 (70.01-77.10)	72.61 (68.73-76.72%)	75.03 (70.47-79.39)
ILI Peak Time (days)	99.74 (96.86-102.70)	107.10 (103.00-111.40)	116.25 (110.91-122.00)	100.29 (93.27-107.23)	96.95 (88.67-104.65)

*Table 6.14 - Results from 5,000 simulations of the metapopulation model with targeted homogeneous vaccination coverage in secondary schools only*

#### VARYING THE $\varepsilon_1$ PARAMETER

Figure 6.15 shows the effect of varying the  $\varepsilon_1$  parameter in the model. The variation in the  $\varepsilon_1$  parameter has a negligible effect until we consider the mean time for all patches in the metapopulation to be infected – here, for all vaccination coverage levels in the secondary school patches the epidemics took longer to infect all patches as the  $\varepsilon_1$  parameter increased to 1.



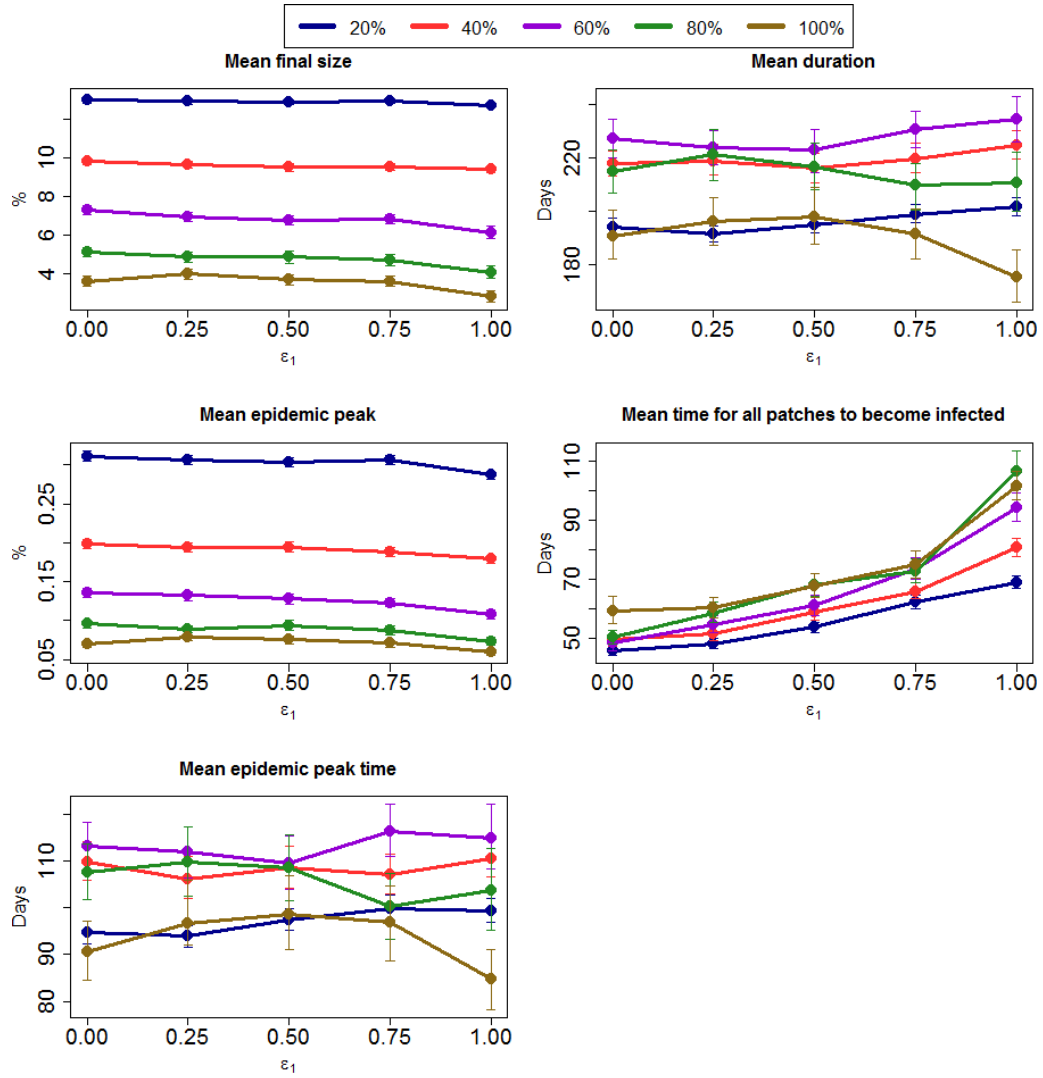


Figure 6.15 - Epidemic results with targeted homogeneous secondary school vaccination and varying  $\varepsilon_1$  parameter

#### TARGETED HETEROGENEOUS VACCINATION IN SECONDARY SCHOOLS ONLY

With a vaccination programme targeting only the secondary schools in the metapopulation but coverage heterogeneity persisting, Figure 6.16 shows the impact of the increasing number of low-coverage secondary schools and the mean final size of the ILI epidemics.

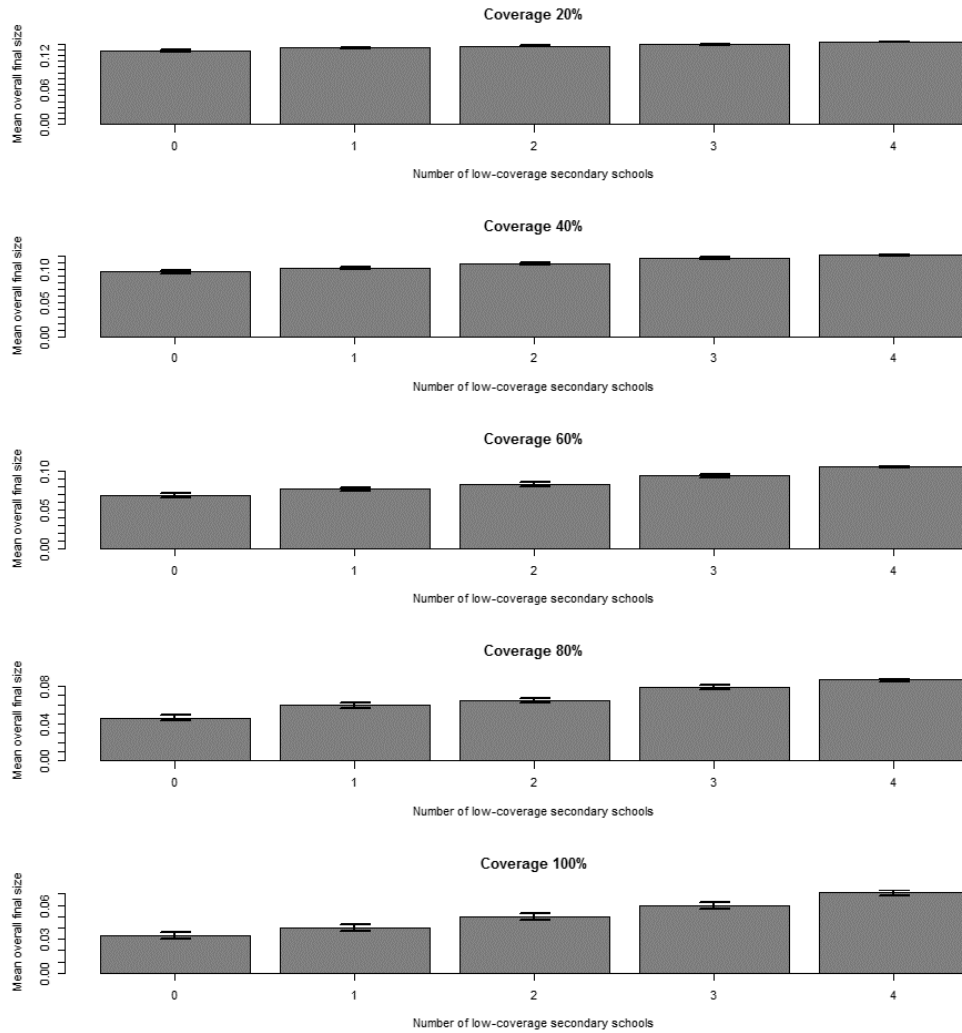


Figure 6.16 - Mean ILI final size for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in secondary schools only

At 20% coverage in secondary schools, the mean final size of the epidemics increased from 12.79% (95% CI: 12.64-12.93%) to 14.32% (95% CI: 14.23-14.42%) as the number of low-coverage schools increased from 0 to 4. The difference between the mean final size with homogeneous targeted coverage and the maximum number of low-coverage secondary schools increases as the targeted coverage increases to 100%. At 60% coverage, the mean final sizes for epidemics in metapopulations with 0 and 4 low-coverage schools were 6.83% (95% CI: 6.58-7.07%) and 10.53% (95% CI: 10.41-10.65%) respectively. At 100% coverage, this discrepancy extended from 3.29% (95% CI: 3.02-3.57%) to 7.08% (95% CI: 6.84-7.32%) respectively.

Results for the mean duration, the mean peak, the mean time for all patches to become infected and the mean peak time are displayed in the appendix.

Table 6.15 shows the comparison of targeted vaccination in secondary schools at four coverage levels with the scenario of one low-coverage secondary school when 5,000 additional simulations at varying vaccination coverage levels were executed for 0 or 1 low-coverage secondary schools. For all levels of vaccination coverage there was strong evidence that a single low-coverage secondary school can increase the mean final size of ILI epidemics in the metapopulation.

Vaccination coverage 20%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
12.77% (12.59-12.95%)	13.36% (13.23-13.48%)	W=7,060, p<<0.001
Vaccination coverage 40%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
9.58% (9.32-9.80%)	10.37% (10.18-10.59%)	W=5,291, p<<0.001
Vaccination coverage 60%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
6.65% (6.22-7.04%)	7.68% (7.32-8.01%)	W=3,200, p<<0.001
Vaccination coverage 80%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
4.65% (4.21-5.05%)	5.82% (5.44-6.18%)	W=2,255, p<<0.01
Vaccination coverage 100%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
3.71% (3.38-4.08%)	4.26% (3.85-4.67%)	W=3,357, p=0.02632

Table 6.15 - Comparing the final size of ILI epidemics with targeted heterogeneous vaccination in secondary schools only

#### VARYING THE $\tau$ PARAMETER

The  $\tau$  parameter was varied to examine the effect of the level of heterogeneity between high-coverage secondary schools and low-coverage secondary schools.

Figure 6.17 shows that the mean final size of epidemics in the metapopulation was increased as the level of heterogeneity between low- and high-coverage patches was increased from  $\tau = 0.25$  to  $\tau = 0.75$ . With the maximum number of low-coverage secondary schools in the metapopulation, the mean final size of epidemics increased from 13.59% (95% CI: 13.44-13.71%) with  $\tau = 0.25$  to 15.04% (95% CI: 14.95-15.12%) with  $\tau = 0.75$  when vaccination coverage was 20%. At coverage of 100% the mean final size of epidemics was 5.08% (95% CI: 4.78-5.36%) for  $\tau = 0.25$  and 10.52% (95% CI: 10.37-10.66%) for  $\tau = 0.75$ .

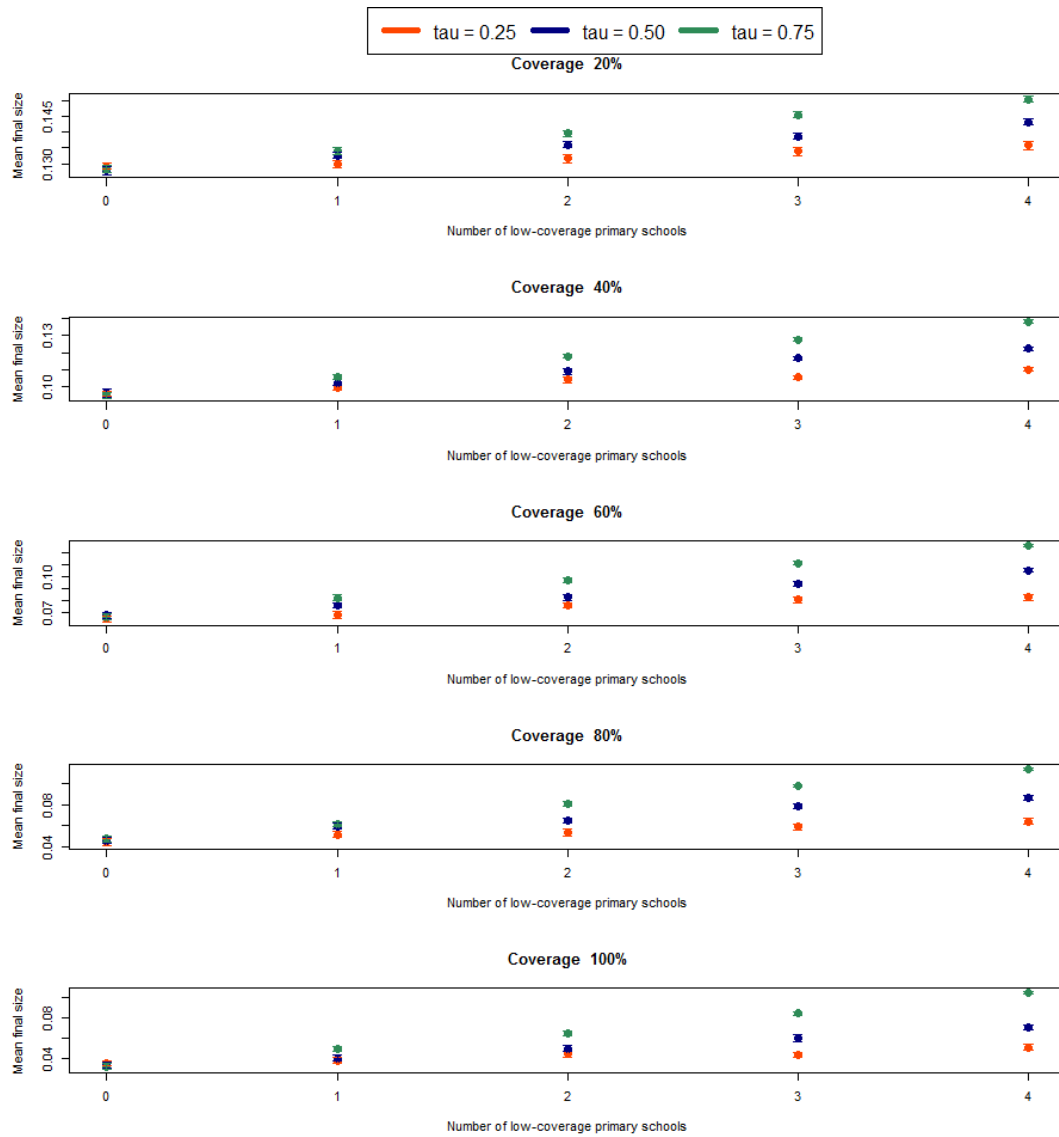


Figure 6.17 - Examining variation in the  $\tau$  parameter on the mean final size

Further results describing the impact of variation in the  $\tau$  parameter are displayed in the appendix.

INTENDED HETEROGENEITY THROUGH FIXED, CONCENTRATED VACCINATION COVERAGE

	Homogeneous coverage	Concentrated coverage
Results for the mean final size		
No vaccination	16.40% (16.36-16.44%)	N/A
20% coverage	12.56% (12.45-12.67%)	13.92% (13.85-14.00%)
40% coverage	9.03% (8.86-9.20%)	11.19% (11.07-11.30%)
60% coverage	6.40% (6.22-6.57%)	8.11% (7.93-8.28%)
80% coverage	4.38% (4.20-4.57%)	5.49% (5.31-5.69%)
Results for the mean duration		
No vaccination	169.9 days (168.8-171.0 days)	N/A
20% coverage	184.3 days (182.3-186.4 days)	173.9 days (172.0-175.6 days)
40% coverage	197.2 days (194.2-200.3 days)	186.5 days (184.2-188.9 days)
60% coverage	194.0 days (189.9-198.0 days)	194.5 days (190.1-198.2 days)
80% coverage	172.5 days (168.2-177.1 days)	182.0 days (178.2-186.1 days)
Results for the mean peak		
No vaccination	0.468% (0.466-0.471%)	N/A
20% coverage	0.305% (0.301-0.310%)	0.369% (0.364-0.373%)
40% coverage	0.193% (0.189-0.198%)	0.263% (0.259-0.268%)
60% coverage	0.134% (0.130-0.138%)	0.174% (0.169-0.179%)
80% coverage	0.099% (0.096-0.102%)	0.121% (0.117-0.126%)
Results for the mean time for all patches to become infected		
No vaccination	52.7 days (52.1-53.4 days)	N/A
20% coverage	51.3 days (50.2-52.4 days)	49.3 days (48.3-50.2 days)
40% coverage	55.6 days (54.2-57.1 days)	51.9 days (50.8-52.9 days)
60% coverage	59.0 days (57.5-60.7 days)	57.0 days (55.5-58.5 days)
80% coverage	60.3 days (58.6-62.0 days)	60.5 days (58.8-62.3 days)
Results for the mean peak time		
No vaccination	85.3 days (84.6-86.2 days)	N/A
20% coverage	88.8 days (87.2-90.4 days)	84.5 days (83.1-85.9 days)
40% coverage	94.6 days (92.3-97.3 days)	89.8 days (88.0-91.5 days)
60% coverage	93.2 days (90.4-96.4 days)	94.9 days (92.4-97.5 days)
80% coverage	82.8 days (79.8-85.9 days)	87.9 days (85.0-90.6 days)

*Table 6.16 - Targeted vaccination coverage in secondary schools with both homogeneous coverage and concentrated coverage*

Results for intended heterogeneity within a targeted vaccination policy in secondary schools are consistent with those results for primary schools, where some schools receive 100% vaccination whilst others receive none. The mean final size of epidemics in the metapopulation reduces with an increase in vaccination coverage, but heterogeneity increases the mean final size over the same results for homogeneous coverage (Table 6.16).

Concentrating mean vaccination coverage in selected secondary schools is detrimental to public health vaccination programmes that seek to minimise the potential final size of epidemics in the metapopulation. Similar results are seen for the mean size of the epidemic peak, with an increase in vaccination coverage decreases the mean epidemic peak from the baseline result, but concentrated vaccination coverage increase the mean epidemic peak over that through a homogeneous policy.

The mean duration of epidemics increases above baseline for coverage levels of 20% and 40%, but then reduces for the higher coverage levels. At these higher levels of coverage, heterogeneity through the concentration of vaccination coverage increases the mean duration of epidemics above that expected in the homogeneous case. The mean time of the epidemic peak behaves in a similar way to the mean duration when vaccination coverage is increased both with and without heterogeneity.

#### INTENDED HETEROGENEITY WITH VACCINATION IN ALL TARGETED PATCHES

Heterogeneous coverage strategies that administered vaccinations in all secondary school patches failed to reduce the mean final size of epidemics, results consistent with the heterogeneous vaccination strategies used in primary schools. The four coverage levels included in simulations could not improve on the mean final size of epidemics with homogeneous coverage (Figure 6.18 to Figure 6.21).

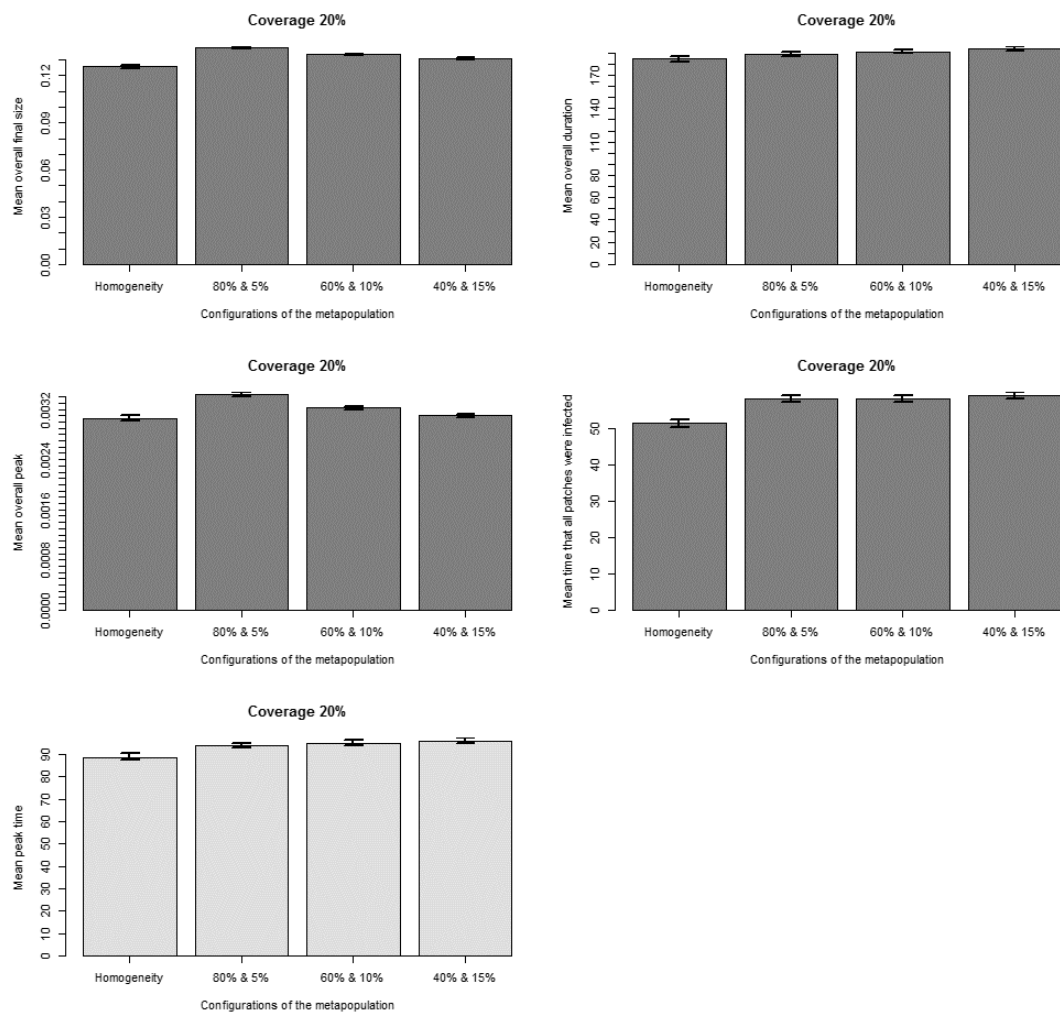


Figure 6.18 - Heterogeneity in a targeted vaccination programme for secondary schools with mean overall coverage of 20%

The mean final size of epidemics reached its maximum when heterogeneity between the two groups in the secondary school patches reached its highest degree. With one school with 80% coverage and four schools with 5% coverage the mean final size of epidemics was 13.76% (95% CI: 13.71-13.81%), up from 12.56% (95% CI: 12.45-12.67%) with homogenous 20% coverage (Figure 6.18). The increase in the mean size of the epidemic peak followed the same trend.

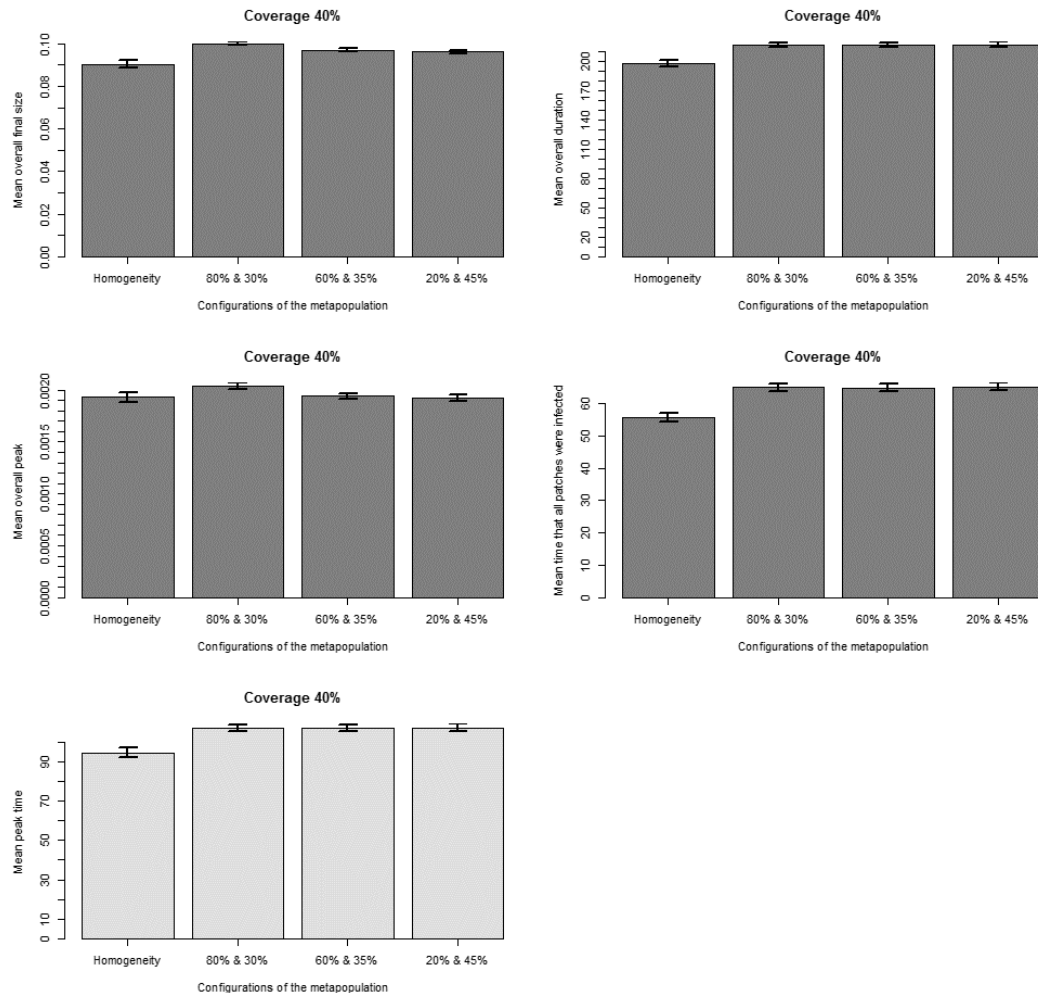


Figure 6.19 - Heterogeneity in a targeted vaccination programme for secondary schools with mean overall coverage of 40%

The mean duration of epidemics reached a maximum of 193.53 days (95% CI: 192.09-194.97) with one school with 40% coverage and four schools with 15% coverage, up from 184.32 days (95% CI: 182.20-186.57) with homogeneous coverage. The mean time of the epidemic peak behaved in the same way. All three heterogeneous vaccination strategies increased the mean time for the epidemic to reach all metapopulation patches, increasing from 51.25 days (95% CI: 50.19-52.30) to a maximum of 58.87 days (95% CI: 57.99-59.84) with one school with 40% coverage and four schools with 15% coverage. However, there was very little variation in this metric across all three heterogeneous vaccination strategies at 20% overall coverage.

Heterogeneity in vaccination uptake among secondary schools resulted in larger epidemics than those occurring with homogeneous 40% coverage (Figure 6.19). The mean final size of epidemics rose from 9.03% (95% CI: 8.86-9.20%) to a maximum of 9.99% (9.91-10.06%) with one school with 80% coverage and four schools with 30% coverage, the highest degree of heterogeneity between the two groups in the secondary school patches. This vaccination strategy also resulted in the highest mean peak of 0.204% (95% CI: 0.201-0.207%), up from 0.193% (95% CI: 0.188-0.198%) with homogeneity.

There was little variation between the mean duration of epidemics for the heterogeneous vaccination strategies: 215.89 days (95% CI: 213.54-218.30), 216.46 days (95% CI: 214.13-218.77) and 216.57 days (95% CI: 214.20-218.76) respectively. There was also little variation for the mean time for epidemics to spread to all metapopulation patches and for the mean time of the epidemic peak, but all metrics for the heterogeneous strategies increased on the homogeneous vaccination strategy.

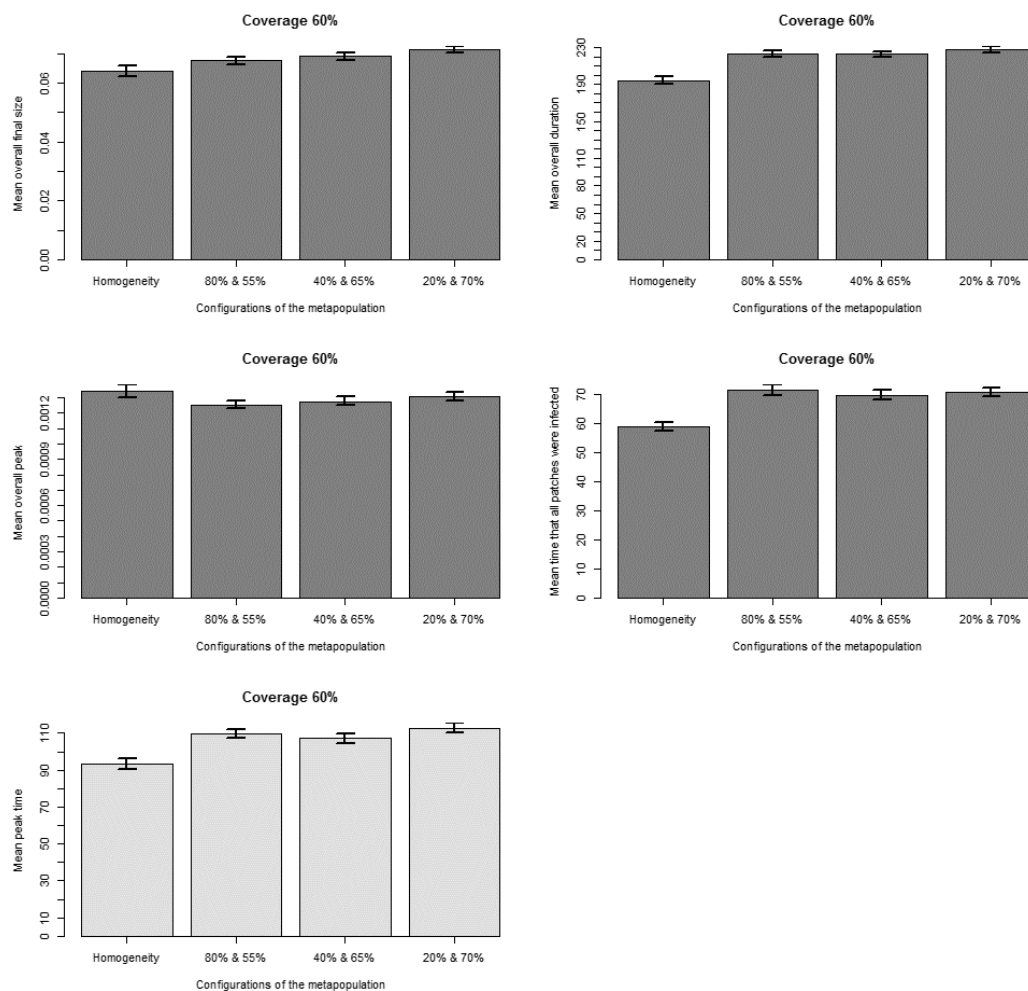


Figure 6.20 - Heterogeneity in a targeted vaccination programme for secondary schools with mean overall coverage of 60%



The vaccination strategy with the greatest degree of heterogeneity resulted in the largest increase in the mean final size of epidemics above that achieved by the homogeneous vaccination strategy with 60% coverage (Figure 6.20). Vaccinating one secondary school with 20% coverage and 70% coverage in 4 schools resulted in a mean final size of 7.13% (95% CI: 7.02-7.23%), up from 6.39% (95% CI: 6.21-6.57%) with homogeneity. This strategy also resulted in the longest mean duration (227.51 days (95% CI: 224.24-230.58)), highest mean epidemic peak (0.131% (95% CI: 0.128-0.134%)) and the longest mean time for the epidemic peak to occur (112.12 days (95% CI: 110.12-115.26)). The vaccination strategy with one school with coverage of 80% and four schools with 55% had the longest mean time for epidemics to spread to all metapopulation patches, at 71.50 days (95% CI: 69.94-73.30).

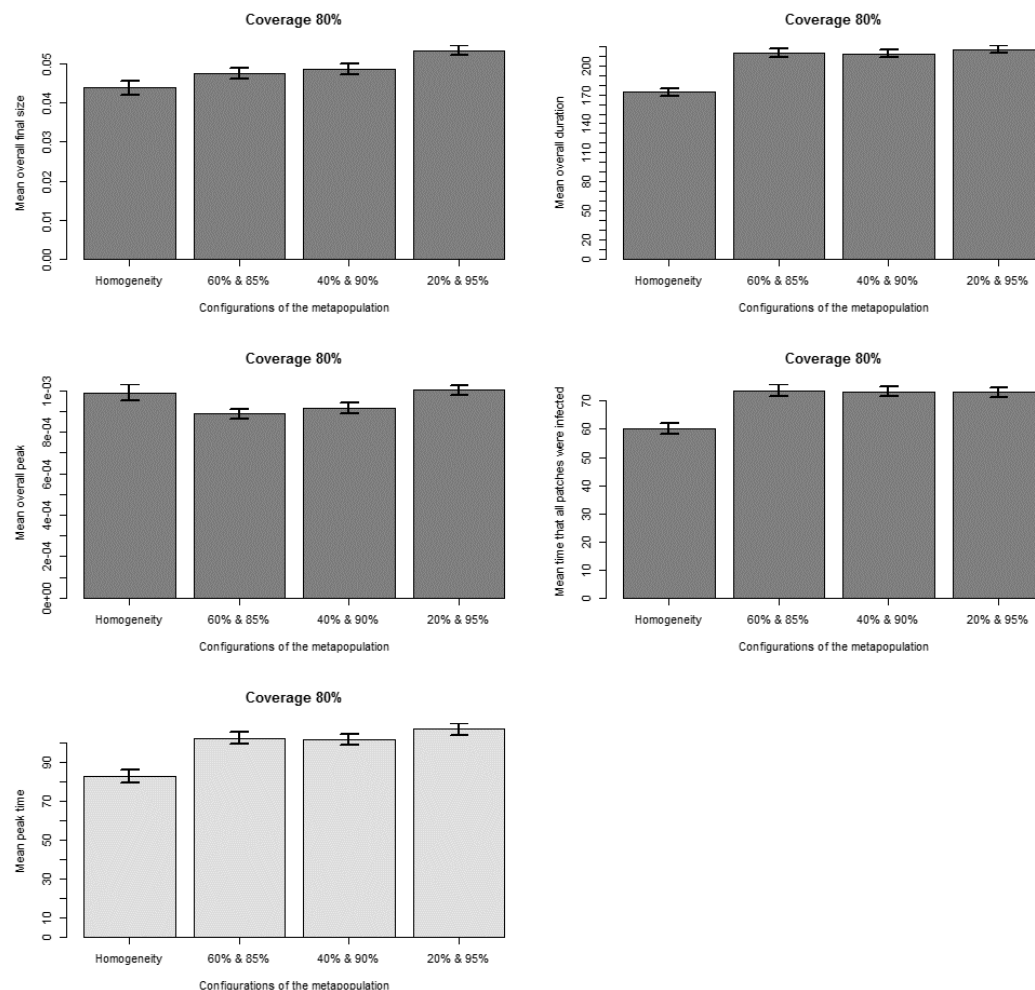


Figure 6.21 - Heterogeneity in a targeted vaccination programme for secondary schools with mean overall coverage of 80%

There was very little variation in the mean epidemic duration, the mean time for all patches to be infected and the mean time of the epidemic peak between the three vaccination strategies using heterogeneous uptake for mean overall coverage of 80% (Figure 6.21). The largest variation between these three strategies is seen in the mean final size and the mean size of the epidemic peak.

Vaccinating four secondary schools with 95% coverage and one school with 20% coverage resulted in a mean final size of 5.33% (95% CI: 5.21-5.46%), up from 4.38% (95% CI: 4.22-4.56%) with homogeneity. The same heterogeneous strategy had a mean epidemic peak of 0.100% (95% CI: 0.098-0.103%), though not statistically different to the mean epidemic size with homogeneity of 0.099% (95% CI: 0.095-0.103%).

#### SUMMARY FOR TARGETED VACCINATION IN SECONDARY SCHOOLS

Vaccinating only secondary schools is not sufficient to eliminate the potential for epidemics to spread in the metapopulation - 100% coverage reduces the mean final size of epidemics to 3.58% (95% CI: 3.32-3.86%). In terms of reducing the mean final size of epidemics, targeted vaccination in primary schools is more effective than in secondary schools.

Variation in the proportion of an individual's contacts that take place in their own patch has a strong relationship with the mean time for all metapopulation patches to become infected. Also, unlike the simulated scenarios with 100% homogeneous coverage in primary schools, epidemics still spread to all 31 patches with full coverage in secondary schools.

Unintended coverage heterogeneity increases the mean final size of epidemics as the number of low-coverage secondary schools increases, for all levels of coverage. At 20% targeted coverage, the mean final size of epidemics increased from 12.79% (95% CI: 12.65-12.92%) to 14.32% (95% CI: 14.23-14.41%) as heterogeneity in uptake increases. For maximum targeted coverage, the mean final size increased from 3.29% (95% CI: 2.99-3.58%) to 7.09% (95% CI: 6.85-7.33%). In addition, there was very strong evidence that the existence of a single low-coverage secondary school in the metapopulation directly increases the mean final size of epidemics at all levels of coverage.

Variation in the  $\tau$  parameter to change the difference between a low-coverage secondary school and a high-coverage secondary school affected the mean final size of epidemics and the mean size of the epidemic peak. Increasing the difference between the low- and high-coverage schools increases the number of susceptible individuals in the metapopulation sufficiently to result in a larger burden of disease.

Concentrating vaccination coverage in specific secondary schools rather than achieving homogenous vaccination across them all consistently increased the size of epidemics in the metapopulation. This result was also seen for the mean epidemic peak. Contrary to the results for intended heterogeneity in the primary school population, heterogeneous coverage in secondary schools decreased the mean time needed for the epidemics to spread across all patches of the metapopulation, other than for 80% coverage – an average time of 60.3 days (95% CI: 58.6-62.0) for homogenous coverage and 60.5 days (95% CI: 58.8-62.3) for concentrated coverage through heterogeneity. Using heterogeneous coverage with all five secondary schools included in the vaccination strategy consistently resulted in a greater

mean final size than the equivalent homogenous coverage level. The only metric that reduced was the mean size of the epidemic peak, though only with overall coverage of 60% or 80% and still with minimal heterogeneity between the two groups in the secondary school patches.

#### VACCINATION IN BOTH PRIMARY AND SECONDARY SCHOOLS

##### HOMOGENEOUS VACCINATION IN BOTH PRIMARY AND SECONDARY SCHOOLS

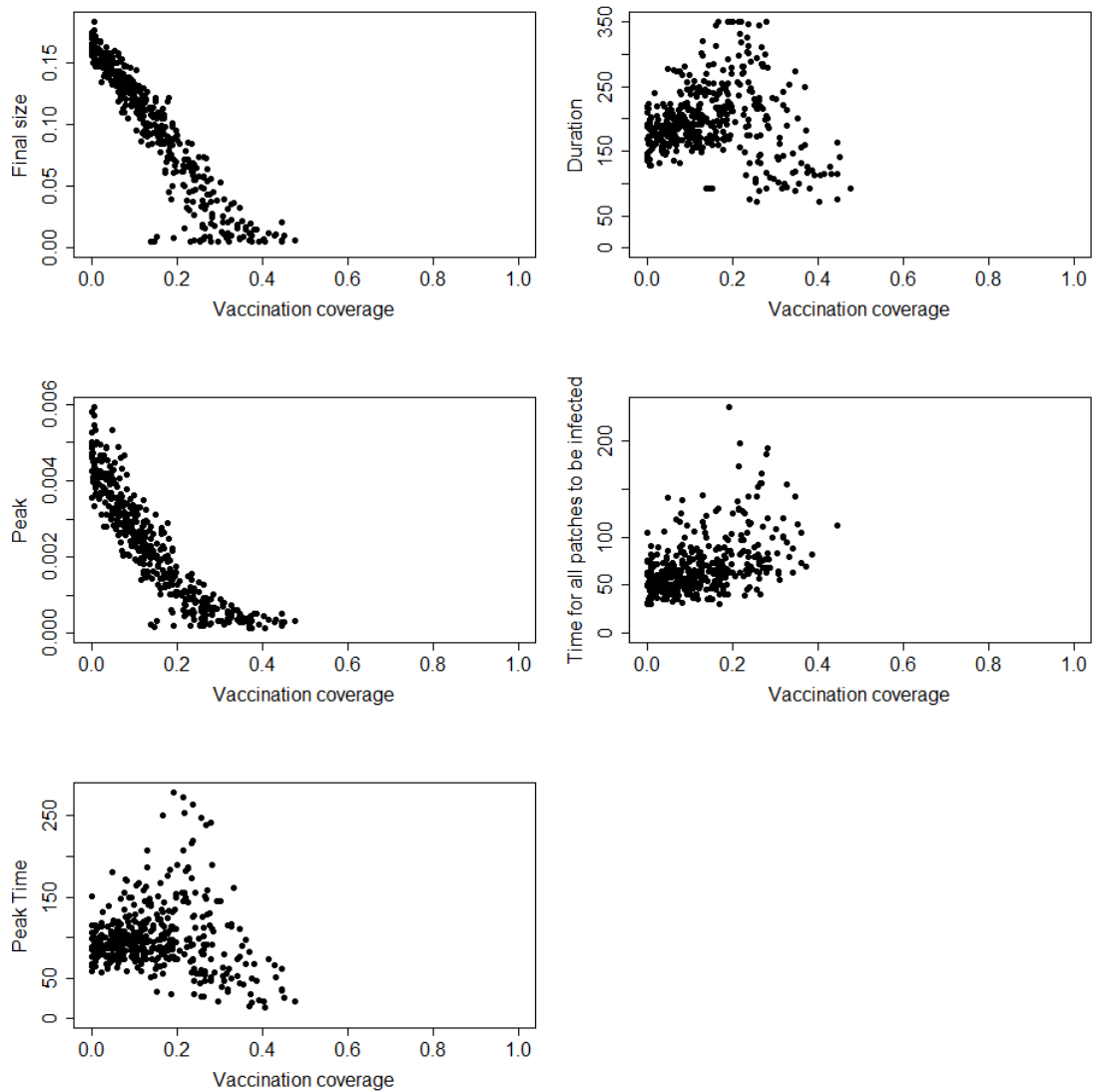


Figure 6.22 - Results from 5,000 simulations of the metapopulation model with homogeneous vaccination coverage in both primary and secondary schools.

Increasing homogeneous vaccination coverage decreases ILI final size, ILI Duration, ILI Peak and ILI Peak Time (Figure 6.22). ILI epidemics with a final size greater than 0.5% do not occur once vaccination coverage exceeds 47.8%. The relationship between vaccination coverage and the time for all metapopulation patches to become infected is less clear, but after vaccination coverage reaches

44.5% further ILI epidemics of a final size greater than 0.5% did not occur that included infection in all metapopulation patches.

Further results from the model are shown in Table 6.17. For simulations with vaccination coverage of 20% in both primary and secondary schools the mean ILI final size was 7.29% (95% CI: 6.99-7.57%), reduced from 16.40% (95% CI: 16.36-16.44%) when the school-based vaccination programme was not available. ILI duration and the epidemic peak reduce as vaccination coverage increases.

	Vaccination coverage				
	Mean (95% CI)				
	20%	40%	60%	80%	100%
ILI Final Size	7.29% (6.99-7.57%)	0.873% (0.715-1.07%)	N/A	N/A	N/A
ILI Duration (days)	237.28 (229.21-245.04)	130.52 (115.70-146.92)	N/A	N/A	N/A
ILI Peak	0.128% (0.121-0.134%)	0.028% (0.024-0.031%)	N/A	N/A	N/A
ILI time for all patches to be infected (days)	79.71 (75.94-83.63)	107.89 (71.00-151.00)	N/A	N/A	N/A
ILI Peak Time (days)	122.82 (115.87-129.33)	60.50 (49.38-71.85)	N/A	N/A	N/A

*Table 6.17 - Results from 5,000 simulations of the metapopulation model with homogeneous vaccination coverage in both primary and secondary schools*

#### VARYING THE $\epsilon_1$ PARAMETER

By varying the  $\epsilon_1$  parameter we examined the impact on epidemics in the metapopulation of different proportions of an individual's daily contacts taking place within their own patch (Figure 6.23). Results for the mean final size of epidemics in the metapopulation follow those results discussed for other vaccination scenarios, that is that there is little variation as the  $\epsilon_1$  parameter is increased, though for the lowest level of vaccination coverage  $\epsilon_1 = 1$  saw the lowest mean final size of 6.89% (95% CI: 6.60-7.18%). A more obvious result for a metapopulation configuration with homogeneous vaccination coverage is that epidemics can occur in the metapopulation with homogeneous vaccination coverage of 60% at values of  $\epsilon_1$  less than 0.75, indicating that the  $\epsilon_1$  parameter is a key determinant of the mean final size at vaccination coverage levels near to those required to eliminate epidemics in the metapopulation.

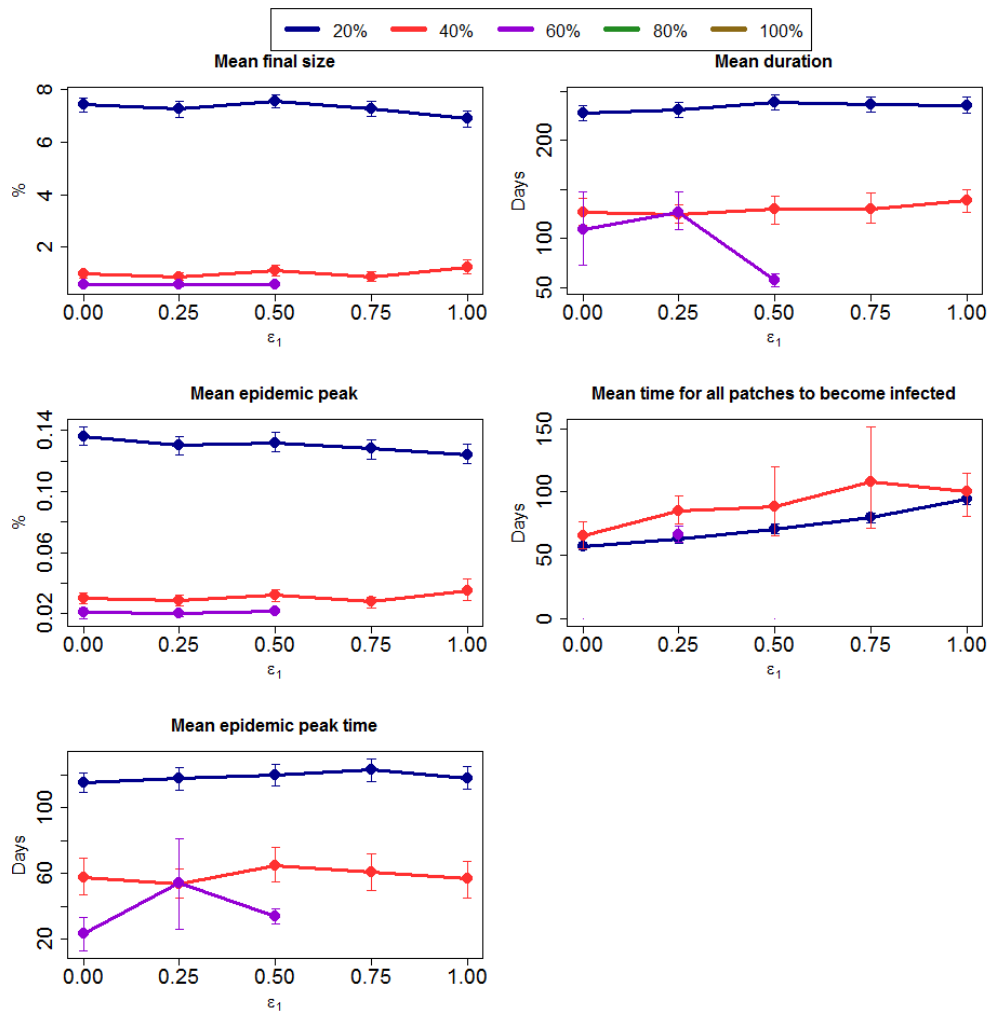


Figure 6.23 - Epidemic results with homogeneous primary and secondary school vaccination and varying  $\epsilon_1$  parameter

#### HOMOGENEOUS VACCINATION IN BOTH PRIMARY AND SECONDARY SCHOOLS WITH HETEROGENEOUS UPTAKE WITHIN PRIMARY SCHOOLS

Maintaining homogeneous vaccination coverage across both primary and secondary school groups whilst varying the number of low-coverage primary schools, Figure 6.24 shows that the final size of ILI epidemics across the metapopulation is associated with the number of low-coverage primary schools only when the normal vaccination coverage reaches high levels – with coverage of 20% there is noticeable variation when the number of low-coverage primary schools is increased. With higher vaccination coverage the mean final size of epidemics steadily increased. Coverage of 60% sees epidemics occurring when 6 or more primary schools have lower coverage. When coverage reached 80% or greater then epidemics occurred only with 14 or more low-coverage primary schools, and no outbreaks occurred with any level of heterogeneity with targeted coverage of 100%.

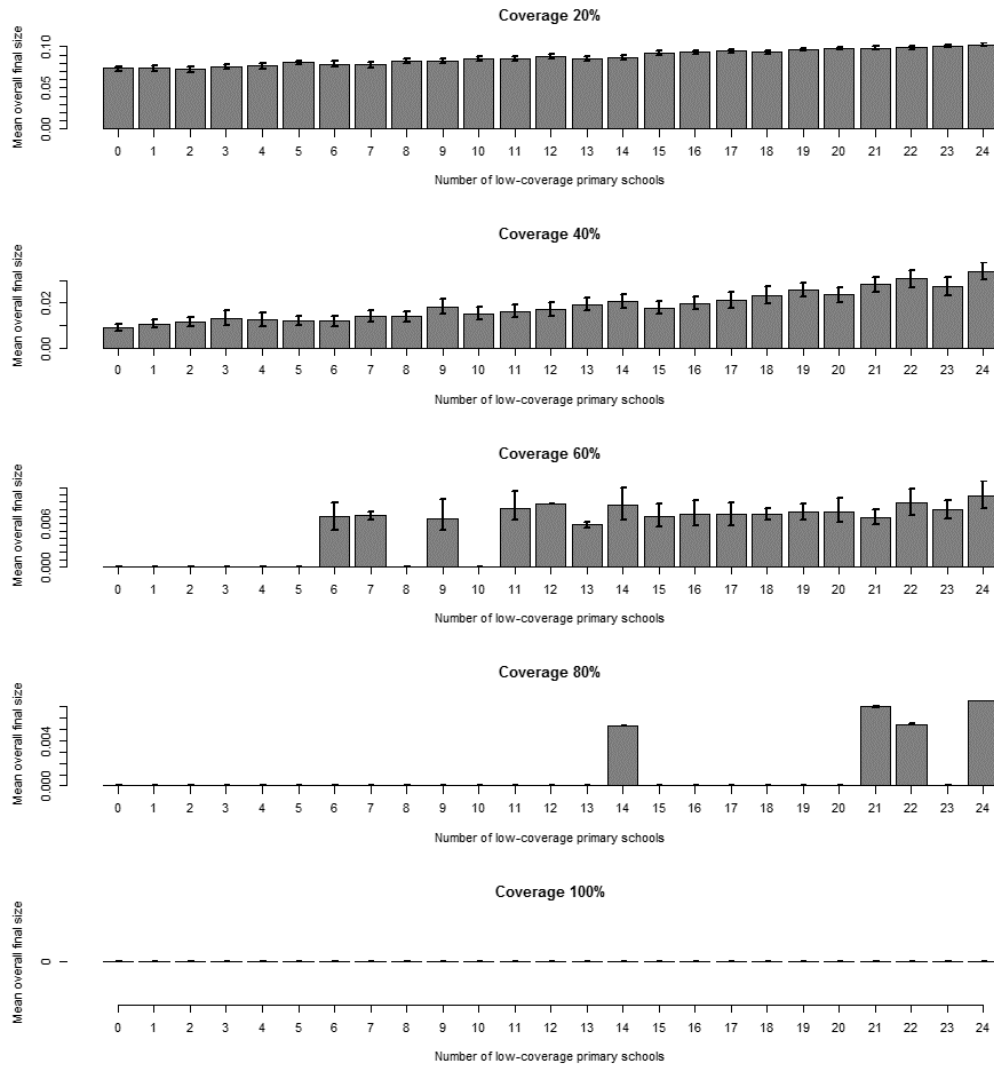


Figure 6.24 - Mean ILI final size for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage primary schools

Results for the mean duration, the mean peak, the mean time for all patches to become infected and the mean peak time are displayed in the appendix.

#### THE IMPACT OF A SINGLE LOW-COVERAGE PRIMARY SCHOOL IN THE METAPOPULATION WITH HOMOGENOUS COVERAGE ACROSS PRIMARY AND SECONDARY SCHOOLS

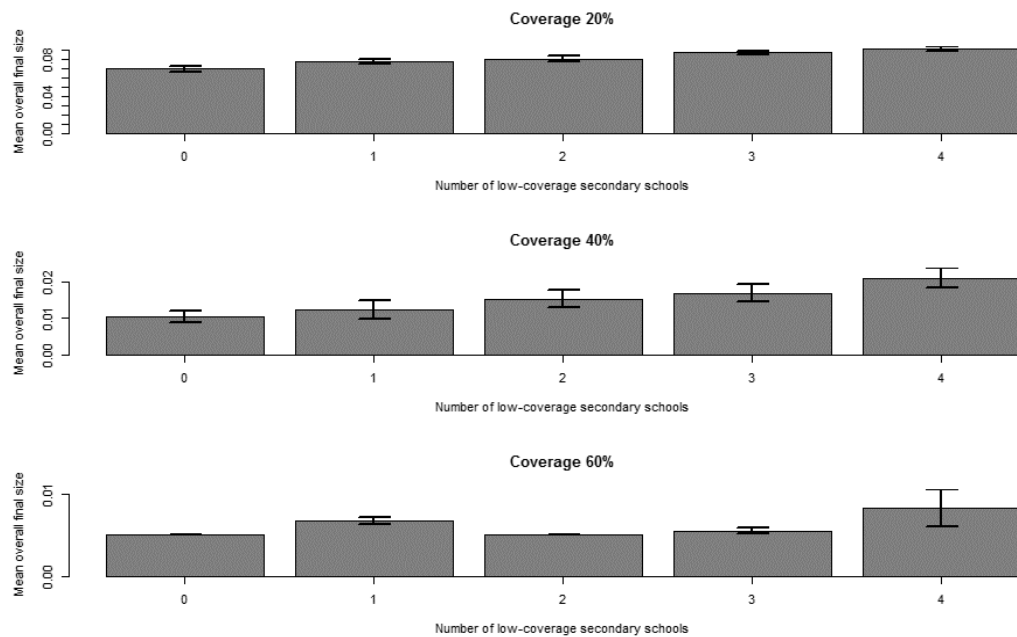
5,000 additional simulations to examine the impact of one low-coverage primary school in the metapopulation with vaccination coverage set between the same five intervals as in Figure 6.24 are show in Table 6.18. Results from Wilcoxon Tests comparing the mean final size of ILI epidemics with 0 low-coverage primary schools to epidemics with 1 low-coverage primary schools indicate no evidence for a difference between the metapopulations with 20% and 40% coverage. At 60% vaccination coverage the addition of a single low-coverage primary school facilitated epidemic spread when

achieving 60% homogeneous coverage did not. Epidemics did not occur for vaccination coverage of both 80% and 100%.

Vaccination coverage 20%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
7.11% (6.93-7.30%)	7.27% (7.09-7.44%)	W=113,915, p=0.4279
Vaccination coverage 40%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
1.17% (1.03-1.32%)	1.11% (0.990-1.25%)	W=2,864, p=0.529
Vaccination coverage 60%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
N/A	0.566% (0.566-0.566%)	N/A

*Table 6.18 - Comparing the final size of ILI epidemics with homogenous vaccination, but with heterogeneous coverage in primary schools only*

# HOMOGENEOUS VACCINATION IN BOTH PRIMARY AND SECONDARY SCHOOLS WITH HETEROGENEOUS UPTAKE WITHIN SECONDARY SCHOOLS



*Figure 6.25 - Mean ILI final size for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage secondary schools*

Figure 6.25 shows the impact of an increasing number of low-coverage secondary schools in a metapopulation with homogeneous vaccination in both primary and secondary schools. For vaccination coverage of both 20% and 40%, increasing the unintended heterogeneity in uptake increases the mean final size of epidemics steadily. For vaccination coverage of 60%, the lack of association between mean final size and heterogeneity is mostly likely due to a very small number of outbreaks that occurred with such high vaccination coverage. No epidemics occurred with vaccination coverage of 80% and 100%.

Results for the mean duration, the mean peak, the mean time for all patches to become infected and the mean peak time are displayed in 10.7 in the appendix.



THE IMPACT OF A SINGLE LOW-COVERAGE SECONDARY SCHOOL IN THE METAPOPOPULATION WITH HOMOGENOUS COVERAGE ACROSS PRIMARY AND SECONDARY SCHOOLS

Vaccination coverage 20%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
7.16% (6.98-7.34%)	7.74% (7.58-7.91%)	W=89,601, p<<0.001
Vaccination coverage 40%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
1.01% (0.912-1.11%)	1.12% (1.00-1.25%)	W=3,246.5, p=0.4147
Vaccination coverage 60%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
N/A	0.709% (0.579-0.840%)	N/A

*Table 6.19 - Comparing the final size of ILI epidemics with homogeneous vaccination coverage across both primary and secondary schools but heterogeneity within secondary schools*

Table 6.19 shows the comparison of homogenous vaccination across both primary and secondary schools at four coverage levels with the scenario of one low-coverage secondary school obtained by executing a further 5,000 simulations of the model with varying vaccination coverage levels. One low-coverage secondary school does not impact the mean final size of ILI epidemics in the metapopulation at 40% vaccination coverage but it can for the lowest level of coverage at 20%, and epidemics did not occur in the metapopulation with coverage of 80% or 100%.

THE IMPACT OF A SINGLE LOW-COVERAGE PRIMARY SCHOOL AND A SINGLE LOW-COVERAGE SECONDARY SCHOOL IN THE METAPOPOPULATION WITH HOMOGENEOUS COVERAGE ACROSS PRIMARY AND SECONDARY SCHOOLS

Homogeneous vaccination across the metapopulation but with one primary school and one secondary school failing to achieve the same level of vaccination coverage as the other schools increases the mean final size of ILI epidemics in the community (Table 6.20). 5,000 simulations were executed to expand on results presented in Table 6.18 and Table 6.19. For both 20% and 40% coverage levels, there was strong evidence that the existence of a low-coverage primary school and a low-coverage secondary school increased the mean final size of epidemics in the metapopulation. Epidemics did not occur with vaccination coverage greater of 80% and 100%.

Vaccination coverage 20%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
7.34% (7.16-7.53%)	8.01% (7.86-8.15%)	W=86,057, p<<0.001
Vaccination coverage 40%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
0.994% (0.896-1.10%)	1.31% (1.19-1.46%)	W=3,343.5, p=0.002461
Vaccination coverage 60%		
0 low-coverage schools mean (95% CI)	1 low-coverage school mean (95% CI)	Wilcoxon Test
N/A	0.762% (0.515-0.957%)	N/A

*Table 6.20 - Comparing the final size of ILI epidemics with homogeneous vaccination coverage across both primary and secondary schools but heterogeneity within both primary and secondary schools*

#### INTENDED HETEROGENEITY THROUGH FIXED, CONCENTRATED VACCINATION COVERAGE

Theorising a vaccination programme targeting several schools for 100% coverage, there were 4 different configurations for 20% coverage in primary and secondary schools - baseline homogeneity, 9 primary schools with 0 secondary schools, 5 primary schools with 1 secondary school and finally 1 primary school with 2 secondary schools (Figure 6.26). At this coverage level the introduction of heterogeneity in vaccination uptake increases the mean final size of epidemics from 6.85% (95% CI: 6.66-7.03%) to a maximum of 11.14% (95% CI: 11.01-11.26%) with full vaccination in 1 primary school and 2 secondary schools. This heterogeneity also increases the mean size of the epidemic peak from 0.140% (95% CI: 0.135-0.144%) to a maximum of 0.266% (95% CI: 0.261-0.271%).

In contrast, both the mean epidemic duration and mean time of the epidemic peak decreased after heterogeneity was introduced. The mean duration decreased from 200.3 days (95% CI: 196.1-204.1 days) to a minimum of 183.4 days (95% CI: 181.1-185.7 days), reducing the duration of epidemics by approximately 17 days. The mean time of the epidemic peak also decreased from 97.6 days (95% CI: 94.4-100.8 days) to 88.2 days (95% CI: 86.5-89.8 days).

The metric with the most variation was the mean time for all metapopulation patches to become infected. At baseline it took a mean time of 66.0 days (95% CI: 64.2-67.8 days) for all 31 patches to be infected. Configuring the metapopulation to fully vaccinate only 9 primary schools increased that time to 93.4 days (95% CI: 81.2-85.6 days), almost one month longer. However, concentrating the low level of vaccination coverage in secondary schools by fully vaccinating 2 secondary schools plus 1 primary school decreased the mean time for all patches to become infected to 57.2 days (95% CI: 55.9-58.5 days).

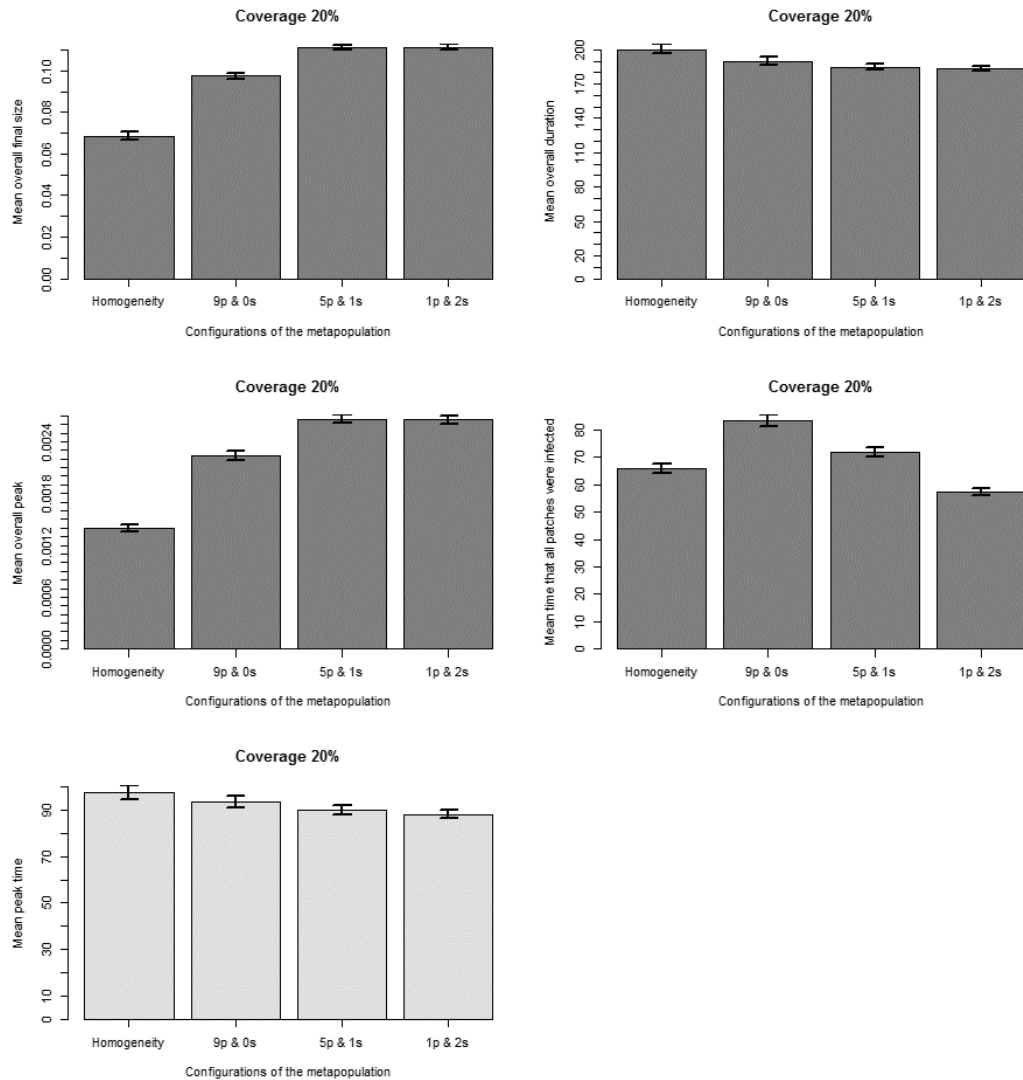


Figure 6.26 - Different configurations of 20% coverage achieved in primary and secondary schools

Two configurations of 20% coverage concentrated in specific schools are shown in Figure 6.27 (9 primary schools) and Figure 6.28 (1 primary school and 2 secondary schools). Concentrating vaccination coverage in primary schools reduces the epidemic peak in the primary school age group below the peak of the secondary school age group, as well as seeing that several primary schools have only minor epidemics in their patch. In contrast, concentrating coverage in secondary schools in the second configuration allows 24 primary schools to experience full epidemics, resulting in a larger epidemic peak in the primary school age group.

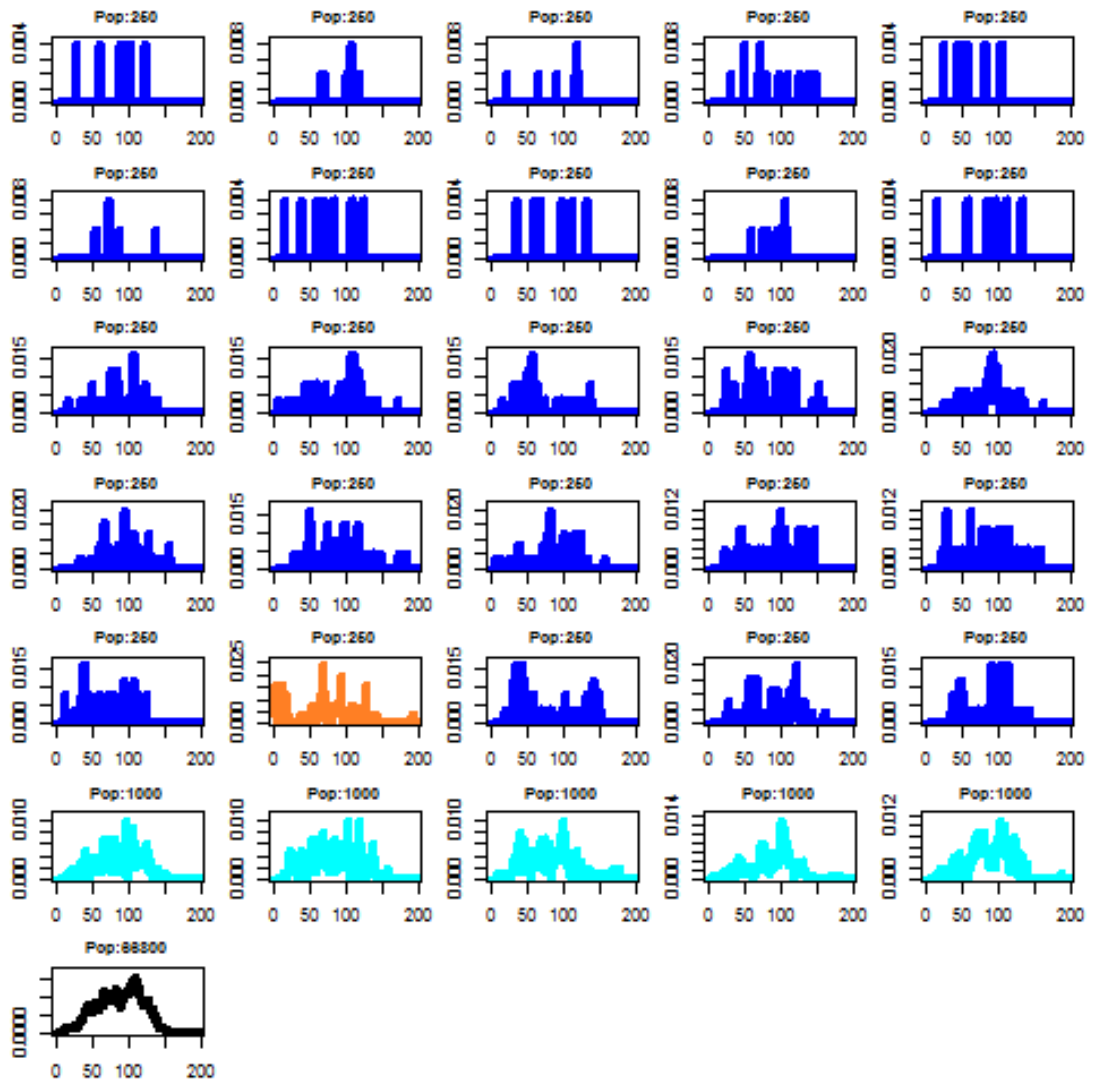


Figure 6.27 - The patch epidemic curves for a metapopulation configuration with concentrated vaccination coverage in 9 primary schools

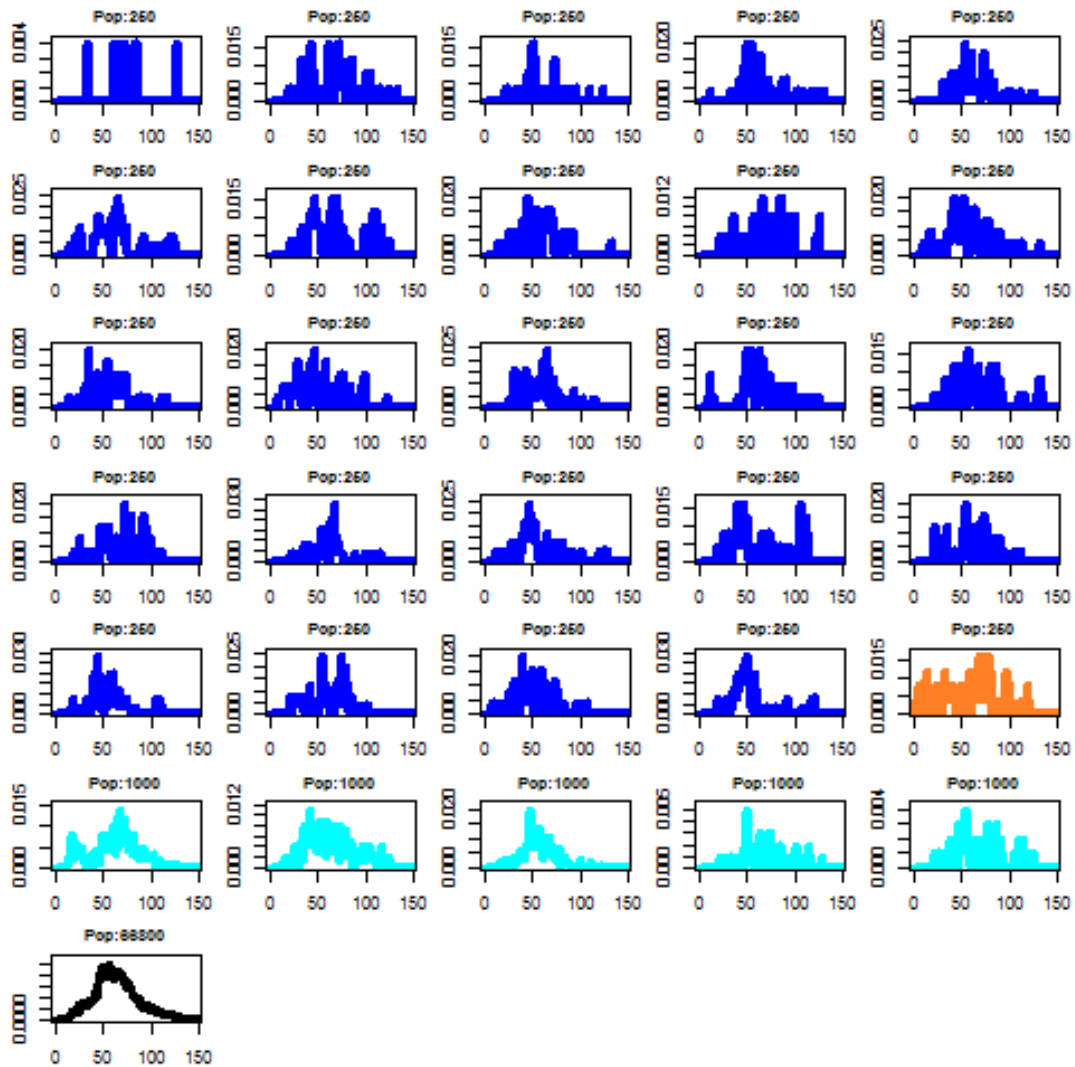


Figure 6.28 - The patch epidemic curves for a metapopulation configuration with concentrated vaccination coverage in 1 primary school and 2 secondary schools

There were 6 different configurations for 40% coverage in primary and secondary schools (Figure 6.29). Introducing heterogeneity in the vaccination coverage across the metapopulation increased all metrics for disease burden. The mean final size of epidemics rose from 1.18% (95% CI: 1.08-1.29%) at baseline to a maximum of 4.78% (95% CI: 4.60-4.95%), though with very little variation between the 5 configurations of the metapopulation with heterogeneous vaccination coverage. Indeed, similar results are seen by an increase in the mean duration of the epidemics, the mean epidemic peak and the mean epidemic peak time, all with little variation once heterogeneity was introduced.

The mean time for all metapopulation patches to be infected varied according to the configuration of vaccine administration. With homogenous 40% coverage across the schools the mean time for all patches to be infected was 81.6 days (95% CI: 75.2-89.0). This increased to a mean of 111.2 days (95% CI: 106.1-116.3) with 40% coverage concentrated in the primary school population. As the vaccination coverage became less concentrated in primary schools through the increase in the number of

secondary schools that were fully vaccinated, the mean time for all metapopulation patches to become infected decreased. With the 40% coverage concentrated in secondary schools as much as possible (i.e. 2 primary schools and 4 secondary schools fully vaccinated) the mean time for the epidemic to reach all metapopulation patches reduced to 75.9 days (95% CI: 73.2-78.7), a time quicker than the baseline result.

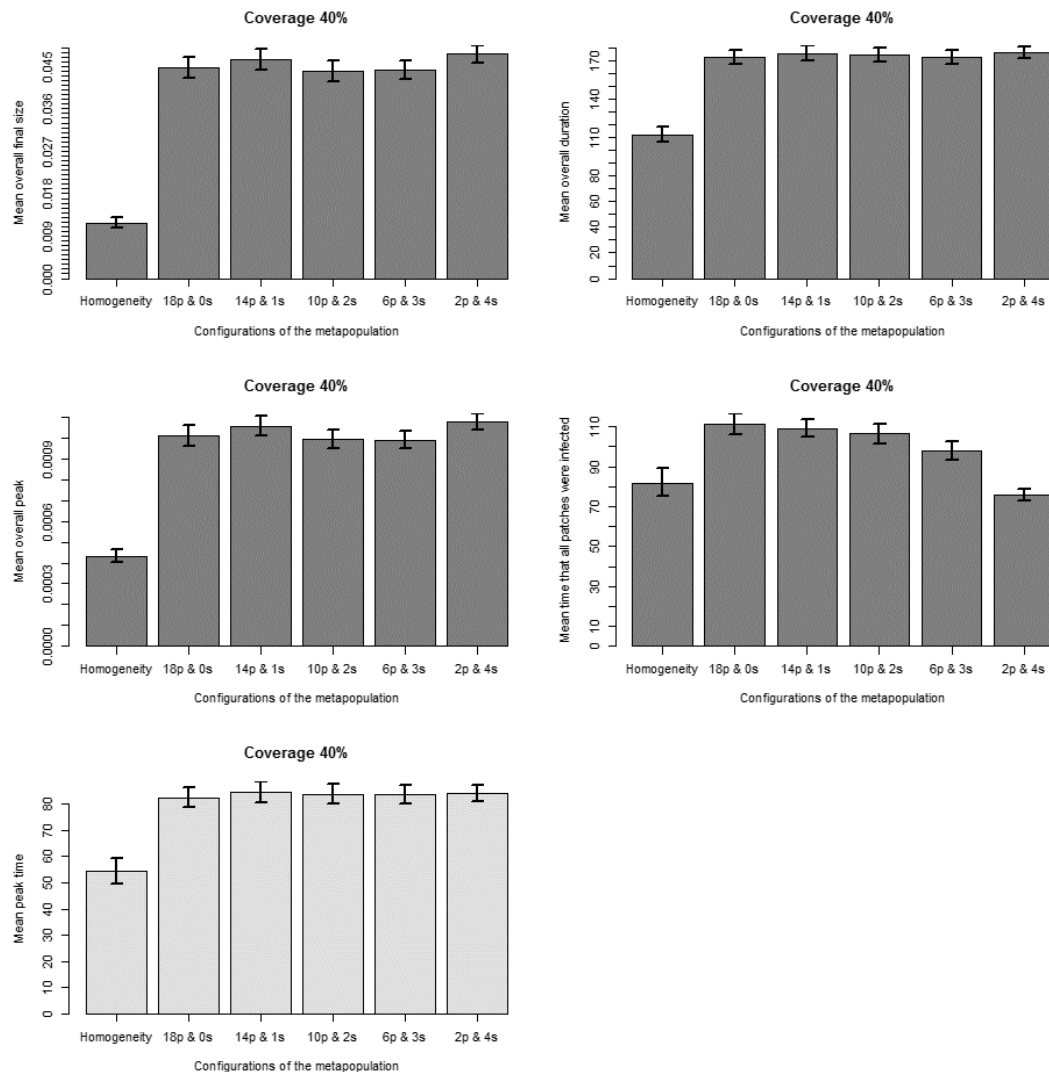


Figure 6.29 - Different configurations of 40% coverage achieved in primary and secondary schools

Two metapopulation configurations with concentrated vaccination coverage of 40% of school children are shown in Figure 6.30 (18 primary schools), along with Figure 6.31 (2 primary schools and 4 secondary schools). Concentrating vaccination coverage in primary schools sufficient protection to the primary school age group to see that 18 of 25 primary schools had very minor epidemics on their patch, but secondary schools were completely unprotected. In this configuration, the epidemic peak for the primary school age group reached 0.15% but the secondary school peak reached 0.35%.

However, switching concentration to secondary schools reduced the epidemic peak in that age group to 0.1%, with primary school epidemics peaking at almost four times that.

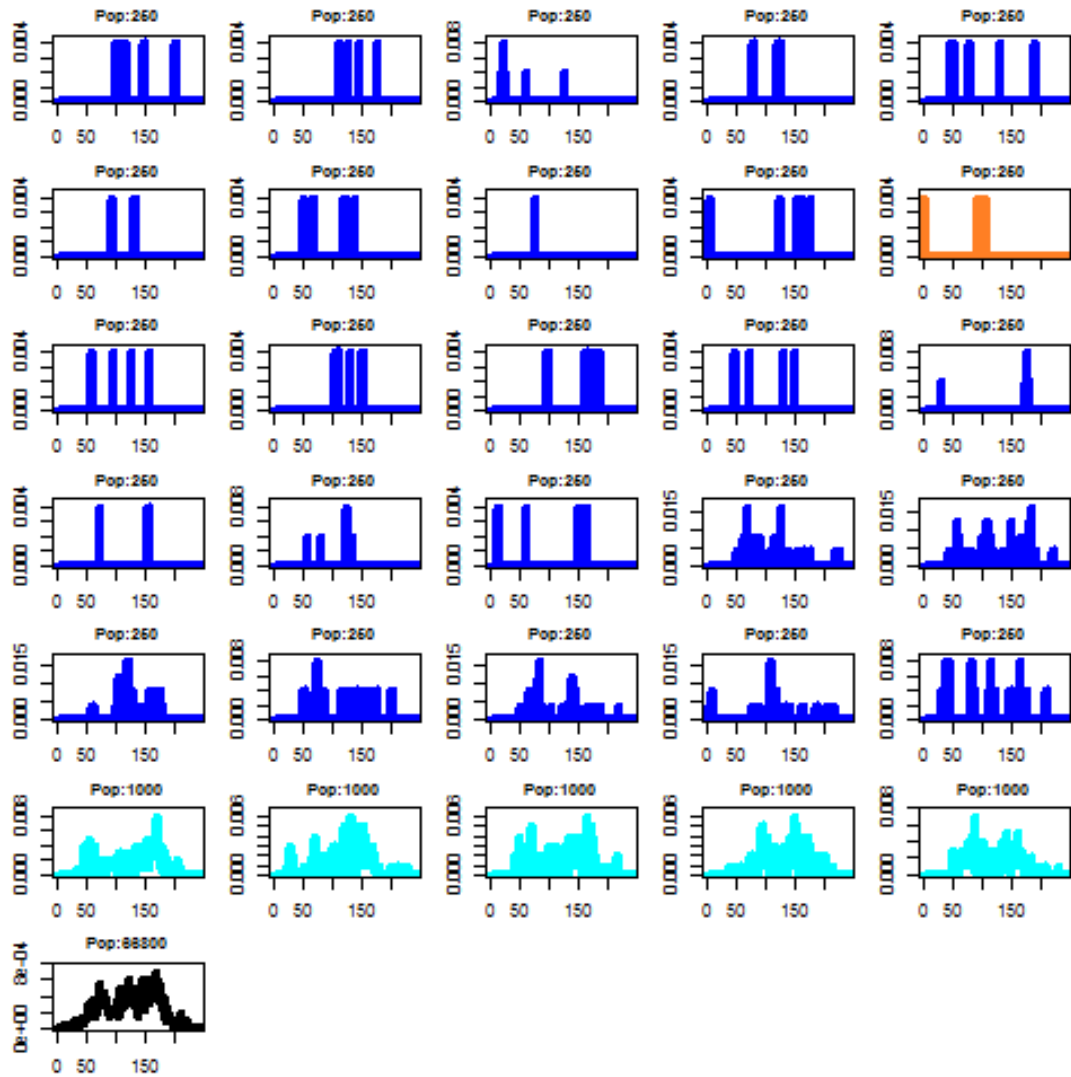


Figure 6.30 - The patch epidemic curves for a metapopulation configuration with concentrated vaccination coverage in 18 primary schools

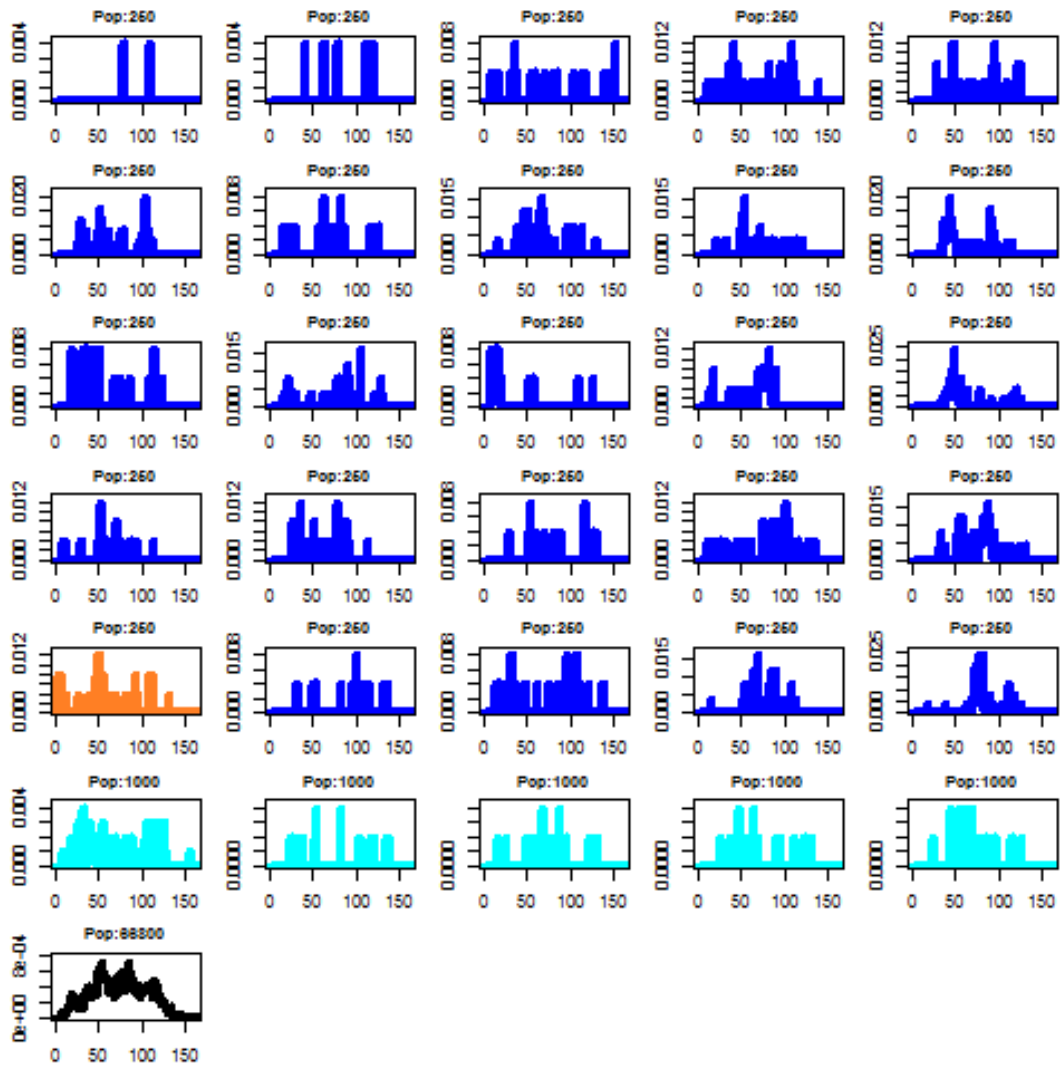


Figure 6.31 - The patch epidemic curves for a metapopulation configuration with concentrated vaccination coverage in 2 primary schools and 4 secondary schools

There were 5 different configurations for 60% coverage in primary and secondary schools (Figure 6.32). All metrics to examine the potential burden of disease increased when vaccine coverage heterogeneity was introduced to the metapopulation, most notably in the mean final size of epidemics which jumped from a mean of 0.609% (95% CI: 0.536-0.685%) to a maximum of 1.43% (95% CI: 1.31-1.55%).

The most interesting result is that the epidemics spread to all metapopulation patches, even with a large number of patches reporting 100% vaccination coverage. Previous results show that epidemics are unable to reach all metapopulation patches with homogeneous coverage of 44.5% or greater, but with heterogeneity introduced with 60% coverage the simulated epidemics were able to reach all metapopulation patches in 91.6 days (95% CI: 89.2-94.1 days) with 19 primary schools and 2 secondary schools reporting 100% vaccination coverage.



The mean duration of epidemics in the metapopulation increased from a mean of 76.7 days (95% CI: 69.0-82.8 days) to a maximum of 110.9 days (95% CI: 104.0-118.1 days) with 19 primary schools and 2 secondary schools reporting 100% vaccination coverage. Maintaining 60% vaccination coverage across the school patches but with increased heterogeneity extended the mean epidemic duration by approximately one month, even with overall vaccination coverage that would otherwise be sufficient to stop epidemics altogether (Figure 6.22).

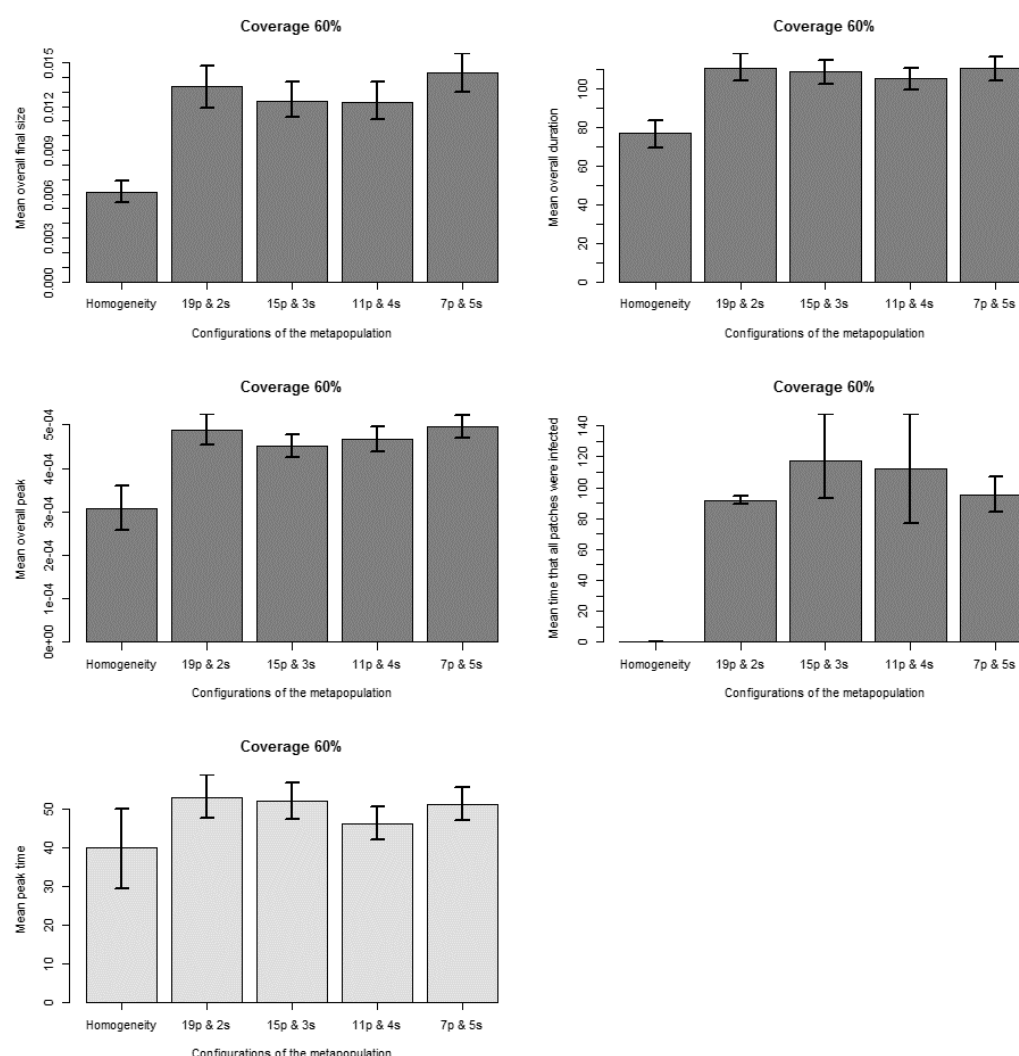


Figure 6.32 - Different configurations of 60% coverage achieved in primary and secondary schools

There were 4 different configurations for 80% coverage in primary and secondary schools - baseline homogeneity, 24 primary schools with 3 secondary schools, 20 primary schools with 4 secondary schools and finally 16 primary schools with 5 secondary schools (Figure 6.33).

In contrast to the results reported for 60% vaccination coverage with heterogeneity, 80% coverage prevents epidemics from spreading to all 31 metapopulation patches. There is little variation in the other metrics for reporting the total disease burden for different configurations of the

metapopulation. However, even with very high overall vaccination coverage of 80%, the introduction of heterogeneity in coverage allows for sustained transmission of influenza that results in epidemics with a mean final size above 0.6% of the population, with such epidemics lasting up to a mean of 88 days (95% CI: 72.9-104.8 days).

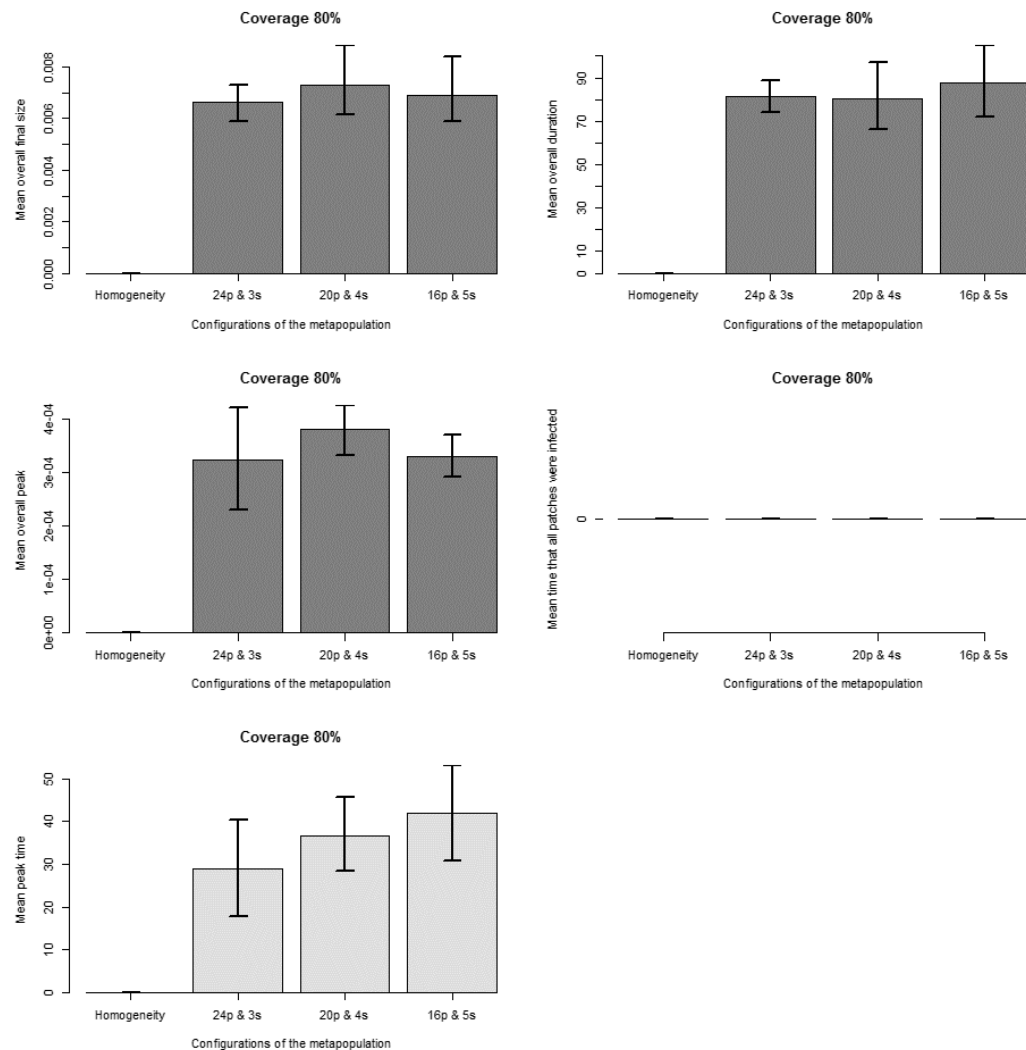


Figure 6.33 - Different configurations of 80% coverage achieved in primary and secondary schools

# INTENDED HETEROGENEITY WITH VACCINATION IN ALL TARGETED PATCHES

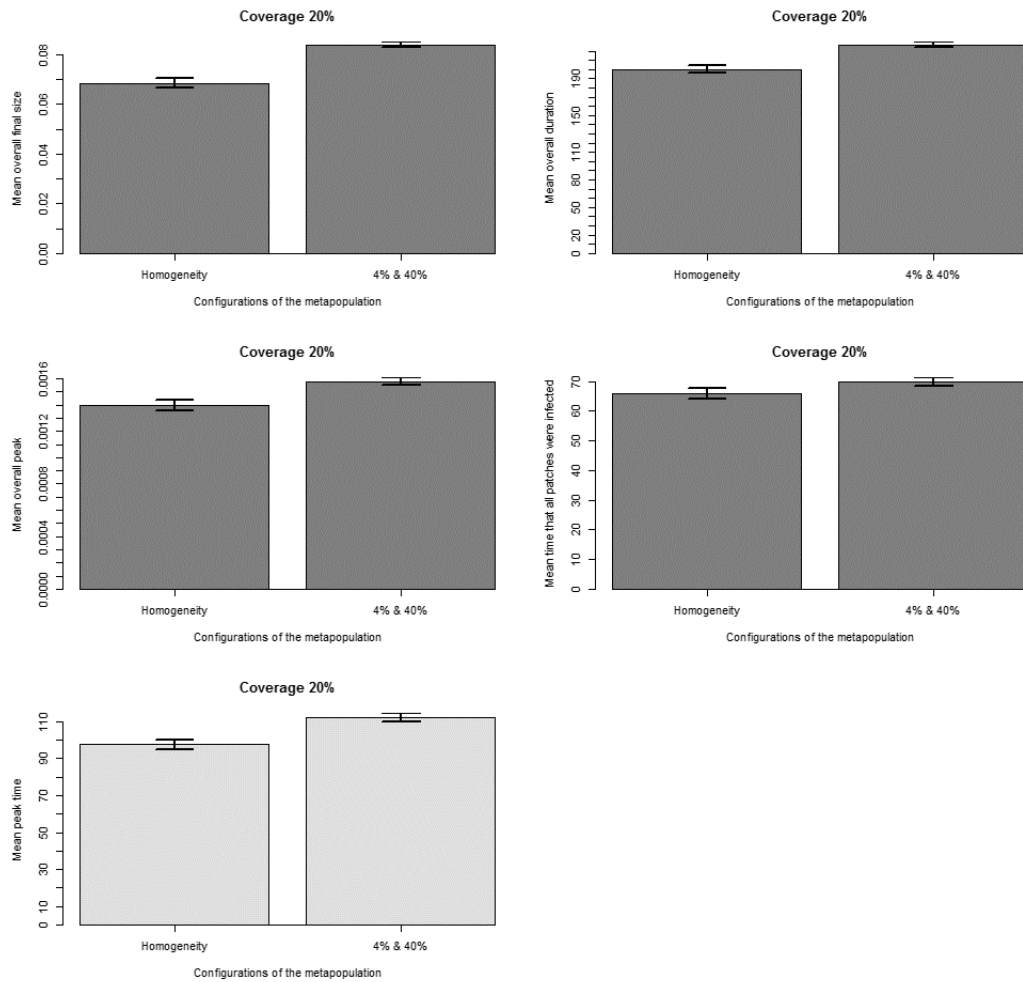


Figure 6.34 - Heterogeneous vaccination coverage with 20% vaccination in all school patches

Vaccinating each primary school to achieve 4% coverage and each secondary school to achieve 40% coverage did not reduce the total burden of disease over a homogenous 20% vaccination strategy (Figure 6.34). The mean final size of epidemics increased from 6.85% (95% CI: 6.65-7.05%) to 8.38% (95% CI: 8.28-8.49%). The mean duration of epidemics increased from 200.29 days (95% CI: 196.36-204.10) to 226.53 days (95% CI: 223.51-229.31), almost a month longer than with the homogeneous coverage. The mean time for all metapopulation patches to become infected increased to 69.83 days (95% CI: 68.54-71.20), from 66.04 days (95% CI: 64.16-67.86).

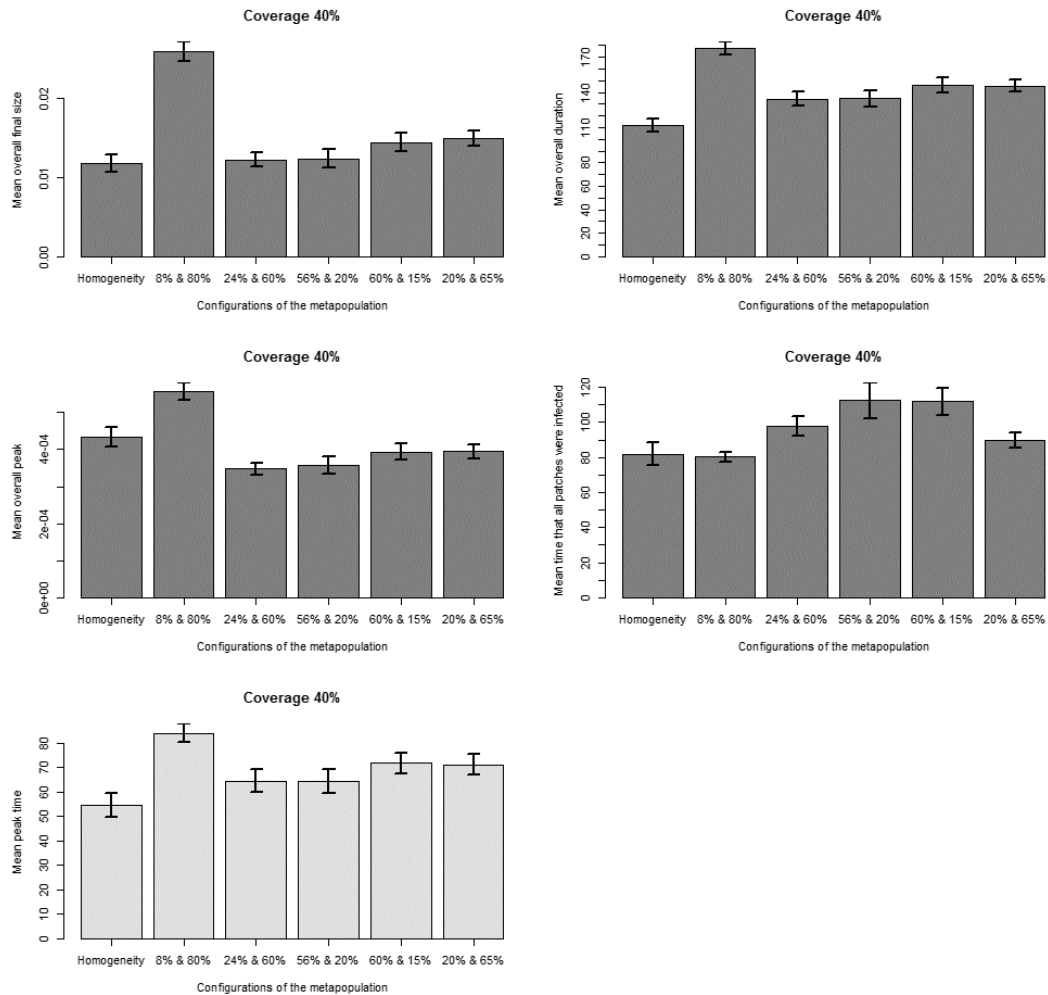


Figure 6.35 - Heterogeneous vaccination coverage with 40% vaccination in all school patches

Achieving mean overall coverage of 40% in the two school groups with different heterogeneous vaccination strategies has very different results (Figure 6.35). There was little difference between the mean final size of epidemics with homogeneous coverage (1.19% (95% CI: 1.08-1.30%)) and two heterogeneous strategies – vaccinating primary schools to 24% coverage and secondary schools to 60% coverage (1.22% (95% CI: 1.14-1.32%),  $W=141943.5$  and  $p=0.9507$ ), and then vaccinating primary schools to 56% coverage with secondary schools at 20% coverage (1.24% (95% CI: 1.13-1.35%),  $W=10,484$  and  $p=0.8054$ ). The largest increase in the mean final size of epidemics was with the heterogeneous vaccination strategy that used the greatest degree of heterogeneity between the two school groups – vaccinating primary schools to just 8% coverage and secondary schools to 80% resulted in a mean final size of 2.59% (95% CI: 2.48-2.71%).

Heterogeneous vaccination coverage was successful in reducing the mean size of the epidemic peak when vaccinating 24% of primary school children and 60% secondary school children (0.035% (95% CI: 0.033-0.036%)) and also when vaccinating 56% of primary school children and 20% of secondary school children (0.036% (95% CI: 0.034-0.038%)), down from 0.043% (95% CI: 0.041-0.046%) with

homogeneous coverage. However, heterogeneous vaccination coverage was unable to reduce any of the other metrics when compared to the performance of the homogeneous strategy.

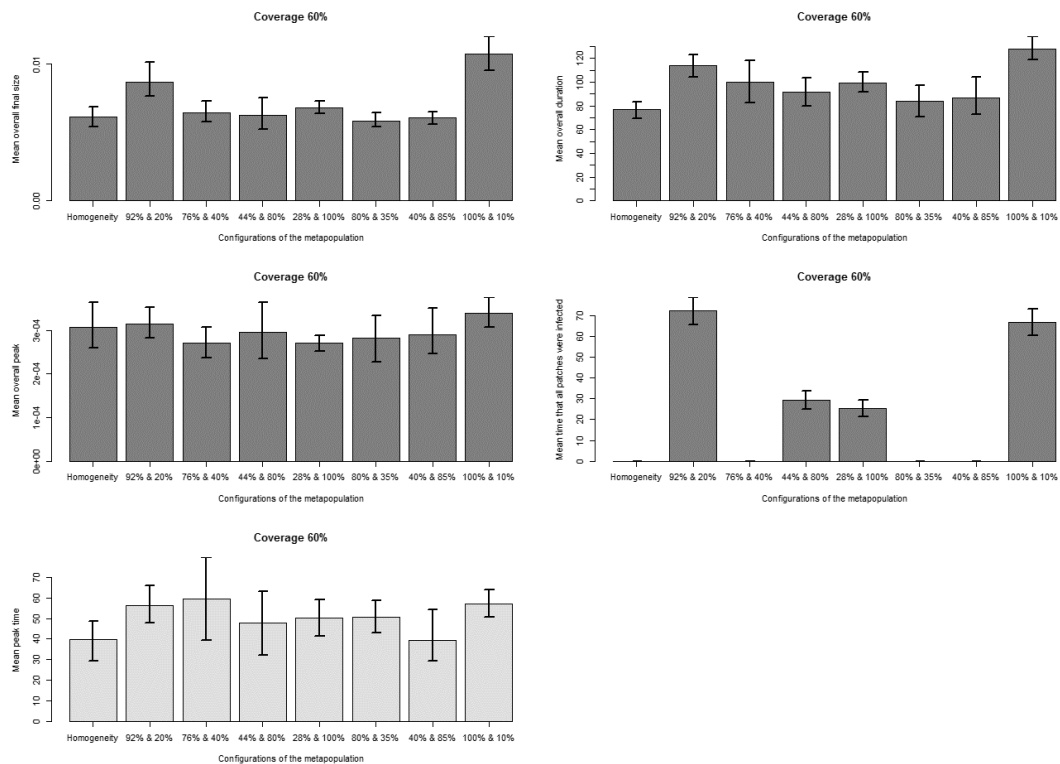


Figure 6.36 - Heterogeneous vaccination coverage with 60% vaccination in all school patches

Figure 6.36 shows that the vaccination strategies with the highest degree of heterogeneity between the primary and secondary school groups resulted in the largest mean final size of epidemics in the metapopulation. Two strategies with coverage heavily concentrated in the primary school population had epidemics with a mean final size of 0.871% (95% CI: 0.766-1.01%) (92% coverage in primary schools and 20% coverage in secondary schools) and 1.06% (95% CI: 0.947-1.20%) (100% coverage in primary schools and 10% coverage in secondary schools) respectively. Concentrating vaccination coverage in secondary schools and reducing the degree of heterogeneity did not result in epidemics that were statistically different in size to those that occurred with 60% homogeneous coverage.

60% homogeneous coverage prevents the epidemics from reaching all metapopulation patches. However, the four vaccination strategies with the highest degrees of heterogeneity between the two groups (i.e. those vaccination strategies that concentrated coverage the most in either group) resulted in epidemics able to spread to all 31 metapopulation patches. Concentrating coverage in primary schools, the epidemics spread to all patches in 72.58 days (95% CI: 66.10-79.30) (92% coverage in primary schools and 20% coverage in secondary schools) and 66.90 days (95% CI: 60.20-73.37) (100% coverage in primary schools and 10% coverage in secondary schools). With concentration highest in secondary schools, the epidemics spread to all patches in 29.48 days (95% CI: 25.15-33.50) (44%

coverage in primary schools and 80% coverage in secondary schools) and 25.60 days (95% CI: 21.70-29.54) (28% coverage in primary schools and 100% coverage in secondary schools).

No epidemics occurred in the 4 metapopulation configurations with overall 80% vaccination coverage in primary and secondary schools.

#### SUMMARY FOR TARGETED HOMOGENEOUS VACCINATION ACROSS PRIMARY AND SECONDARY SCHOOLS

The potential for epidemics in the metapopulation is completely reduced with 47.8% homogeneous vaccination in both primary and secondary schools. 5,000 simulations with the level of homogeneous vaccination assigned to a value between 0 and 1 resulted in no epidemics at all above this level of vaccination, and no epidemics spreading to all metapopulation patches with coverage above 44.5%.

However, reducing the  $\epsilon_1$  parameter to 0, 0.25 and 0.50 resulted in epidemics occurring in the metapopulation with homogeneous vaccination coverage of 60%. Epidemics occurring with 60% coverage did not spread to all 31 metapopulation patches. Those epidemics that did reach all patches of the metapopulation with vaccination coverage of 20% and 40% did so in a slower mean time as the  $\epsilon_1$  parameter was increased.

Unintended heterogeneity in vaccination coverage through low-coverage primary schools has a similar impact on the mean final size of epidemics as a metapopulation with targeted vaccination in primary schools – each additional low-coverage primary schools incrementally increases the mean final size of epidemics. In addition, with 60% homogeneous coverage across both school groups a large number of low-coverage primary schools of 6 or greater saw epidemics occur in the metapopulation. For 80% coverage this threshold was 14 low-coverage primary schools. However, a single low-coverage primary school in the metapopulation did not increase the mean final size of epidemics. Unintended heterogeneity through low-coverage secondary schools only has an impact at 60% coverage, as no epidemics occurred at 80% coverage even with 4 low-coverage secondary schools. In contrast to the results on the impact of a single low-coverage primary school, a single low-coverage secondary school has a measurable impact on the mean final size of outbreaks in the metapopulation at 20% coverage – the final size of epidemics increased from 7.16% (95% CI: 6.98-7.34%) to 7.74% (95% CI: 7.58-7.91%) with one secondary school achieving 10% coverage whilst all other primary and secondary schools achieved 20% coverage. For higher levels of homogeneous coverage the evidence for an impact of a low-coverage secondary school was much weaker. However, epidemics in a metapopulation with either 20% or 40% homogeneous vaccination coverage will have larger mean final sizes if both a primary school and a secondary school achieve only half the targeted coverage level. At 60% homogeneous coverage the evidence for a difference was again much weaker.

Intended heterogeneity through targeting 100% vaccination coverage in specific primary or secondary schools consistently increased the mean final size of epidemics from an equivalent homogeneous

coverage level. With overall 20% coverage, the mean final size increased from 6.85% (95% CI: 6.66-7.03%) with homogeneous coverage to 9.75% (95% CI: 9.58-9.90%) concentrated in 9 primary schools, to a maximum of 11.14% (95% CI: 11.01-11.26%) when concentrated in 2 secondary schools and 1 primary school. Similar trends were seen for the 40%, 60% and 80% coverage concentrated in specific primary or secondary schools, with heterogeneous coverage consistently increasing the mean final size of epidemics in the metapopulation. In contrast, the mean duration of epidemics increases with heterogeneity at overall 40%, 60% and 80% but decreases with heterogeneity at overall 20% coverage. Also, concentrating overall 20% and 40% coverage in secondary schools decreased the mean time required for the epidemic to spread to all metapopulation patches. 60% homogeneous coverage stops epidemics from spreading in the same way, but not overall 60% concentrated coverage in which epidemics always spread to all metapopulation patches.

Heterogeneous vaccination strategies that include all school patches in the vaccination programmes fail to reduce the mean final size of epidemics in the metapopulation when compared to their homogenous coverage equivalents. With strategies that achieve 60% coverage overall, those strategies that had the highest degree of heterogeneity with concentration of coverage in primary schools resulted in the largest outbreaks in the metapopulation. Highly heterogeneous coverage between both school groups resulted in epidemics that spread to all metapopulation patches, when other strategies with less or no heterogeneity in uptake resulted in epidemics confined to fewer than all 31 patches. Concentrating vaccination coverage in secondary schools caused the epidemics to spread to all 31 patches faster than those epidemics in metapopulations with vaccination concentrated in primary school patches. This is unsurprising as concentrating coverage in secondary schools increases the level of coverage in only five of the 31 metapopulation patches, leaving 26 patches with reduced vaccination coverage.

## **DISCUSSION**

This study sought to examine the impact of both unintended and intended heterogeneities in the uptake of a school-based vaccination programme using an age-structured stochastic transmission model and a theoretical patch-structured metapopulation.

The effectiveness of vaccination programmes was studied by estimating the reduction in the total burden of disease at different levels of coverage. In addition, the impact of heterogeneity in vaccination coverage – both unintended heterogeneity (through low uptake in some schools) and intended heterogeneity (through vaccination programme design by concentrating coverage in certain schools) – was estimated by comparing the total burden of disease for vaccination programmes without heterogeneity to those programmes with different heterogeneities.

## MAIN DIFFERENCES BETWEEN THE THREE VACCINATION PROGRAMMES

Neither the homogenous targeted vaccination policies in primary or secondary schools is sufficient to stop epidemics occurring in the metapopulation. Only vaccination in both school groups was sufficient to reduce the potential of epidemics, with results from Figure 6.23 showing that vaccination coverage above 47.8% would suffice. 100% coverage in primary schools and secondary schools separately resulted in epidemics with mean final sizes of 1.84% (95% CI: 1.49-2.22%) and 3.58% (95% CI: 3.32-3.86%) respectively. Targeted vaccination policies that vaccinate all individuals in the target population reduce the size of the mean epidemic peak and the mean duration of the epidemics greater when targeting primary schools, rather than secondary schools, but both policies are inferior to homogeneous vaccination of both groups.

## THE IMPACT OF THE MIXING PARAMETER

Increasing  $\epsilon_1$  from 0 to 1 with no additional vaccination in place other than those in clinical at-risk groups decreased the mean final size of epidemics in the metapopulation. Epidemics with  $\epsilon_1 = 0$  had a mean final size of 16.50% (95% CI: 16.47-16.54%) and epidemics with  $\epsilon_1 = 1$  had a mean final size of 16.28% (95% CI: 16.23-16.32%). As previously discussed, both extrema are unlikely to represent true values for this parameter, as  $\epsilon_1 = 0$  corresponds to school children not having daily contacts with other individuals in their school, whilst  $\epsilon_1 = 1$  corresponds to no inter-patch mixing takes place within age groups.

There was strong evidence for an albeit minor difference in the mean final size with  $\epsilon_1$  set to 0.25 and 0.75 (a mean of 70 fewer infections when  $\epsilon_1 = 0.75$ ), as well as between 0.50 and 0.75 (a mean of 47 fewer infections when  $\epsilon_1 = 0.75$ ), but no evidence for an impact on the mean final size between 0.25 and 0.50. Excluding the unrealistic extrema, all other metrics had similar degrees of small variation except for the mean time for all patches to become infected. These results make intuitive sense, as increasing the proportion of an individual's daily contacts in their own patch will decrease the proportion of daily contacts with individuals in other patches, slowing the spread of the epidemic.

With vaccination programmes in place, variation in  $\epsilon_1$  was associated with minimal variation in all metrics other than the mean time for all metapopulation patches to become infected. However, it is clear that to understand the potential total burden of disease caused by ILI or influenza, the proportion of daily contacts that an individual makes in their patch is not a key parameter. This is likely due to the fact that variation in the  $\epsilon_1$  parameter does not change the total number of daily contacts made by someone in our metapopulation, therefore an infectious individual will have just as many daily contacts when  $\epsilon_1 = 0$  as when  $\epsilon_1 = 1$ . This means that the total number of new infections in the metapopulation at each time step is not affected by variation in  $\epsilon_1$ .



## THE IMPACT OF THE $\tau$ PARAMETER

Variation in the degree of heterogeneity in vaccination uptake between low-coverage and high-coverage schools was directly associated with changes in the mean final size of epidemics and the mean size of the epidemic peak. The default value for the  $\tau$  parameter was 0.5, but increasing vaccination coverage heterogeneity by increasing  $\tau$  to 0.75 directly increased both the mean final size and the mean size of the epidemic peak for all coverage levels in both targeted vaccination programmes.

### The impact of unintended heterogeneity

#### FINAL SIZE OF EPIDEMICS

For all levels of vaccination coverage, increasing the number of low-coverage schools in the metapopulation consistently increases the expected mean final size of epidemics.

The difference between the mean final size of those epidemics in metapopulations with no heterogeneous uptake and those epidemics in metapopulations with maximum heterogeneity in uptake increases as the targeted vaccination coverage increases. These results are unsurprising but emphasise the importance of achieving homogeneity in vaccination uptake when administering targeted vaccination programmes that require very high acceptance rates.

A single low-coverage metapopulation patch is not a major cause for concern for public health officials if that low-coverage patch is a primary school – for all vaccination coverage levels considered, the existence of a single low-coverage primary school did not increase the mean final size of epidemics. However, a single low-coverage secondary school did increase the mean final size of epidemics for all targeted coverage levels considered in the model. Again, this is an unsurprising result as the population of a secondary school metapopulation patch represents a larger proportion of the metapopulation than the population of a primary school metapopulation patch.

With homogeneous vaccination across both primary and secondary schools, unintended heterogeneity through low-coverage primary schools increases the mean final size of epidemics, but more importantly increases the potential for epidemics to occur when homogeneous coverage would prevent this. 6 low-coverage primary schools in a vaccination programme targeting 60% homogeneous coverage introduced epidemics to the metapopulation. 14 low-coverage primary schools facilitated epidemic spread at 80% coverage. For public health officials, it is therefore important to ensure that several low-coverage primary schools is avoided when vaccination coverage is high, else the greatest potential benefit of such a vaccination programme would not be realised.

A single low-coverage primary school in a metapopulation with homogeneous coverage across both school groups will not increase the mean final size of epidemics at any coverage level. However, a

single low-coverage secondary school would increase the final size of epidemics when targeted coverage reaches only 20% in other schools. Public health officials should therefore be vigilant for single schools reporting low uptake during a homogeneous vaccination programme.

#### DURATION AND THE TIMING OF THE PEAK OF EPIDEMICS

The impact of unintended heterogeneity on the mean duration and mean timing of the epidemic peak is less straightforward than the impact on the mean final size. Variation in the mean duration of epidemics with targeted vaccination in primary schools was minor, most likely due to chance through the stochastic processes of the transmission model. A stronger relationship was seen when secondary schools were targeted for vaccination – at low levels of coverage the epidemics were shortened with an increasing number of susceptible individuals in the secondary school patches, but for high levels of coverage the opposite effect was achieved. For the lowest coverage levels, increasing uptake heterogeneity reduces the effectiveness of the vaccination programme by increasing the pool of susceptible individuals, facilitating a quicker epidemic. At the highest levels of coverage, an effective vaccination policy is compromised by increasing the pool of susceptible individuals, allowing the epidemic to run for longer but with greater difficulty due to relatively high vaccination coverage. This trend is repeated for the timing of the peak.

With homogeneous coverage across both school groups, coverage levels of 40% saw longer epidemics as heterogeneity increased through low-coverage primary schools. The same is true for heterogeneity introduced through secondary schools. Such a trend was not visible for the less effective programme with 20% coverage.

#### SIZE OF THE EPIDEMIC PEAK

The mean size of the epidemic peak is closely related to the mean final size of epidemics in the metapopulation. For both targeted vaccination policies in either primary or secondary schools, increasing heterogeneity in vaccine uptake increases the mean size of the epidemic peak and it increases quicker with higher targeted vaccination coverage. With homogenous vaccination across both school groups this trend continues.

#### TIME FOR ALL METAPOPOPULATION PATCHES TO BECOME INFECTED

Increasing unintended heterogeneity in vaccination uptake in both a targeted vaccination policy and a homogeneous vaccination policy either reduces the mean time required for all metapopulation patches to become infected, or allows the epidemic to spread to all patches when a vaccination policy without heterogeneity would succeed in stopping this.

At 100% targeted vaccination coverage in primary schools, epidemics failed to reach all metapopulation patches until 5 primary schools had low-coverage, sufficiently increasing the pool of susceptible individuals in that age group. The threshold to stop epidemics spreading to all

metapopulation patches was much lower with the homogeneous vaccination programme across both school groups, but with 60% coverage epidemics spread to all 31 patches when 14 primary schools had low-coverage. However, even with 4 low-coverage secondary schools the epidemic did reach this far. The reason for this discrepancy between the impacts of heterogeneity between the two age groups is most likely due to the greater number of assortative daily contacts in the primary school age group than in the secondary school age group.

#### **THE IMPACT OF INTENDED HETEROGENEITY THROUGH FIXED, CONCENTRATED COVERAGE**

##### **FINAL SIZE OF EPIDEMICS**

Although vaccination consistently reduced the mean final size of epidemics from 16.40% (95% CI: 16.36-16.44%) with no school-based vaccination programme, both targeted vaccination programmes using concentrated coverage of 100% uptake in specific schools were less effective than their homogeneous equivalents - that is the mean final size of epidemics in metapopulations with homogeneous vaccination coverage was always smaller than the mean final size of epidemics with concentrated vaccination coverage. For example, at 20% homogeneous vaccination coverage in primary schools the mean final size of epidemics was 11.41% (95% CI: 11.26-11.55%), whilst with concentrated coverage the mean final size reduced to only 13.47% (95% CI: 13.38-13.55%), with the same trend seen for 40%, 60% and 80% overall coverage. Any vaccination programme using concentrated coverage in this manner would be less effective than its homogeneous coverage equivalent and would therefore be dominated in an incremental cost-effectiveness analysis.

When vaccinating both school groups, heterogeneity in vaccination uptake through the concentration of coverage in specific schools increased the expected final size of epidemics for all coverage levels. Indeed, with 80% homogeneous coverage the heterogeneity in uptake saw epidemics occur in the metapopulation where homogeneous 80% coverage would prevent it. Intended heterogeneity through the concentration of vaccination coverage is less effective at reducing the mean final size of epidemics in the metapopulation than the homogeneous equivalent and would therefore be dominated in an incremental cost-effectiveness analysis.

##### **DURATION AND THE TIMING OF THE PEAK OF EPIDEMICS**

Concentrated vaccination coverage of 40%, 60% and 80% increased both the mean duration of epidemics and the timing of the epidemic peak over the homogeneous equivalents. Aside from the primary aim of reducing the expected final size of epidemics, vaccination programmes should also reduce the expected duration of an epidemic in the population, so concentrated vaccination programmes with coverage above 20% fail to meet these criteria.

If many primary and secondary schools have no vaccination protection, the epidemic duration in each school would be quicker in each school and would spread quickly to each metapopulation patch. For

those schools with full vaccination coverage, Figure 6.27 shows that epidemics in these patches were short, with sporadic cases incapable of seeding sustained transmission in each patch.

#### SIZE OF THE EPIDEMIC PEAK

The size of the epidemic peak was consistently increased by concentrating vaccination coverage in specific schools, at all levels of coverage. At 20% overall coverage the vaccination strategy with the smallest epidemic peak, other than the homogeneous strategy, was one that saw most coverage concentrated in primary schools with 9 schools receiving full vaccination. Moving coverage from primary schools to secondary schools increased the mean size of the epidemic peak. At higher levels of coverage there were no statistical differences between epidemic peaks. Similar results were seen in the targeted vaccination programme, with the concentration of vaccination coverage in specific schools of one age group consistently increasing the mean size of the epidemic peak.

#### TIME FOR ALL METAPOPOPULATION PATCHES TO BECOME INFECTED

When vaccinating both school groups, the mean time for all patches to become infected for the 20% and 40% coverage levels was greatest when a greater number of primary schools received full vaccination. Moving coverage concentration into the larger secondary school patches reduced the time for the epidemic to spread to all patches. This result is unsurprising - the metapopulation contains many more primary schools than secondary schools, so maximising the number of patches with full vaccination leads to a reduction in the number of susceptible individuals in each of those patches.

At 60% overall coverage there was little difference between the heterogeneous vaccination strategies, though each heterogeneous strategy meant that the epidemic could spread to all metapopulation patches when the homogenous strategy prevented this. Each heterogeneous strategy required a large number of primary school patches to be fully vaccinated, limiting the potential for the epidemic to spread to all patches. Variation in the number of primary schools with full vaccination is not sufficient to change the time for all patches to become infected.

#### THE IMPACT OF INTENDED HETEROGENEITY WITH VACCINATION IN ALL TARGETED PATCHES

##### FINAL SIZE OF EPIDEMICS

Modifying a vaccination programme with homogenous vaccination coverage in a small community to one that incorporates heterogeneous coverage between two target populations does not reduce the expected mean final size of epidemics, at any coverage level. In an economic evaluation comparing two or more potential vaccination strategies the key performance metric is the reduction in the mean final size. As the heterogeneous vaccinations strategies failed to perform better at homogenous strategies in reducing the mean final size of epidemics it is highly unlikely that a heterogeneous vaccination strategy would dominate a homogenous strategy.

At just 20% overall coverage between both primary and secondary school groups, heterogeneous coverage concentrated in the secondary schools increased the expected mean final size from 6.85% (95% CI: 6.65-7.05%) to 8.38% (95% CI: 8.28-8.49%). As the expected expenditure on this heterogeneous coverage level would be equal to the expenditure of 20% overall coverage between both school groups, the fewer health benefits realised by the heterogeneous coverage strategy means that it would be dominated by the homogeneous strategy in an economic analysis. Indeed, an increased mean final size of epidemics would also increase healthcare resource use in the population, making the heterogeneous vaccination strategy more expensive and less effective, therefore strongly dominated by the homogeneous vaccination strategy.

At 40% overall coverage, all alternative heterogeneous vaccination strategies again fail to perform better than the homogenous vaccination strategy. Heterogeneous vaccination strategies matching 60% overall coverage also failed to reduce the mean final size of epidemics. The most interesting result was that the worst performing heterogeneous vaccination strategies were those that concentrated coverage in the primary school patches, rather than those that concentrated coverage in secondary school patches which performed worse at 40% overall coverage. Heterogeneous vaccination strategies that spread coverage more evenly performed better in reducing the mean final size, but did not perform better than the homogenous 60% coverage. Therefore, in an economic evaluation a more cost-effective intervention than homogenous 60% coverage would not be likely.

With overall coverage of 80%, epidemics did not occur in the population. Heterogeneity in coverage between the primary and secondary school groups did not increase the potential for sustained community-level transmission in the metapopulation.

#### DURATION AND THE TIMING OF THE PEAK OF EPIDEMICS

Heterogeneous vaccination coverage does not reduce the duration of epidemics in the metapopulation, for any vaccination strategy at any coverage level. The timing of the epidemic peak also does not occur any earlier than the homogenous vaccination strategy for any coverage level. Vaccination strategies with the greatest degree of coverage heterogeneity between the two school groups resulted in the longest epidemics, due to the pool of susceptible individuals created in one school group caused by concentrating vaccination coverage in the other school group.

#### SIZE OF THE EPIDEMIC PEAK

Heterogeneous coverage did perform better in reducing the mean size of the epidemic peak, but only with specific strategies at a particular overall coverage level. With heterogeneity in the vaccination coverage between the two school groups but vaccinating the equivalent of 40% of the school population, the mean size of the epidemic peak decreased when vaccinating 24% of primary school children and 60% secondary school children (0.035% (95% CI: 0.033-0.036%)) and also when vaccinating 56% of primary school children and 20% of secondary school children (0.036% (95% CI:

0.034-0.038%)), down from 0.043% (95% CI: 0.041-0.046%) with homogeneous coverage. However, for strategies at 20% and 60% coverage the mean size of the epidemic peak is not reduced by heterogeneous coverage.

#### TIME FOR ALL METAPOPOPULATION PATCHES TO BECOME INFECTED

With both 20% and 40% coverage, the mean time for all metapopulations to become infected is either increased by heterogeneous vaccination coverage, or remains the same as the homogeneous coverage strategy. Increasing the time required for all patches to become infected is likely to be an advantage to public health and outbreak response teams reacting to the outbreak.

However, heterogeneous vaccination strategies with 60% coverage overall failed to perform as well as the equivalent homogeneous vaccination coverage strategy – the epidemics with 60% homogeneous coverage did not reach all metapopulation patches, but the heterogeneous vaccination strategies with the greatest degree of coverage heterogeneity between the two school groups facilitated this by providing a sufficiently large pool of susceptible individuals in one of the school groups to feed epidemics in the other. The strategies with the highest concentration of coverage in the primary school patches saw epidemics reach all 31 patches after two months, and strategies with large concentration in secondary schools saw epidemics reach all 31 patches in less than one month. The imperfect vaccine modelled in this exercise permitted infections even in metapopulation patches with 100% coverage.

#### LIMITATIONS OF THE STUDY

##### THEORETICAL COMMUNITY AND POPULATION STRUCTURE

Though we structured the population to be representative of a small administrative district of England, in both age distribution of the population and the appropriate number of schools, we needed to assume that the number of daily contacts that individuals in the school patches had with individuals in their own age group was influenced by the  $\epsilon_1$  parameter. Results from our analysis demonstrate that this assumption does not impact on the mean final size of epidemics if it is agreed that the extreme case of  $\epsilon_1 = 1$  is highly unlikely. But the  $\epsilon_1$  parameter did influence the speed at which the epidemics spread across all metapopulation patches. Without any data on an appropriate distribution for the values of the  $\epsilon_1$  parameter, our results could certainly be improved if this data were available.

##### STOCHASTIC FADEOUT AND RESEEDING OF EPIDEMICS

62.9% of simulated epidemics resulted in an overall ILI final size less than 0.5% of the total population and were therefore considered to be stochastic fadeouts. This proportion of simulations is high, though our model used data previously fit to models describing a mild influenza season. We chose not to reseed epidemics that faded quickly for simplicity, though it is an option that would have been interesting to explore. Indeed, this technique is not uncommon and would not have been

computationally expensive [23]. By not reseeding epidemics we may have underestimated the total burden of seasonal influenza outbreaks in our metapopulation by removing the potential for additional simulated outbreaks that may have exceeded the size of those we reported.

#### VACCINATION PROGRAMMES AND STRATEGIES

We investigated the impact of many different vaccination programmes and strategies, some of which are unlikely to be implemented. Our aim was to study the consequences of heterogeneous uptake. Many vaccination programmes report heterogeneity in uptake between different areas or regions [1, 7, 13, 24, 25] but none with heterogeneity as extreme as those strategies investigated in parts of this analysis.

It is highly unlikely that a school-based vaccination programme would be implemented that would result in one or more schools receiving no vaccinations whilst others in the same district would achieve 100% coverage. However, this exercise in modelling heterogeneity through concentrated coverage was a useful exercise in examining the consequences of high vaccination concentration in patches of a metapopulation. Some schools in communities may have a large concentration of children from families with religious or philosophical reasons to reject the offer to participate in school-based vaccination programmes [7, 26] but a scenario where one or more schools in a community report no vaccination coverage whilst others achieve complete coverage is unlikely. Vaccinating 100% of an eligible population or sub-population is unlikely because vaccination is clinically inappropriate for some children.

#### CONTACT PATTERN UNCERTAINTY

The contact patterns used in our model were taken from the POLYMOD contact matrix [14], dividing the population into seven age groups. We did not explore the consequences of uncertainty in these contact patterns, instead we used the mean daily number of contacts for individuals in each age group in order to inform our model with widely-used contact pattern data.

#### MEASURING THE $\epsilon_1$ PARAMETER TO INCLUDE IN FUTURE MODELS

The daily contact patterns of school children have been estimated in many studies using different techniques. The use of both contact diaries [14, 27] and electronic sensors [28, 29] have been very successful in quantifying the mean daily number of contacts for school children. These data, however, are unable to provide an estimate for the value of the  $\epsilon_1$  parameter used in our model: the studies by both Beutels et al. (2006) and Mossong et al. (2008) report the total number of conversational and physical contacts with all individuals, whilst the studies by both Fournet et al. (2014) and Stehle et al. (2011) measured the number of face-to-face interactions of twenty-second duration within between individuals standing up to 1.5m apart within the same school. However, these datasets cannot be combined to estimate the  $\epsilon_1$  parameter in our model.

To ascertain an estimate for the  $\varepsilon_1$  parameter we require the proportion of the total number of daily contacts for an individual and the total number of daily contacts for an individual within their assigned metapopulation patch. In a contact diary-type study, this would require the individual to notify data handlers of the number of contacts within their age group that occurred both inside and outside their school. For an electronic sensor-type study, this requires electronic sensors to be distributed further than the confines of a chosen school, thereby greatly increasing the total number of electronic sensors needed for a study which may make the study unfeasible.

#### ADDITIONAL PARAMETER UNCERTAINTY

Several parameters used in the model were point-estimate parameters taken from the literature. These included the length of the incubation and infectious periods; the age-specific hospitalised case fatality ratio; and other key parameters. Further use of the level of uncertainty in the estimates for these parameters allows for additional modelling opportunities to establish the parameter space over which the conclusions reached are valid.

#### USE OF A SPATIAL MODEL

Other modelling studies that use a spatially explicit metapopulation have provided useful results on epidemic transmission in populations. For example, Hosseini et al. (2013) showed that a gigantic metapopulation patch in such a framework can alter the dynamics of epidemic transmission, due to its connectivity to nearby smaller patches and the pool of susceptible individuals within it [30]. Our metapopulation model included a large patch containing all adult inhabitants of the theoretical community, and even with extremely high targeted vaccination coverage in either of the two school groups, community-wide transmission was sustained in our metapopulation model. It may be that the susceptible adults and young children in the external patch permitted this sustained transmission and ensured that epidemics spread even to those patches with very high vaccination coverage, but we are unable to confirm this hypothesis without expanding the model structure further.

In addition, we assumed that a proportion  $1-\varepsilon_1$  of daily contacts within an individual's age group would take place outside of their own patch, but we assumed that these would be split evenly over all other patches for simplicity. In reality, this proportion is likely to be influenced by other factors not included in our model, such as household structure, population concentration within the studied district and the proximity of an individual's school to other schools in their district.

#### MODELLING VACCINATION COVERAGE AND EPIDEMICS OVER A SINGLE INFLUENZA SEASON

Similar to the issues reported in Chapter 5, we only modelled vaccination uptake and epidemics over the course of a single influenza season. Modelling over a longer time horizon requires the addition of extra complexity to the model to account for immunity-waning, multiple strains of influenza and



antigenic drift. Increasing the time horizon of our study would allow for comparisons with other analyses of seasonal influenza vaccination coverage that have used multiple influenza seasons [10].

A consequence of using a longer time horizon is that the model would then need to account for the annual migration of a proportion of primary school children to secondary schools, with a proportion of secondary school children migrating to the adult population and external metapopulation patch. This will impact the proportion of susceptible individuals through previously-acquired immunity.

## CONCLUSION

Chapter 5 demonstrated that at the national level and without heterogeneities within the two school-age groups, a heterogeneous vaccination strategy between primary and secondary schools is the optimal strategy from the perspective of the healthcare provider. However, this study has demonstrated that including coverage heterogeneities within each of the two school age groups at a local level reports a reduction in the effectiveness of school-based vaccination programmes. Heterogeneity in coverage, by accident or design, does not perform better than the equivalent homogenous vaccination strategy at any coverage level.

To our knowledge, this is the first attempt at modelling school-level uptake for seasonal influenza vaccination. Our model may provide public health officials with important information on how to design their seasonal influenza vaccination programmes if our suggested modifications to the modelling framework can be addressed in future research projects.

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## **Chapter 7 - The effect of measles on health-related quality of life: a patient-based survey**

Portions of this section were presented as a poster presentation at the Public Health England Annual Conference in Warwick in September 2013; published in *The Lancet* as a conference abstract in November 2013 [1]; delivered as an oral presentation at The Lancet Public Health Science conference in London in November 2013; and published in *PLoS ONE* in September 2014 [2].

### **ABSTRACT**

#### **BACKGROUND**

Measles is a highly contagious and potentially fatal illness preventable through vaccination. Outbreaks in the UK and many other European countries have been increasing over recent years, with over 3,207 laboratory-confirmed cases reported by Public Health England from January 2012 to the end of June 2013. To aid rational decision making regarding measles control versus other use of healthcare resources, it is important to measure the severity of measles in units that are comparable to other diseases. The standard metric for this in the UK is the quality-adjust life year (QALY). To our knowledge, the impact of measles on health-related quality of life (HRQoL) in terms of QALYs has not been quantified.

#### **OBJECTIVE**

We sought to quantify the impact of measles on HRQoL.

#### **METHODS AND FINDINGS**

Individuals with confirmed measles were sent questionnaires requesting information on the short-term impact of the illness on their HRQoL using the EuroQol EQ-5D-3L questionnaire. HRQoL was reported for the day the questionnaire was received, the worst day of infection and at follow-up three weeks later. 507 questionnaires were sent to individuals with confirmed measles with 203 returned (40%). The majority of respondents were not vaccinated. The mean time off work or school was 9.6 days. The mean duration of perceived illness was 13.8 days. The mean number of QALYs lost was 0.019 (equivalent to 6.9 days). The overall burden of disease in terms of QALYs lost in England based on the total number of confirmed cases in the twelve month period from 1st June 2012 was estimated to be 44.2 QALYs.

## **CONCLUSION**

The short-term impact of measles infection on HRQoL is substantial, both at the level of the individual patient and in terms of the overall disease burden. This is the first attempt to quantify QALY-loss due to measles at a population level, and provides important parameters to guide future intervention and control measures.

## **INTRODUCTION**

So far the focus of this thesis has been the societal and economic impact of influenza infection and the mathematical modelling of preventive vaccination programmes. During the course of this research programme we had the opportunity to investigate the societal and economic impact of measles infection by working closely with colleagues from Public Health England and their Outbreak Investigation Teams in both Liverpool (for the measles outbreak in Cheshire and Merseyside) and Colindale (for investigating the outbreaks from a national perspective) during the measles outbreaks in the United Kingdom that occurred in 2012 and 2013.

This section discusses a plan to investigate the societal impact of measles infection, including the first attempt to quantify the impact of measles on health-related quality of life.

## **BACKGROUND**

Measles is a highly infectious notifiable disease that can be severe in infants, pregnant women and immunocompromised individuals [3, 4]. Measles is preventable through the measles-mumps-rubella vaccination programme (MMR), with measles vaccination introduced in the UK in 1968 [3]. Previous measles outbreak reports focus on the epidemiology of the disease [5-7], rather than the overall disease burden in terms of health-related quality of life (HRQoL). The impact of infectious diseases on HRQoL is a developing field of research, whose aim is to express the burden of disease not only in number of cases but also in disease days and the impact of these disease days. Doing so enables a comparison between diseases and helps in the fair allocation of resources. In England the evaluation of resource allocation is formalised in cost-effectiveness analyses [8, 9].

A standard method to measure the disease burden is the use of quality-adjusted life years (QALYs), a generic measure incorporating both the length of time that patients experience health reduction and the magnitude of the health reduction [10]. To calculate QALYs first the condition-specific health utilities, which give an estimate of the impact on HRQoL for the condition in question, must be established.

To our knowledge, no measure of health utilities has previously been attempted for measles, despite the global significance of this infection. This study attempts to gather health utilities specific to measles during the 2012-13 regional measles epidemics in England, as well as other direct and indirect

effects of a measles epidemic on a population including symptoms during infection; disruption at home due to time off work or school for individuals with confirmed measles; hospitalisations and carer time off work.

#### **RESEARCH QUESTIONS**

1. What is the impact of measles infection at home, in terms of days of school/work missed through illness and as acting as a primary caregiver for those with measles infection?
2. What is impact of measles infection in terms of HRQoL and how does this compare to other infectious disease outbreaks?
3. What was the overall burden of disease during the 2012-13 regional measles epidemics in England?

#### **METHODS**

In this study, standardised postal questionnaires were sent to individuals with confirmed or suspected measles. Questionnaires were sent to individuals with suspected measles in the North West England outbreak from 1<sup>st</sup> June 2012 and the study was extended throughout England from 2<sup>nd</sup> October 2012 to 5<sup>th</sup> July 2013 targeting only individuals with confirmed measles.

#### **CASE DEFINITION**

Individuals with suspected measles were confirmed positive if they were measles immunoglobulin M-positive on saliva or through polymerase chain reaction testing in urine, saliva or a throat swab. A suspected measles case was defined using the following criteria from Vivancos et al. 2012 [7]:

- Clinical presentation: fever and measles-like rash and one or more of the following symptoms: cough, conjunctivitis, coryza, or Koplik's spots.
- Residence / reported from: residence or history of travel to endemic, outbreak or adjacent areas, or being a close contact of a confirmed or probable case of measles.

#### **EXCLUSION CRITERIA**

Individuals in traveller communities with laboratory-confirmed measles were not invited to participate in the study, because Public Health England engages with this community through different protocols and procedures [11]. A member of the traveller community was defined as someone self-identifying as a member of the traveller community or someone living on a traveller site, whether authorised or not authorised.

We excluded individuals with confirmed measles with a reported symptom onset date more than two weeks before case status was confirmed to minimise the time between perceived symptom onset and receiving the first questionnaire.

### **EUROQOL EQ-5D-3L**

The EuroQol EQ-5D-3L is a generic multi-attribute health-state classification system [12, 13]. HRQoL is assessed in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is assessed using three levels: no problems, some problems and severe problems, facilitating the evaluation of 243 ( $= 3^5$ ) different health states. The EuroQol scoring algorithm converts the responses into a health utility specific to the individual's health state. A visual analogue scale (VAS) invites the individual to rate their health state on a scale from 0 – 100, with 0 being the worst health state imaginable and 100 being the best health state imaginable.

Three age-specific EQ-5D-3L questionnaires were used: the standard EQ-5D-3L for all individuals aged 13 years and older; the child-friendly EQ-5D-Y for all individuals aged between 7 – 12 years [14] and a proxy version of the standard EQ-5D-3L for individuals aged less than 7 years to be completed by the child's parent or guardian. All three versions of the questionnaire use both the same algorithm and scoring tariff to convert responses into health utilities.

### **QUESTIONNAIRES**

Individuals were sent an initial questionnaire requesting details of their illness and its impact on their HRQoL for both the worst day of infection and the day that the questionnaire was received using the EQ-5D-3L. Three weeks later they were sent a follow-up questionnaire to obtain a further HRQoL measurement at recovery. Individuals who did not return the first questionnaire were sent it a second time along with the follow-up questionnaire three weeks later. We assumed that a three week period was sufficient for typical symptoms of measles to subside [15], and we assumed that if individuals reported that they had recovered then they were no longer suffering a measles-related reduction in their HRQoL. The value of HRQoL reported by individuals who reported having recovered was treated as their baseline HRQoL for the purposes of calculating QALY loss.

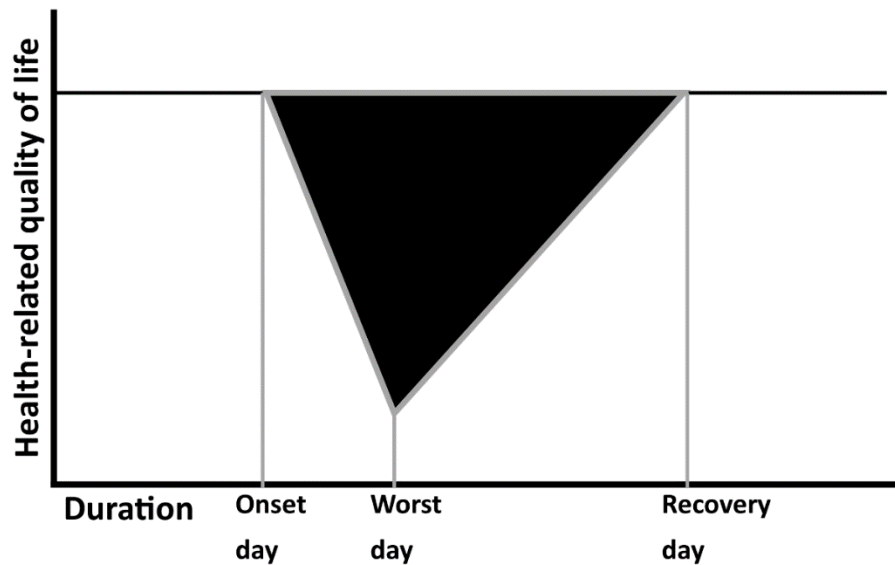


Figure 7.1 - Assumed short-term loss in health-related quality of life caused by measles infection

To assess the impact of measles infection on HRQoL, patients must complete the EQ-5D-3L when healthy (at recovery) and for the worst day of infection. We assumed that the QALY loss associated with measles for each individual can be represented by a triangular shape, as shown in Figure 7.1. As a comparison, we also estimated HRQoL directly using the VAS, with HRQoL given by VAS score divided by 100.

Notification of potential study participants was received by the specialist epidemiologist for measles at Public Health England in Colindale who excluded ineligible patients. Letters and questionnaires were sent using a database updated daily with new notifications of suspected measles cases. In the analysis that follows, we consider only those individuals with laboratory-confirmed measles.

#### ANONYMISED DATA

All questionnaires sent to confirmed or suspected measles cases were anonymised. A questionnaire was linked to the appropriate follow-up questionnaire using the HP Zone ID, an anonymised ID data field used on Public Health England databases. Sensitive patient identifiers such as the distribution address were handled by Public Health England, whereas the returned and anonymous questionnaires were processed by researchers at the London School of Hygiene and Tropical Medicine, with no links or access to the original sensitive information. All medical records used in the analysis were also anonymised by Public Health England using the HP Zone ID.



## **ETHICS APPROVAL**

In accordance with The Health Service (Control of Patient Information) Regulations 2002 No. 1438 Section 251 Regulation 3 [16], Public Health England may process confidential patient information with a view to monitoring and managing the following:

- Outbreaks of communicable disease;
- Incidents of exposure to communicable disease;
- The delivery, efficacy and safety of immunisation programmes.

## **DATA ANALYSIS**

Data were analysed using Microsoft Excel 2007 and R (version 3.0.2) [17]. Public Health England obtained hospitalisation records for individuals who received the questionnaire, so hospitalisation rates were compared between responders and non-responders to test for severity bias. HRQoL data were analysed only for those patients who completed all five dimensions of health on the EQ-5D-3L in addition to reporting the duration of their illness. Reported 95% confidence intervals of the means are based on 1,000 bootstrap replications.

The EQ-5D-3L requires the respondent to complete all five dimensions of the classification system in order to calculate a health-state utility. Omitting the response to any of the dimensions means the remaining responses cannot be used for this purpose, therefore a missing-value regression analysis was conducted using the VAS score to estimate the EQ-5D-3L utility where patients had completed the VAS but not all five dimensions of health. When assessing the HRQoL in individuals with haemophilia Miners et al. [18] showed a correlation between EQ-5D-3L utility and the VAS scores ( $R = 0.67$ ,  $p < 0.0001$ ).

## **RESULTS**

683 questionnaires were sent; 507 to individuals with confirmed measles and 176 to individuals with unconfirmed/suspected measles. 203 questionnaires were returned from those with confirmed measles (40.0%). 45 questionnaires from individuals with unconfirmed/suspected measles were returned (25.6%). From the 203 individuals with confirmed measles who returned their first questionnaires we received 63 follow-up questionnaires (31.0%). 103 of the returned first questionnaires had been completed after recovery from measles so the HRQoL measurement on the day of completion could be used as the recovery HRQoL measurement.

## RESPONSES, DEMOGRAPHICS AND VACCINATION DATA

### RESPONSES

Figure 7.2 shows a flow chart detailing the process of identifying individuals with confirmed measles through to receiving their returned questionnaires and using their responses to calculate HRQoL results from the EQ-5D-3L questionnaires.

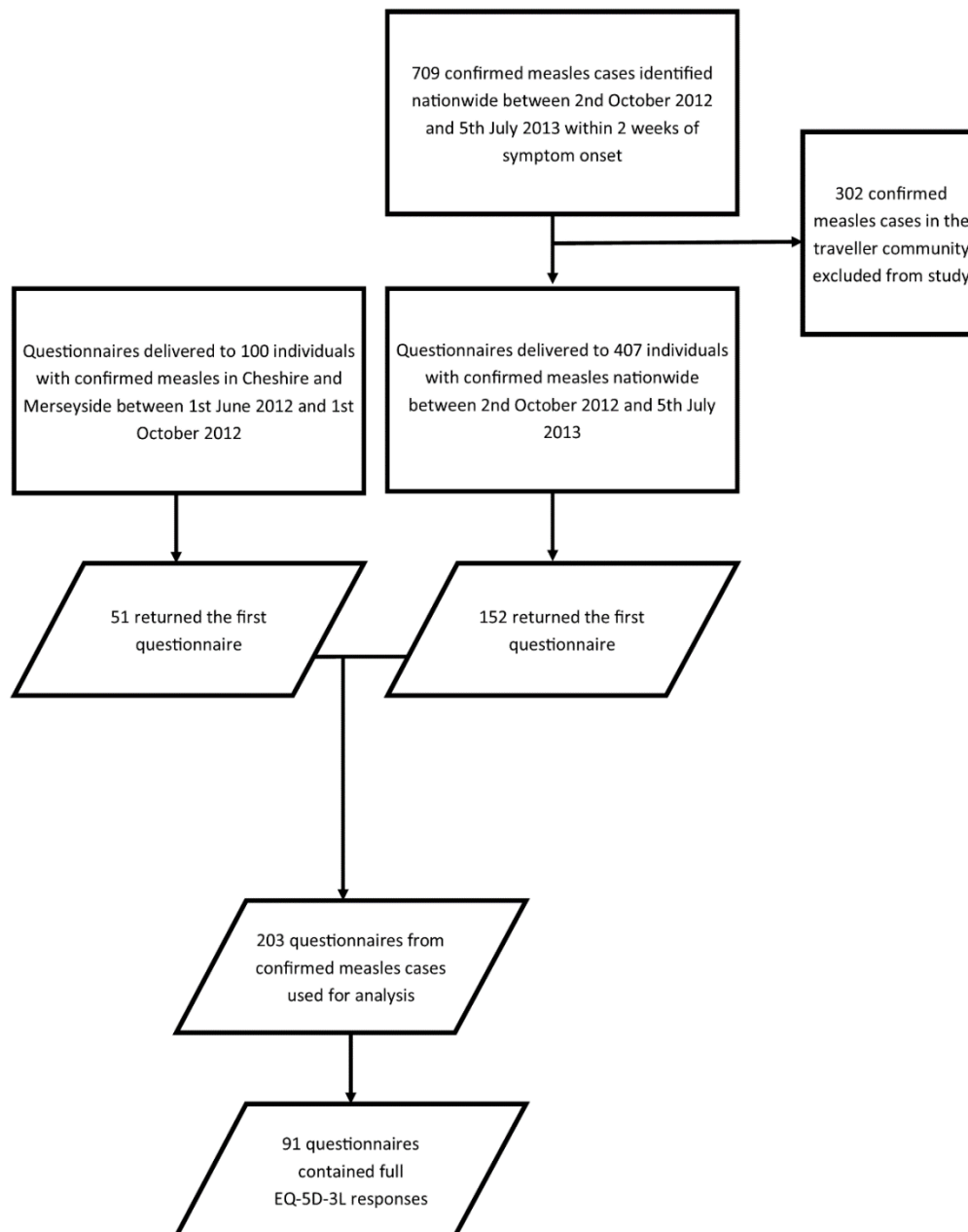


Figure 7.2 - Flow chart for the study showing the number of questionnaires that were distributed to confirmed measles cases; the number of questionnaires returned for analysis; and the number of questionnaires returned for analysis that included the necessary information for EQ-5D-3L health utilities to be calculated

709 individuals with confirmed measles were identified as potentially suitable for recruitment to the study but 302 of these were excluded on the basis that the individuals were members of the traveller community. From the remaining 507 individuals sent a questionnaire we received completed responses from 203. These 203 responses were used in all parts of the analysis except for the HRQoL calculations with the EQ-5D-3L, as only 91 returned questionnaires contained all the data necessary to facilitate those calculations.

70 returned questionnaires came from individuals with confirmed measles aged under seven years; 25 questionnaires came from individuals aged between seven and twelve years and the remaining 108 questionnaires came from individuals aged over 12 years.

#### DEMOGRAPHICS AND VACCINATIONS

101 (49.8%) of the 203 responses were from female patients. 68 (33.5%) of the respondents were under five years old (Figure 7.3). 188 (92.6%) had not yet received their first dose of the MMR vaccine. The age distribution of those individuals who returned the questionnaire was similar to the age distribution of confirmed measles cases invited to participate (Figure 7.3).

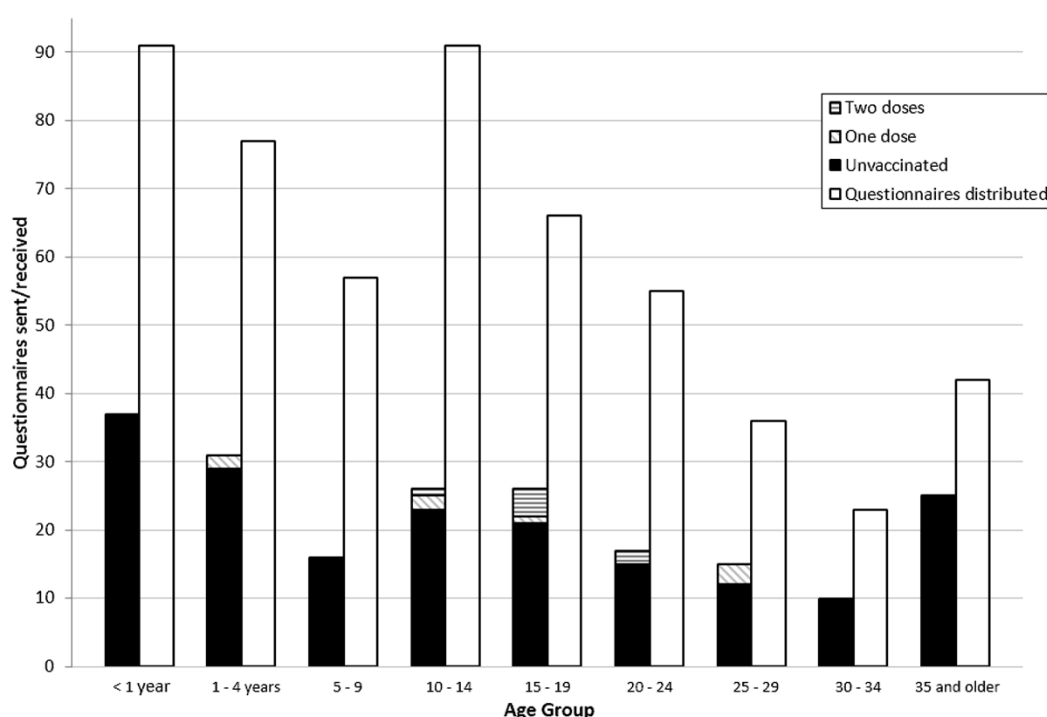


Figure 7.3 - Age-specific distribution of questionnaires sent, questionnaire response, and vaccination status for confirmed cases of measles

## SEVERITY BIAS

Among the 507 individuals with confirmed measles to whom questionnaires were sent, Public Health England could not obtain hospitalisation records for 20 individuals (3.9%) as their GP's database had not been updated with any details of potential hospitalisations post-notification. Of the remaining individuals, 75 of the 199 individuals who were hospitalised returned their questionnaire and 120 of the 288 individuals not hospitalised returned theirs. We found that there was no evidence that hospitalised individuals were more likely to return the questionnaires ( $\chi^2 = 0.78$  and  $p = 0.38$ ).

The remaining results refer only to the 203 questionnaires returned by individuals with confirmed measles.

## MEASLES INFECTION

### REPORTED SYMPTOMS

Symptom	Number of individuals with confirmed measles
Rash	189 (93.1%)
Tiredness	188 (92.6%)
Poor appetite	188 (92.6%)
Cough	183 (90.1%)
Severe temperature	183 (90.1%)
Sore mouth	166 (81.8%)
Runny nose	155 (76.4%)
Aches and pains	150 (73.9%)
Watery eyes	143 (70.4%)
Blood-shot eyes	137 (67.5%)
Swollen eyelids	134 (66.0%)
Sneezing	126 (62.1%)
None	2 (1.0%)

*Table 7.1 - Reported symptoms of 203 individuals with confirmed measles*

189 (93.1%) individuals with confirmed measles reported a rash on their worst day of infection (Table 7.1). The rash was the most common reported symptom on the worst day of infection, followed by tiredness (92.6%), poor appetite (92.6%), cough (90.1%), severe temperature (90.1%) and a sore mouth (81.8%).

### REPORTED COMPLICATIONS

Table 7.2 shows the number of individuals with confirmed measles reporting complications of their infection. The most common complication was fever, with 187 individuals reporting this (92.1%). 50 individuals (24.6%) reported having otitis media. Only 7 individuals (3.4%) reported no complications of their infection with the remaining 196 (96.6%) reporting at least one from the list above.

Complication	Number of individuals with confirmed measles
Fever	187 (92.1%)
Coughing	162 (79.8%)
Confusion	153 (75.4%)
Diarrhoea	129 (63.5%)
Conjunctivitis	114 (56.2%)
Vomiting	113 (55.7%)
Laryngitis	89 (43.8%)
Otitis media	50 (24.6%)

*Table 7.2 - Reported complications of measles infection from 203 individuals with confirmed measles*

#### IMPACT AT HOME

128 (63.1%) individuals with confirmed measles reported spending time off work or school due to measles infection (Table 7.3), of whom those who had fully recovered reported a mean time spent at home of 9.6 days (95% CI: 9.3 - 11.7). 75 (36.9%) individuals with confirmed measles reported that a caregiver spent time away from work during their infection, of whom those who had fully recovered reported a mean time spent away from work by carers of 7.3 days (95% CI: 5.7 - 7.9). 74 (36.5%) individuals reported spending at least one night in hospital, of whom those who had fully recovered reported a mean length of stay of 4.2 nights (median 4.0 nights). The median worst day of perceived symptoms was the fifth day and the mean duration of perceived symptoms was 13.8 days (95% CI: 12.6 – 15.1).

#### CONTACT WITH THE HEALTH SERVICES

193 (95.1%) individuals with confirmed measles reported at least one contact with the health services. The remaining 10 individuals may have come to the attention of the local Health Protection Unit (HPU) through contact tracing of another confirmed measles case or may have been reported directly to the HPU by a teacher, parent or guardian, thereby not having any contact with the health services before their case status was confirmed. The median number of contacts with the health services was 3.0 during the period of infection but this was highly skewed with a mean of 4.0 and 5 people having more than 10 contacts. The mean time between perceived symptom onset and first contacting the different local health services was about 3.6 days irrespective of which service (NHS Direct, GP, A&E, etc.) was first contacted.

	Among confirmed measles cases (n=203)	Age under 7 years (n=70)	Age 7-12 years (n=25)	Age 13 years and over (n=108)
Worst day (median, mean, mode)	5, 5.61, 4	5, 5.58, 5	6, 7.56, 5	5, 5.15, 4
Mean duration of perceived symptoms (95% CI)	13.8 days (12.6 – 15.1)	12.8 days (11.0 – 14.9)	13.5 (10.4 – 17.1)	14.4 (12.7 – 16.2)
Individuals reporting time off work or school	128 (63.1%)	26 (37.1%)	22 (88.0%)	80 (74.1%)
Mean time off work or school for patients (95% CI)	9.6 days (9.3 – 11.7)	8.6 days (6.8 – 10.5)	9.1 days (7.4 – 10.8)	10.1 days (8.8 – 11.5)
Individuals reporting time off work for primary caregivers	75 (39.6%)	31 (44.3%)	10 (40.0%)	34 (31.5%)
Mean time off work for primary caregivers (95% CI)	7.3 days (5.7 – 7.9)	7.0 days (4.9 – 9.2)	7.7 days (4.3 – 11.3)	7.2 days (5.0 – 9.5)
Individuals reporting at least one night in hospital	74 (36.5%)	23 (32.9%)	2 (8.0%)	49 (45.4%)
Number of nights spent in hospital (median, mean, mode)	4.0, 4.2, 1.0	3.0, 4.0, 1.0	4.0, 4.0, 4.0	4.0, 4.4, 1.0

*Table 7.3 - Impact of measles infection. The mean time off work or school for patients and for primary caregivers is the mean time for those who reported at least one day of absence. Likewise, the number of nights in hospital applies only to those individuals who reported at least one night in hospital. 95% confidence intervals of the mean are based on 1,000 bootstrap replications. The first column shows results for the whole sample; the subsequent 3 columns split the sample into the three age groups considered*

## EQ-5D-3L DIMENSIONS RESULTS

91 of the 203 confirmed measles cases completed all five dimensions of health for the EQ-5D-3L on the worst day of infection and after a full recovery from measles infection and reported the duration of perceived symptoms, thus enabling the calculation of QALYs lost. On the worst day of infection, these individuals reported their health according to each of the EQ-5D-3L dimensions of health as shown in Table 7.4.

194 of the 203 individuals with confirmed measles (95.6%) who returned a questionnaire also returned a completed VAS.

Evaluating HRQoL on the worst day of infection (n = 91)			
EQ-5D dimensions of health	No problems	Some problems	Severe problems
Mobility	10 (11.0%)	35 (38.5%)	46 (50.5%)
Self-care	20 (22.0%)	35 (38.5%)	36 (39.6%)
Usual activities	3 (3.3%)	17 (18.7%)	71 (78.0%)
Pain or discomfort	9 (9.9%)	45 (49.5%)	37 (40.7%)
Anxiety or depression	33 (36.3%)	34 (37.4%)	24 (26.4%)

*Table 7.4 - Responses to each dimension of health for the worst day of infection for individuals with confirmed measles who provided the full data set to facilitate the calculation of QALY loss associated with measles*

## HEALTH-RELATED QUALITY OF LIFE

The overall QALY loss, calculated using the EuroQol EQ-5D-3L, associated with measles was 0.019 QALYs per patient (95% CI: 0.016 – 0.022), the equivalent of 6.9 QALDs per patient (95% CI: 5.84 – 8.02) (Table 7.5).

	Health-related quality of life results (n = 91)	Age under 7 years (n=15)	Age 7-12 years (n=18)	Age 13 years and over (n=58)
EQ-5D Baseline HRQoL (95% CI)	0.96 (0.93 – 0.98)	0.89 (0.78 – 0.98)	0.98 (0.96 – 1.00)	0.94 (0.91 – 0.97)
EQ-5D Worst day HRQoL (95% CI)	0.00 (-0.09 – 0.09)	-0.26 (-0.43 – -0.08)	-0.07 (-0.22 – 0.10)	-0.05 (-0.13 – 0.04)
VAS Background (95% CI)	92 (90 – 94)	93 (91 – 95)	91 (87 – 95)	89 (86 – 91)
VAS Worst day (95% CI)	21 (17 – 24)	18 (14 – 22)	19 (13 – 25)	19 (15 – 23)
Overall QALY loss (95% CI)	0.019 (0.016 – 0.022)	0.017 (0.012 – 0.022)	0.020 (0.014 – 0.028)	0.019 (0.016 – 0.023)
Overall QALD loss (95% CI)	6.90 (5.84 – 8.02)	6.29 (4.51 – 8.11)	7.28 (5.07 – 10.10)	6.94 (5.73 – 8.33)

*Table 7.5 - Impact on HRQoL of measles for the 91 individuals with confirmed measles for whom QALY loss could be calculated using the EQ-5D-3L. 95% confidence intervals of the mean are based on 1,000 bootstrap replications. The first column shows results for the whole sample; the subsequent 3 columns split the sample into the three age groups considered*



## HRQoL THROUGH THE VAS

The overall QALY loss associated with measles using the VAS score was the equivalent of 4.92 QALDs (95% CI: 4.15 – 5.86) or 0.013 QALYs (95% CI: 0.011 – 0.016). There is very strong evidence that the VAS gives different results when compared to the EQ-5D-3L algorithm using the paired Wilcoxon test ( $V = 649$ ,  $p < 0.0001$ ) using the HRQoL results from the 91 individuals with confirmed measles who completed all aspects of the EuroQol EQ-5D questionnaire.

## OVERALL BURDEN OF REGIONAL EPIDEMICS

Public Health England reported that there had been 2,366 laboratory-confirmed cases of measles in England for twelve months from 1<sup>st</sup> June 2012, the beginning of the study period [19, 20]. Using our estimates above for the burden of measles infection, the age-adjusted overall burden of disease in this period was approximately 16,164 QALDs (95% CI: 15,740 – 16,645), or 44.2 QALYs (95% CI: 43.2 – 45.6). 1,534 of these confirmed cases would have taken time off work or school, resulting in 14,527 age-adjusted days of lost productivity (95%CI: 14,215 – 14,848). When including primary caregivers taking time off work, a further 904 people would have taken time off work resulting in an age-adjusted total number of 23,110 days of lost productivity (95%CI: 22,661 – 23,522). 95% confidence intervals of the mean are based on 1,000 bootstrap replications.

## MISSING DATA ANALYSIS

Each patient was sent a maximum of three EQ-5D-3L questionnaires: for the worst day of infection, for the date that the first questionnaire was received and the recovery HRQoL reading. From a maximum of 744 eligible questionnaires from both individuals with confirmed measles and individuals with unconfirmed/suspected measles, 397 contained both a EQ-5D-3L questionnaire with responses to all dimension of HRQoL and a completed VAS score.

Assuming that EQ-5D responses were missing at random and that the VAS score can be used to predict missing EQ-5D utilities, we used a multiple imputation method through the Amelia II statistical package in R [21] to impute EQ-5D utilities where the individual had completed the VAS. This added 26 more observations and the overall QALY loss from the interpolated data was equivalent to 6.81 days (95% CI 5.68 – 8.04), very similar to the QALY and equivalent QALD loss from non-interpolated data reported in Table 7.5.

## IMPLICATIONS FOR MISSING HRQoL DATA

*49 (70%) of the 70 EQ-5D proxy questionnaires for children aged under 7 years for the worst day of infection returned were missing in the self-care dimension (*

Table 7.6). This suggests that parents or guardians have difficulty completing this dimension of the EQ-5D-3L as a proxy for their young children. 28 of the returned EQ-5D proxy questionnaires (40%)

did not have a response recorded in the mobility dimension. Fewer missing responses were returned for the remaining three dimensions.

None of the 25 EQ-5D-Y questionnaires for children aged 7 – 12 years had a missing response for any of the five dimensions on the worst day of infection. Few EQ-5D-3L questionnaires for individuals aged 13 years and older had missing responses for the dimensions of health: 5 questionnaires (4.6%) were missing a response in the mobility dimension, with fewer missing responses in the remaining dimensions.

	Responses	Complete responses	Missing: Mobility	Missing: Self-care	Missing: Usual activities	Missing: Pain	Missing: Depression
<b>EQ-5D proxy</b>	70	20 (28.6%)	28 (40.0%)	49 (70.0%)	16 (22.9%)	8 (11.4%)	12 (17.1%)
<b>EQ-5D-Y</b>	25	25 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>EQ-5D</b>	108	102 (94.4%)	5 (4.6%)	3 (2.8%)	3 (2.8%)	2 (1.9%)	2 (1.9%)
	<b>203 (100%)</b>	<b>147 (72.4%)</b>					

*Table 7.6 - Number of missing responses to each EQ-5D dimension of health on the worst day of infection*

## MEASURING HRQoL USING AGE-SPECIFIC EQ-5D-3L

The standard EQ-5D-3L was used by individuals aged 13 years and older. The mean QALD-loss attributable to measles for this group was 6.9 days (95% CI: 4.9 – 9.1). For individuals aged between 7 – 12 years the EQ-5D-Y was used to report a mean QALD-loss of 7.3 days (95% CI: 3.7 – 13.0). For infants aged under 7 years the EQ-5D (proxy) was used to report a mean QALD-loss of 6.2 days (95% CI: 3.6 – 9.0). Using the independent Mann-Whitney test there was no evidence that the measured HRQoL loss is dependent on the EQ-5D-3L questionnaire used ( $W = 483.5$  and  $p = 0.64$  when compared to EQ-5D-Y;  $W = 433.5$  and  $p = 0.99$  when compared to EQ-5D proxy).

## DISCUSSION

We have used the confirmed measles cases reported since June 2012 to calculate the short-term impact on HRQoL of measles, with measurements taken during the 2012-13 regional measles epidemics in England. We found that measles infection causes a short-term QALY-loss of 0.019 QALYs, or 6.9 QALDs, per patient, with perceived symptoms lasting 13.8 days. For context, the short-term impact on HRQoL of H1N1v influenza was 0.008 QALYs, or 2.92 QALDs, per patient [22]. The impact on HRQoL of natural varicella was 0.0027 QALYs, or 0.99 QALDs (<15 years old) [23] and 0.0038 QALYs, or 1.39 QALDs ( $\geq 15$  years old) per patient [24].

To our knowledge this is the first attempt to calculate the impact on HRQoL of measles infection. This study was a patient-based retrospective study that invited all eligible confirmed cases of measles since mid-2012 in the general population to participate. The response rate was reasonable for a postal survey with a return rate of 40%. In addition to quantifying the short-term impact of measles on HRQoL we have also described the wider impact in terms of time off work or school for individuals with measles and their primary caregivers.

With MMR coverage still below the herd immunity threshold, the potential for further measles outbreaks still exists within England. Following this study, cost-effectiveness analyses for possible interventions for such outbreaks may now be performed using QALYs, so that a single generic metric is compared across all analyses.

Using the VAS to derive health QALDs underestimates the impact of measles infection on HRQoL in comparison to the EQ-5D-3L, according to our sample of individuals with confirmed measles. Indeed, the VAS is not a preference-based system so it should not be used alone to calculate QALYs [25].

*55.2% of individuals with confirmed measles who returned their questionnaires did not provide all of the data necessary to calculate QALY loss associated with measles infection. Completion was poor for the EQ-5D proxy version administered to parents or guardians to complete on behalf of a child aged less than 7 years; 70% of returned EQ-5D proxy questionnaires had a missing response to the self-care dimension (*

Table 7.6). This is hardly surprising, since it is unclear how one ought to answer such a question, but it means that the proxy form of the EQ-5D-3L may not be appropriate for evaluating a young child's HRQoL. Fewer completion issues were evident with the EQ-5D-3L for individuals with confirmed measles aged 13 and older, and no completion issues were evident for the EQ-5D-Y administered to children aged 7 – 12 years. In contrast to the missing responses to the questions about health dimensions, 95.6% of individuals with confirmed measles who returned a questionnaire also returned a completed VAS; this suggests that individuals with confirmed measles found it easier to complete the VAS than the EQ-5D-3L dimensions.

We found that estimated HRQoL loss is not dependent on the EQ-5D-3L questionnaire used, i.e. the EQ-5D proxy and EQ-5D-Y give similar values of HRQoL when compared to the standard EQ-5D-3L. However, we note that both the EQ-5D-Y and EQ-5D proxy questionnaires currently use the same scoring tariff as the EQ-5D-3L. That is, the value of different health states measured by the EQ-5D-3L is assumed to be identical for all respondents in our study. This assumption has been challenged in the past [26-28] and EuroQol are currently developing a child-specific tariff for the EQ-5D-Y.

We note that in the regional epidemics in Cheshire and Merseyside only 18% of confirmed cases were hospitalised [7], in comparison to 36.5% of our sample reporting spending at least one night in hospital, though the authors of that study suggested that the hospitalisation data from that study may underestimate the true rate. From our sample of confirmed cases we did not find evidence that the more severe cases were more likely to respond to our questionnaire.

## **LIMITATIONS**

### **RETROSPECTIVE ANALYSIS**

This study was a retrospective evaluation of the impact of measles infection on short-term HRQoL, using self-reported metrics. It would be preferable to evaluate short-term HRQoL loss in a controlled environment with daily EQ-5D-3L questionnaire completion and additional laboratory confirmation of items such as onset date and duration of infection. However, our study protocol followed similar evaluations of HRQoL loss for other infectious disease and was successfully designed and executed during a nationwide measles outbreak.

#### LINEAR DETERIORATION IN HRQoL

We assumed that the deterioration in HRQoL is linearly related to the duration of infection and used a triangular shape to describe the QALY loss. This assumption could be tested if HRQoL were measured more often over the course of measles infection, providing sufficient information to gauge how HRQoL varies during infection. However, this proposal may be infeasible as it places a larger burden on the individuals with measles during their period of infection. When Hollmann et al. (2013) [29] calculated the impact of H1N1 influenza on patients in Spain they assumed that the health utility corresponding to the worst day of infection is experienced constantly throughout infection. This assumption means that HRQoL drops to its lowest possible level from day one of infection and returns to its highest level upon recovery. In comparison to our method, this doubles the impact on HRQoL.

#### CHANGE THE EQ-5D TARIFF TO THE NEW EQ-5D-Y TARIFF

At the time of writing the EuroQol EQ-5D-Y instrument for estimating health utilities in children of ages 8 – 15 years does not have its own tariff for the valuation of health states. Instead, researchers using the EQ-5D-Y are recommended to use the adult tariff from the EQ-5D. We administered EQ-5D-Y questionnaires but each response was valued using the EQ-5D adult tariff. It is unclear if the new tariff will significantly change the total burden of disease for measles during the outbreaks in 2012-13 but the analysis should be updated when the new EQ-5D-Y tariff is published.

#### ECONOMIC COSTS

Our study to estimate the impact of measles infection on HRQoL did not include the financial impact of measles infection for those individuals with measles or their caregivers. Collecting information to describe this financial impact falls outside the blanket ethical approval obtained by Public Health England to collect data was part of regular outbreak surveillance. The process of obtaining additional ethical approval to collect data on the financial impact of measles infection in the home would have delayed the distribution of questionnaires by several months, so we did not include such a section in the questionnaires.

However, our study to estimate the economic impact of the measles outbreak in Merseyside (see Chapter 8) was unable to quantify the impact of infection at home in a way that would have been possible with additional ethical approval for Public Health England. The authors of the original costing analysis did not have access to the details of each notified case in Merseyside so were unable to gather data on out-of-pocket expenses incurred by families affected during the outbreak.

Public Health England is the only organisation in England that has the ability to reach each individual with suspected measles during future outbreaks. Applying for ethical approval to collect data on out-

of-pocket expenses incurred at home before an outbreak has occurred would permit an easy extension to the study to quantify the full impact of measles outbreaks in the community.

#### POTENTIAL RECALL BIAS

Individuals were unlikely to complete the EQ-5D-3L for the worst day of their illness on that day, as we were unable to send questionnaires to individuals until after confirmation of measles was received, which was likely to be after the worst day of illness. This may be a source of recall bias but we attempted to minimise this by sending questionnaires to confirmed cases as quickly as possible. The median time between the perceived symptoms onset and the date of completing the questionnaire was 12.0 days (mean 16.8 days, mode 5.0 days). Using the independent Wilcoxon test we found no evidence that the short-term impact on HRQoL was associated with the length of time between perceived symptoms onset and the date of completion of the questionnaire. Those individuals completing the questionnaire within one week of perceived symptoms onset reported a mean QALD-loss of 7.88 days (95% CI: 5.1 – 11.92), as compared to those completing the questionnaire between 8 – 14 days (5.64 QALDs, 95% CI: 3.03 – 8.16,  $W = 200$  and  $p = 0.29$ ) and to those completing the questionnaire more than 14 days after symptom onset (6.03 QALDs, 95% CI: 4.30 – 8.12,  $W = 543$  and  $p = 0.19$ ).

#### POTENTIAL MISCLASSIFICATION BIAS

10 patients reported that they did not have any contact with the health services before their case status was confirmed. This may be because they were already known to the local HPU through contact tracing of another confirmed case or were separately reported to the HPU without contacting the health services. However, we recognise that they may have failed to report a contact with the health services before notification to the HPU and therefore could be a source of misclassification bias in our study.

#### PERCEIVED LENGTH OF SYMPTOMS, RATHER THAN THE DURATION OF ILLNESS

In our calculation of QALY loss due to measles we used the reported perceived length of symptoms rather than duration of illness as obtained through serology. However, we feel that this assumption and use of a proxy is justified as an individual will only report a lower health state to their preferred health state when their symptoms affect their wellbeing; thus perceived symptoms are the relevant factor.

## FUNDING

This work was funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

## ACKNOWLEDGMENTS

We would like to thank Adolphe Bukasa for his invaluable help with the data collection process including preparing the questions, preparing the list of individuals with confirmed measles and distributing the questionnaires. We also thank Aisling o'Sullivan and Louise Parker for their help with distributing the questionnaires during their work experience placement at PHE Colindale.

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## **Chapter 8 - The cost of the measles outbreak in Cheshire and Merseyside 2012-13**

Portions of this section were published in Vaccine in March 2016 [1].

### **ABSTRACT**

#### **BACKGROUND**

During 2012 and 2013 in England and Wales there were 3,873 laboratory-confirmed cases of measles, with the outbreak in Liverpool declared over at the end of August 2013 after 650 laboratory-confirmed cases of measles had been diagnosed by the Cheshire & Merseyside Health Protection Unit (CMHPU). CMHPU commissioned the development of a costing model based on a critical literature review and experience to date to identify the total cost of the outbreak for the period 1<sup>st</sup> February – 31<sup>st</sup> May 2012.

#### **OBJECTIVE**

We sought to use the commissioned model results to estimate the total cost of the full outbreak in Liverpool to the date 31<sup>st</sup> August 2013.

#### **METHODS AND FINDINGS**

Identified costs were divided into non-recurrent fixed costs incurred at the beginning of the outbreak and ongoing running costs incurred throughout the outbreak. Additional information on the impact of the outbreak at home was used to inform the model and update the estimates of the cost due to loss of productivity. The full outbreak cost was estimated to be £4.4m (sensitivity analysis £3.9m to £5.2m). In comparison, a further 11,793 MMR vaccinations would have been needed to achieve herd protection at an estimated cost of £182,909. Therefore, investing an additional £1 on immunisation through MMR would have saved £23 incurred as a result of this outbreak had the herd immunity threshold been achieved.

#### **CONCLUSION**

The total cost of the measles outbreak in Cheshire & Merseyside was higher than previous studies on other outbreaks suggested, however our model included a wider range of costs to present the economic impact of measles outbreaks from the societal perspective. Approximately 40% of the total

cost was incurred through direct public health activities to manage the outbreak and contain infection. In contrast, the total cost of meeting the targeted vaccination coverage in the area was just 4.2% the total cost of the outbreak. This study emphasises the importance and economic benefit of preventive measures to control outbreaks of measles through vaccination with MMR.

## **INTRODUCTION**

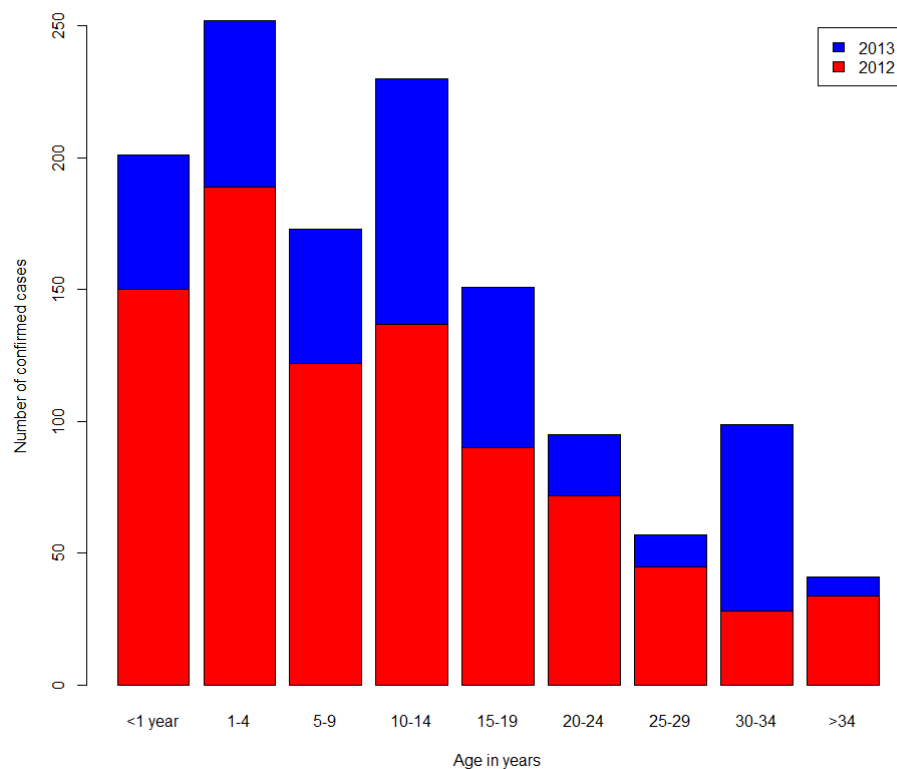
The previous chapter details the investigation into both the societal and health-related quality of life impact of measles infection in England. In addition to this investigation, the nationwide measles outbreak provided researchers with the opportunity to estimate the economic impact of localised measles outbreaks. Researchers from the Liverpool office of Public Health England commissioned a consultancy firm to design a costing model to be used to investigate the economic cost of the first four months of the measles outbreaks that occurred in Merseyside 2012. We used this model to estimate the total economic cost of the full outbreak.

## **BACKGROUND**

### **MEASLES OUTBREAKS IN CHESHIRE & MERSEYSIDE AND NATIONWIDE**

Merseyside is a county in the north west of England, comprising of five metropolitan boroughs: Knowsley, St Helens, Sefton, Wirral and the City of Liverpool. In 2012, Liverpool had an estimated population of 469,700 people (78,609 of whom were aged 16 years old or younger) [2] and over 65% of the population live in the most socioeconomically deprived national quintile [3].

During 2012 and 2013 in England and Wales there were 3,873 laboratory-confirmed cases of measles of which 1,245 were attributed to outbreaks in North West England [4] (Figure 8.1). Declining MMR vaccination coverage in the late 1990s and early 2000s increased the number of susceptible individuals in England and Wales and therefore raised the potential for sustained community-wide measles transmission [5].



*Figure 8.1 - Confirmed measles cases in North West England during 2012 and 2013*

In 2012-13 under-vaccinated areas such as Liverpool [6], North-East England [7] and Manchester [8] experienced large measles outbreaks. The outbreak in Liverpool was declared over at the end of August 2013, after 650 laboratory-confirmed cases of measles had been diagnosed by the Cheshire & Merseyside Health Protection Unit (CMHPU).

An MMR catch-up campaign was announced jointly by Public Health England and the Department of Health with a target of achieving high MMR vaccination coverage sufficient to reach the herd immunity threshold and limit the spread of measles in the community [9], targeting young unvaccinated and partially-vaccinated people. In recent years MMR vaccination coverage dropped well below the threshold for herd immunity (Figure 8.2), providing a large pool of susceptible individuals that was ultimately able to sustain measles transmission in the community for several months.

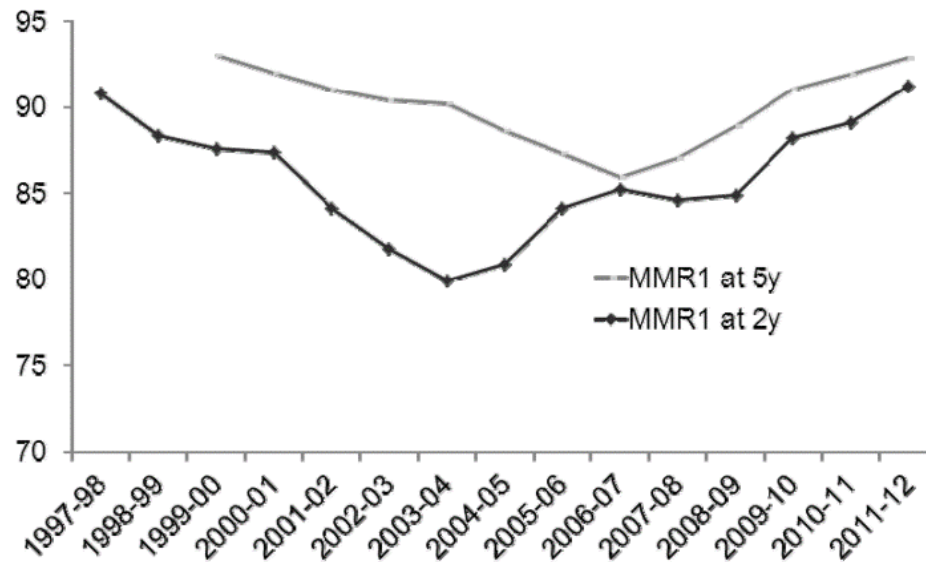


Figure 8.2 - Annual first dose MMR coverage at 24 months and 5 years, England: April 1997 - March 2012

Figure credit: [9].

In addition to increasing MMR vaccination coverage in the community, the local Public Health England (Cheshire & Merseyside Health Protection Unit, CMPHU) responded to the outbreak to facilitate the containment and management of all confirmed and possible cases of measles. This response required that healthcare professionals and organisations from primary care, secondary care, community care, public health and other local authorities collaborate to end community transmission of measles in the local area.

#### CASE DEFINITION

Vivancos et al. (2012) detailed the case definition applied during the outbreak to identify confirmed cases of measles [6]. That definition was:

1. Clinical presentation of fever and measles-like rash, with one or more of the following: cough, conjunctivitis, coryza, or Koplik's spots
2. Residence in Liverpool or adjacent areas, or close contact with a confirmed or probable case of measles, or a history of recent travel to geographical areas with endemic or outbreak measles
3. Incomplete or unknown MMR vaccination status

Each notification received by the CMHPU was treated as a *suspected* case, and all suspected cases incurred costs during the outbreak. Suspected cases were further defined using guidance adapted from the HPA National Measles Guidelines [10]:

**Confirmed case.** An individual with measles IgM positive (blood or saliva) in absence of a history of recent vaccination or confirmed wild measles RNA positive on any clinical specimen.

**Probable case.** An individual with signs and symptoms consistent with measles who was in contact with a laboratory-confirmed case 7-18 days before the onset of symptoms, or assessed as likely by a member of the Health Protection Team based on epidemiological features.

**Possible case.** An individual with some clinical symptoms, though not specific to measles and where another diagnosis is possible.

#### MANAGING THE OUTBREAK IN CHESHIRE & MERSEYSIDE

A co-ordinated response involved managing all confirmed and suspected cases of measles in the community in all healthcare settings, from the initial identification of a suspected case through to the vaccination of people suspected of being in contact with an individual with confirmed measles. Activities carried out during the period of the epidemic are listed below.

**Identification of suspected cases.** General Practitioners and staff at Accident and Emergency units notified the CMHPU of individuals suspected of having symptoms consistent with measles. For each identified individual, laboratory testing was required to confirm their case status.

**Laboratory work and courier.** The main laboratory used to confirm measles infection in individuals suspected of infection was the HPA laboratory at Manchester Royal Infirmary. PCR rapid testing of saliva samples were used, with samples couriered between Manchester and the outbreak area. All results were shared with the CMHPU and the individual's GP.

**Identification of contacts with confirmed or probable cases.** Along with the CMHPU, both primary care and secondary care organisations traced the contacts of suspected measles cases. This activity was a significant time burden on staff involving many telephone conversations with individuals at risk of measles infection to inform them of the risk to their health.

**Direct healthcare costs for suspected cases.** Some individuals with measles required hospitalisation with complications arising from their infection. In addition, some individuals required the assistance of ambulance crews to transport them to an appropriate facility to receive care for their condition.

**Creation of the UrgentCare24 (NHS UC24) clinic.** A new clinic was set-up in the community to deal directly with suspected cases, relieving the burden on other primary care organisations.

**Vaccination of healthcare staff and eligible members of the public, including checking immunisation status of individuals.** Staff in all healthcare organisations with direct access to individuals with suspected measles required their MMR vaccination status to be up to date. This meant several organisations needed to ascertain the vaccination status of all their members of staff and vaccinate those individuals without the recommended two doses of MMR. In addition, staff in General Practice clinics notified patients registered to their practice if their records indicated that they had not received the recommended two doses of MMR and had been eligible to do so. Checking the vaccination status of registered patients was a considerable administrative burden on General Practice staff.

**Prophylaxis for contacts of confirmed or probable cases.** Individuals exposed to measles and for whom either their vaccination status could not be obtained or was inadequate were offered prophylactic treatment in the form of immunoglobulin [11].

**Infection control in hospitals.** Both the admission of patients with complications arising from measles infection and the presentation of suspected measles cases in Accident and Emergency units in the local NHS Trusts gave rise to concern of hospital-based measles transmission. All local NHS Trusts were therefore instructed by the CMHPU to ensure that their Infection Prevention and Control teams were working to prevent such transmission to other patients on their wards.

**Media costs to inform public and local authorities and institutions.** The CMHPU informed the public through media campaigns of the risk of measles infection and the steps to take should any member of their household present with symptoms consistent with measles infection. The stepping-up of the MMR vaccination campaign offered an opportunity for those individuals without sufficient protection from measles infection to rectify this, so public engagement activities and information were commissioned to remind people to check the vaccination status of all individuals in their household.

**Productivity cost to the community.** Measles infection is associated with increased absenteeism due to infection as well as absenteeism for those individuals required to act as primary caregivers to people in their household otherwise incapable of looking after themselves [12].

**Staff costs due to time spent managing the outbreak.** All activities required to contain and manage the epidemic caused a significant time and administrative burden on all organisations involved in the coordinated response. Time spent managing the outbreak was spent at the cost of other duties normally conducted outside of outbreak containment and management. In addition, several

organisations required additional temporary staff to be hired as well as requiring staff to work extra hours and cancel some planned leave to direct resources to the outbreak response.

#### ECONOMIC IMPACT OF PREVIOUS MEASLES OUTBREAKS

Measles outbreaks can have a large economic impact on health services and society. A study published in 2002 estimated the average cost per measles case to be \$307 in the UK [13]. A similar study in Spain covering measles cases diagnosed between 1997 and 2006 reported a mean cost per uncomplicated case of measles of €1,834 and a mean cost per case with complications of €3,559 [14]. Additional results are reported in Table 8.1.

Study	Year of publication	Reported costs
Carabin et al. [13]	2002	\$254 (Canada) \$276 (The Netherlands) \$307 (UK)
Santos Sancho et al. [14]	2009	€1,834 without complications €3,559 with complications
Filia et al. [15]	2007	€1,429 hospitalised cases without complications €1,960 hospitalised cases with complications
Zwanziger et al. [16]	2001	Between \$2,089 - \$2,251 to prevent a single case of measles
Sugerman et al. [17]	2010	\$10,376 per case \$775 family cost for quarantine per child

*Table 8.1 - Reported costs of measles cases*

Further to the mean cost per case of measles, the study published by Filia et al. (2007) reported that the direct cost attributed to managing the measles outbreaks in Italy between 2002-03 was between €17.6m-€22.0m [15]. The regional measles outbreak in Liverpool provided CMHPU an opportunity to describe the total cost of managing the outbreak and to further understand the economic impact of measles infection in the UK.



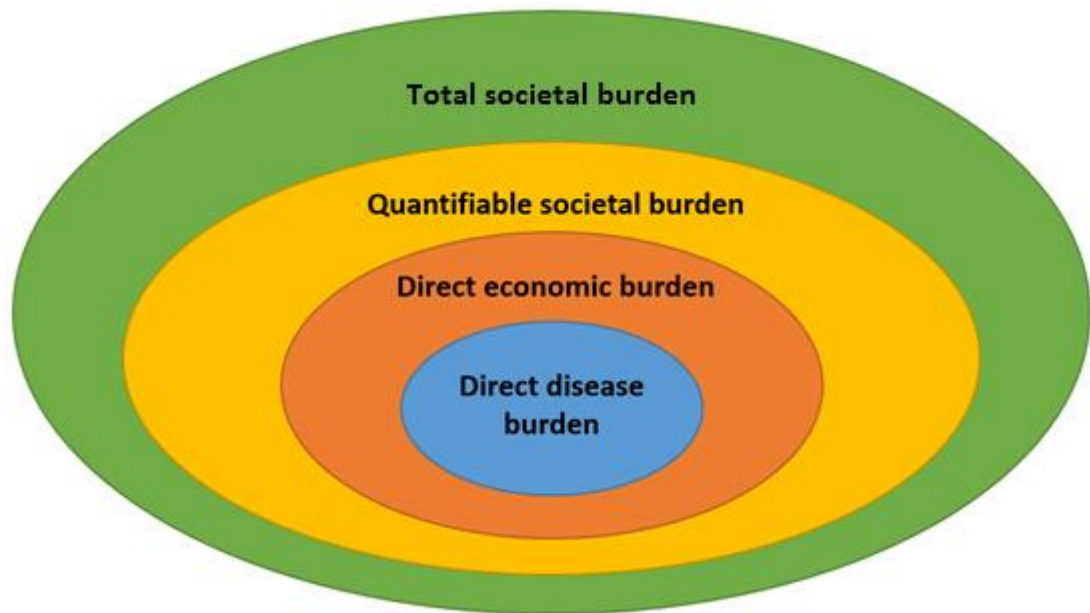


Figure 8.3 - The total burden of outbreaks of infectious diseases

Figure 8.3 shows the different ways and perspectives to describe the burden of infectious disease. The direct disease burden consists of the total number of cases, hospitalisations and deaths in the population, described in outbreak reports (e.g. Vivancos et al. [18]). The direct economic burden quantifies the economic value of that disease burden, assigning monetary values to cases of disease in the form of direct healthcare costs (e.g. citations in Table 8.1). The quantifiable societal burden includes productivity loss in the form of workplace- and school-absenteeism, assigning monetary values to the wider costs in society due to infection. A further burden less straight-forward to describe is the unquantifiable societal burden, consisting of disruption to ordinary routine, the loss of leisure time for individuals acting as caregivers for others infected with disease, etc.

#### COMMISSIONED COSTING REPORT: METHODS

In order to understand the economic impact of measles outbreaks in the region, CMHPU commissioned ICF GHK to estimate the cost of the outbreak. Together, the two organisations defined the time period of interest for the costing exercise to be 1<sup>st</sup> February 2012 – 31<sup>st</sup> May 2012 and restricted only to the local area. At this time, CMHPU reported 306 laboratory-confirmed cases of measles along with 844 potential cases of measles (94 probable, 223 possible and 527 laboratory-negative).

Costs were divided into two categories: direct costs (shared by healthcare providers and public health institutions) and indirect costs to the local economy. Direct healthcare costs included costs attributed

to primary care and secondary care in treating suspected cases, calculated using the Healthcare Resource Group (HRG) tariffs recorded for patients. Public health costs related to the containment and management of the outbreak, with organisations such as CMHPU, Community Trusts, Acute Trusts etc. incurring such costs in controlling the outbreak. Productivity costs were incurred through missed work and school for suspected cases and their carers in addition to ward closures, cancelled admissions, delayed and cancelled appointments in the healthcare organisations.

#### COMMISSIONED COSTING REPORT: INITIAL FINDINGS

For the period 1<sup>st</sup> February 2012 – 31<sup>st</sup> May 2012, ICF reported the total cost of the outbreak was £1.4m (between £1.3m and £1.6m after the sensitivity analysis) [19]. 37% of these costs (£526,100) were borne by secondary care organisations such as RLBUHT (Royal Liverpool, Broadgreen and Liverpool University hospitals) and Alder Hey, followed by 26% (£371,800) borne by CMHPU. The mean cost per confirmed case of measles was £4,980, but as all suspected measles incur some costs before the final laboratory confirmation of case status they reported a final mean cost per reported and suspected case of approximately £1,000. A breakdown of the total cost is presented in Table 8.2, with costs rounded to the nearest £100.

Dividing the total cost into direct healthcare costs, direct public health costs and indirect costs to the local economy, ICF reported that 25% (£353,800) of the total cost was for direct healthcare costs, 60% (£844,300) for direct public health costs and 15% (£212,200) for costs to the local economy. The direct public health costs are comparable to those reported by Parker et al. (2006) [20], who reported a total direct public health cost of £110,870 for 40 measles cases (£3,260 mean public health cost per case) in an outbreak in Indiana.

Organisation	Main cost drivers	Cost	% of total cost
Primary Care Trusts and NHS UC24	Staff costs MMR LES	£90,100	6%
Secondary Care	RLBUHT Alder Hey	£526,100	37%
Community Care	Staff costs	£43,000	3%
General Practitioners	Contact tracing for confirmed measles cases	£103,300	7%
Cheshire & Merseyside HPU	Staff costs	£371,800	26%
North West Ambulance Service	Providing ambulance service	£1,100	<1%
Manchester Royal Laboratory	IgG, PCR and IgM tests	£28,500	2%
Society lost productivity	Estimated lost productivity of potential and unreported cases of measles	£231,600	16%
Local Authority	Associated administration	£14,800	1%
Total cost		£1,410,300	

*Table 8.2 - Total cost of measles outbreak in Liverpool from 1st February 2012 - 31st May 2012*

Table credit: [19].

#### EXTENDING THE ANALYSIS FOR THE FULL OUTBREAK IN CHESHIRE & MERSEYSIDE

Though the ICF report describes the many costs incurred during the period 1<sup>st</sup> February 2012 to 31<sup>st</sup> May 2012, the total duration of the outbreak was much longer. An additional analysis was sought to describe the estimated total cost of the full outbreak, from 1<sup>st</sup> January 2012 to 31<sup>st</sup> August 2013.

Though some costs described in the ICF report would continue throughout the full outbreak, some costs would be incurred only at the beginning of the outbreak (fixed costs such as setting-up the MMR LES and creating additional infection control spaces within acute trusts). This analysis sought to describe the estimated total cost of the full outbreak separated the varying costs in the ICF report then extrapolated them according to the time extension and increased number of suspected cases.

Additionally, some calculations used by ICF to estimate the loss of productivity were updated to include results published in 2014 that describe the impact of measles infection at home in terms of measles-attributed absence from work and school as well as the percentage of individuals with confirmed measles who reported requiring a caregiver to be with them during their infection [12]. These data were published after ICF had completed their analysis.

To further assist public health organisations in understanding the economic impact of measles outbreaks, we sought to present the total cost of achieving MMR herd immunity in Liverpool that may have prevented the sustained community transmission.

#### **RESEARCH QUESTIONS**

1. What was the estimated total cost of the measles outbreak in Cheshire and Merseyside 2012-13, in terms of direct and indirect costs, for all suspected and unreported cases?
2. What would the cost of preventing the outbreak have been? Is preventing the cost of a regional measles outbreak cost-saving in comparison to managing and containing an outbreak?

#### **METHODS**

This section lists the major cost centres and the costs attributed to the outbreak, obtained via consultation with ICF and all stakeholders in the production of the initial costing report.

#### **FULL OUTBREAK COSTS**

##### **PRIMARY CARE AND NHS UC24**

Costs identified by ICF that were incurred by the Primary Care Trusts and the NHS 24hr Urgent Care centre related to the implementation of the MMR LES, staff time taken up in managing the outbreak and postage and packaging fees to distribute leaflets at the beginning of the outbreak to encourage unvaccinated individuals to accept the MMR vaccination. Eight PCTs were affected by the outbreak but costs were collected from the four PCTs with the highest case burden (Liverpool, Knowsley, Hafton & St. Helens and Sefton) with costs for the others (Central & Eastern Cheshire, Warrington, Western Cheshire and Wirral) estimated by assuming proportionality from the data gathered.

##### **SECONDARY CARE**

The ICF report highlighted the two Trusts worst affected by the measles outbreak were the RLBUHT and Alder Hey, but several other smaller NHS Trusts also participated in the outbreak response. Most departments within the Trusts responding to the outbreak contributed by assessing patients in A&E, admitting patients to their intensive care/critical care units, activating infection prevention and control protocols with expertise from their Infectious Disease departments and Virology departments. Secondary Care Trusts also incurred costs through tracing both vaccination status of their members of staff and the contacts of patients being seen at the Trust. Further costs were incurred through the

loss of productivity with ward closures, staff illness and attending meetings with CMHPU to coordinate the response across the local area.

#### COMMUNITY CARE

The Liverpool Community Health organisation consists of many departments that all participated in the management and containment of the outbreak. Costs were incurred through vaccinations, checking the vaccination status of staff members, staff absence during the outbreak and treatment costs for patients attending the walk-in centres managed by the organisation.

#### GENERAL PRACTITIONERS

GPs were the first point of contact and access to the local health services for many suspected cases. The majority of the work conducted by GPs during the outbreak was in assisting the public health response to the outbreak, but an increase in the number of patients requiring a GP appointment during the outbreak meant that additional clinics needed to be implemented or telephone-based services needed to be offered to patients with suspected measles. GPs also incurred costs in tracing the contacts of all individuals with confirmed measles. Costs for GPs were extrapolated from the number of cases per GP surgery, multiplied by 1.5 times the cost of a standard GP consultation [13, 21] as this was the estimated additional time taken to see a suspected measles case.

#### CHESHIRE & MERSEYSIDE HEALTH PROTECTION UNIT

The largest cost for CMHPU was in staff time to manage the public health response to the outbreak. Several members of staff worked long overtime hours and cancelled planned breaks to ensure a robust response to the outbreak. During the outbreak the majority of time working was spent on the outbreak.

#### NORTH WEST AMBULANCE SERVICE

ICF estimated that the North West Ambulance Service was required for a small number of patients with suspected measles. In addition, all staff likely to come into contact with an individual with suspected measles needed their vaccination status to be established and catch-up vaccinations to be administered where required.

#### MANCHESTER ROYAL LABORATORY

The PCR testing to confirm measles infection took place at the laboratory of the Manchester Royal Infirmary. Sample used for testing were sent to Manchester from Liverpool via courier.

## SOCIETY LOST PRODUCTIVITY

In calculating the total cost of lost productivity in Liverpool, ICF divided the cost into four categories: hospitalised confirmed cases of measles, non-hospitalised confirmed cases of measles, potential cases of measles and unreported cases of measles. The proportion of individuals with confirmed measles in Liverpool was estimated at 20.6% [19], and the rate of employment in the area was taken from the Office of National Statistics [22]. ICF assumed that individuals hospitalised due to measles infection or complications arising from measles infection were absent from work/school for two weeks and that infection without hospitalisation required an absence of three days [23]. The number of unreported measles cases was taken from Carabin et al. (2002) [13].

Proportion of confirmed cases reporting work/school absence	63.1%
Absence from work/school for patients	9.6 days (95% CI: 9.3 - 11.7)
Proportion of confirmed cases requiring a caregiver	39.6%
Absence from work for caregivers	7.3 days (95% CI: 5.7 – 7.9)

*Table 8.3 - The impact of measles infection in terms of society lost productivity*

Table credit: [12].

In estimating the full cost of the outbreak, we included the time off work for a caregiver and the proportion of individuals with confirmed measles requiring a caregiver from Thorrington et al. (2014) [12] (Chapter 8). The proportion of individuals absent from work/school due to infection in addition to the mean absence for both patients and their caregivers were also used in the updated analysis. Data are shown in Table 8.3.

## LOCAL AUTHORITY

Liverpool City Council provided information to parents of young children to inform them of the outbreak and potential consequences of measles infection. The cost of producing these materials to provide the information were borne by the Council and recorded as a direct public health cost for the outbreak. All parents of school-age children were contacted through their child's school.

## THE COST OF PREVENTION

Vaccination against measles is an effective method to prevent measles outbreaks. With vaccination coverage below the herd immunity threshold of 95% there exists the potential for sustained measles transmission within the community.

In 2012 11,793 children in Liverpool needed to receive their required MMR dose in order to achieve the herd immunity coverage level [24]. 8,366 children needed to receive their first MMR dose and

3,427 children were eligible for the second dose but had not received it. Administering these additional doses in the community would have been the most effective method of preventing the measles outbreaks in Liverpool. The breakdown of the total vaccination cost required to prevent the outbreaks was calculated to be £182,909 and is presented in Table 8.4.

Activity	Source	Unit cost	Total cost
Vaccination administration and delivery, including practitioner time per child	[25]	£7.64	£90,099
MMR vaccination dose	[26]	£6.37	£75,121
MMR catch-up campaign promotion per child	[25]	£1.50	£17,689

*Table 8.4 - The cost of preventing measles outbreaks through vaccination*

#### SENSITIVITY ANALYSIS

ICF included a sensitivity analysis to estimate the total cost of the outbreak between 1<sup>st</sup> February 2012 and 31<sup>st</sup> May 2012 was between £1.3m and £1.6m. The sensitivity analysis varied five key parameters in the costing model (Table 8.5) that displayed the largest levels of uncertainty after consultation with stakeholders.

	Lower end cost	Best estimate	Higher end cost
Costs of treatment in hospitals other than the two used to obtain the average cost	£1,196	£1,383	£1,730
Cost of contact tracing in hospitals other than the two used to obtain the average cost	£0	Linked to Royal Liverpool estimate	Linked to Royal Liverpool estimate
Staff absence in hospitals other than the two used to obtain the average cost	£0	Linked to Royal Liverpool estimate	Linked to Royal Liverpool estimate
Cost of a GP consultation and tracing of a measles case	£362	£381	£574
Lost productivity costs	0% of cases unreported, 3 days absence	22.5% of cases unreported, 3 days absence	45% of cases unreported, 4 days absence

*Table 8.5 - Parameters used in the sensitivity analysis for the calculated costs of the outbreak between 1st February – 31st May 2012*

Two parameters included in the sensitivity analysis used vaguely-defined distributions to estimate values for the best and higher cost calculations: both the cost of contact tracing in the smaller hospitals

in addition to the cost of staff absence in these hospitals were estimated from the values obtained from RLBUHT and Alder Hey, without sufficient detail given in the methodology.

	<b>Lower end cost</b>	<b>Best estimate</b>	<b>Higher end cost</b>
Costs of treatment in hospitals other than the two used to obtain the average cost	£1,196	£1,383	£1,730
Cost of contact tracing in hospitals other than the two used to obtain the average cost	£0	Trust-specific, as provided by GHK report	1.5 x Trust-specific estimate from GHK
Staff absence in hospitals other than the two used to obtain the average cost	£0	Trust-specific, as provided by GHK report	1.5 x Trust-specific estimate from GHK
Cost of a GP consultation and tracing of a measles case	£362	£381	£574
Lost productivity costs	0% of cases unreported, 9.3 days absence for patients, 5.7 days absence for caregivers	22.5% of cases unreported, 9.6 days absence for patients, 7.3 days absence for caregivers	45% of cases unreported, 11.7 days absence for patients, 7.9 days absence for caregivers

*Table 8.6 - Parameters used in the sensitivity analysis for the estimated total costs of the full outbreak*

The revised multi-variate sensitivity analysis used many of the same parameters but with more robust distributions sourced from the literature for both the cost of contact tracing and staff absence in the smaller hospitals. The parameters used for the best estimated cost were taken directly from the ICF report for each Trust, with the higher end cost estimated as 1.5 times the best estimate. In addition, the costs relating to a loss in productivity were updated using figures from Thorrington et al. (2014) [12] to inform the model with distributions for the length of absence for both patients and their caregivers (Table 8.6). The analysis was conducted in Microsoft Excel.



## RESULTS

### ESTIMATED TOTAL COSTS OF THE OUTBREAK

#### TOTAL COSTS

The estimated total cost of the full outbreak was £4.40m (between £3.85m and £5.15m from the sensitivity analysis). Fixed costs occurring at the beginning of the outbreak accounted for £0.16m (3.8%) and varying costs accounted for £4.23m (96.2%) (Table 8.7).

Organisation	Confirmed, probable, possible and unreported cases estimated total cost	
	Cost (£)	%
<b>Primary Care Trusts</b>	<b>223,000</b>	<b>5%</b>
Varying	204,100	5%
Fixed	18,900	<1%
<b>Secondary Care</b>	<b>994,200</b>	<b>23%</b>
Varying	879,500	20%
Fixed	114,700	3%
<b>Community Care</b>	<b>91,400</b>	<b>2%</b>
Varying	91,400	2%
<b>General Practitioners</b>	<b>315,300</b>	<b>7%</b>
Varying	314,500	7%
Fixed	800	<1%
<b>CMHPU</b>	<b>790,400</b>	<b>18%</b>
Varying	774,600	18%
Fixed	15,800	<1%
<b>Ambulance Service</b>	<b>2,300</b>	<b>&lt;1%</b>
Varying	2,300	<1%
<b>MRI Laboratory Costs</b>	<b>60,500</b>	<b>1%</b>
Varying	60,500	1%
<b>Society Lost Productivity</b>	<b>1,903,500</b>	<b>43%</b>
Varying	1,903,500	43%
<b>Local Authority</b>	<b>14,800</b>	<b>&lt;1%</b>
Fixed	14,800	<1%
<b>Total</b>	<b>4,395,400</b>	

Table 8.7 - Estimated total costs of the outbreak by organisation and by the nature of cost (fixed or varying costs). Costs round to the nearest £100

£1.45m (33.0%) was spent on activities related to those individuals with confirmed measles, whilst £2.95m (67.0%) was spent on activities related to potential and unreported cases of measles.

#### DIRECT HEALTHCARE COSTS

Direct healthcare costs account for £0.678m (15.4%) of the total cost of the outbreak (sensitivity analysis £0.644m to £0.708m). The largest contribution group of organisations to the direct healthcare

costs was the group of secondary care organisations (Table 8.8), with Alder Hey and the Royal Liverpool Trusts incurring estimated total direct healthcare costs of £0.50m together.

Organisation	Direct Healthcare		Direct Public Health		Productivity	
	Cost (£)	%	Cost (£)	%	Cost (£)	%
Primary Care Trusts	-	0%	223,000	13%	-	0%
Secondary Care	575,000	85%	370,000	21%	49,200	3%
Community Care	-	0%	91,400	5%	-	0%
General Practitioners	103,300	15%	212,000	12%	-	0%
CMHPU	-	0%	790,400	45%	-	0%
Ambulance Service	-	0%	2,300	<1%	-	0%
MRI Laboratory	-	0%	60,500	3%	-	0%
Society Lost Productivity	-	0%	-	0%	1,903,500	97%
Local Authority	-	0%	14,800	1%	-	0%
<b>Total</b>	<b>678,300</b>		<b>1,764,400</b>		<b>1,952,700</b>	

*Table 8.8 - Estimated total costs of the full outbreak by organisation type of cost (direct healthcare, public health, and loss of productivity). Costs round to the nearest £100*

The largest proportion of the direct healthcare costs was itemised treatment costs and costs related to admissions for individuals with confirmed or probable measles cases (£0.38m, 42.9%), with other large cost bases being GP surgery costs (£0.10m, 12.0%) and costs related to patients in A&E (£0.10m, 11.4%) (Table 8.9).

Direct Healthcare Cost Area	Cost (£)	%
Accident and Emergency	96,400	11%
Critical or Intensive Care	14,800	2%
Drugs	4,200	<1%
Infectious Disease protocols	91,900	11%
Treatment	367,700	43%
GP consultations	103,300	12%
	678,300	

*Table 8.9 - Estimated direct healthcare costs. Costs are rounded to the nearest £100*

#### DIRECT PUBLIC HEALTH COSTS

Estimated total direct public health costs for the outbreak were £1.764m (40.1%) (sensitivity analysis £1.762m to £1.879m). Of this total the largest contributor was CMHPU with all incurred costs to the organisation associated with the public health response to the outbreak (Table 8.8). Primary and secondary care organisations collectively incurred direct public health costs of £0.68m, the largest contributions of which came from Alder Hey Trust (£0.27m), Royal Liverpool Trust (£0.09m) and Liverpool PCT (£0.09m).

Of the estimated total direct public health costs, £1.07m (60.8%) were incurred through staff time and overtime payments (Table 8.10). The remaining costs were for public health expenditure on activities such as tracing vaccination status, contact tracing and related laboratory costs.

Direct Public Health Cost Area	Cost (£)	%
Accident and Emergency	600	<1%
Cleaning and maintenance	10,000	1%
Critical or Intensive Care	200	<1%
Dental Hospital	100	<1%
Facility management	15,000	1%
General Practice	229,800	13%
Infection Control and Prevention teams and protocols	58,000	3%
Media	15,900	1%
Microbiology and Virology	270,700	15%
Miscellaneous uncategorised	23,900	1%
Occupational Health	68,200	4%
Staff time	1,072,100	61%
	1,764,500	

*Table 8.10 - Estimated direct public health costs. Costs are rounded to the nearest £100*

#### LOSS OF PRODUCTIVITY COSTS

Loss of productivity during the measles outbreaks cost the local community £1.953m (Table 8.8) (sensitivity analysis £1.444m to £2.565m), 44.4% of the total cost. Over 97% of the costs due to loss of productivity were related to non-hospital staff absence from work or school for confirmed, potential and unreported cases of measles (Table 8.11).

Productivity Cost Area	Cost (£)	%
Hospitalised confirmed cases of measles	59,300	3%
Non-hospitalised confirmed cases of measles	331,000	17%
Potential cases of measles	1,158,700	59%
Staff absence due to measles	49,200	3%
Estimated unreported cases of measles	354,500	18%
	1,952,700	

*Table 8.11 - Estimated costs due to loss of productivity. Costs are rounded to the nearest £100*

#### ESTIMATED COST OF PREVENTION

Over the previous five years before the outbreak 8,366 children needed to receive their first MMR dose and 3,427 children were eligible for the second dose but had not received it [24]. The overall cost of delivering 11,793 MMR doses during this period to achieve herd protection across Cheshire and Merseyside was estimated at £182,909 (vaccine administration cost of £90,098, MMR vaccine cost of £75,121 and promotion cost of £17,690). This represents just 4.2% of the full estimated total cost of the 2012-13 Merseyside measles outbreak.

Spending £182,909 on increasing MMR vaccination coverage to the herd immunity threshold would have been the most effective method of preventing the sustained transmission of measles virus in the community and avoiding the costs of management and containment of a large measles outbreak. Therefore, every £1 spent on additional vaccinations would have saved approximately £23 in resources used to control the outbreak, had the herd immunity threshold been achieved.

#### **COST PER CASE ESTIMATES**

##### **COST PER MEASLES CASE**

We estimated that an additional 553 measles cases occurred in the community but were not reported to the healthcare authorities [13]. With 2,458 confirmed, probable and possible measles cases reported we therefore estimated a total number of 3,011 suspected measles cases in the Liverpool outbreak. The cost per suspected measles case was £1,460 for the outbreak, similar to the average cost per suspected measles case of £1,416 reported by Carabin et al. (2002) [13].

The outbreak resulted in 650 individuals with laboratory confirmed measles. The total cost per confirmed measles case was therefore £6,762.

##### **HOSPITAL COST PER ADMITTED CASE**

139 individuals were hospitalised with measles infection during the outbreak. The total cost of direct healthcare measles-related activity was £270,400, therefore the mean hospital cost per admitted case was £1,945.

##### **DIRECT PUBLIC HEALTH COST PER CONFIRMED MEASLES CASE**

The direct public health cost was £1.76m for the outbreak, so the public health cost per confirmed measles case was £2,714.

#### **DISCUSSION**

##### **COMPARISON WITH OTHER STUDIES**

This study found the cost of the Merseyside measles outbreak to be considerably higher than the reported cost of other measles outbreaks reported in the literature. The estimated hospitalisation cost per patient admitted (£1,945) was similar to those reported during outbreaks in Spain (£1,521 in 2012 GBP [14]), Italy (£1,614 in 2012 GBP [15]) and the United States (£2,083 in 2012 GBP [16]), though it was likely to be an underestimate as the total number of cases admitted to hospital includes only those cases admitted at the time of notification of infection, rather than also including those patients who may have been hospitalised long after their notification date.

Three studies in the literature considered the direct costs related to public health activities, reporting much higher costs per case than our findings (£2,714). Two studies reported fewer cases, with one reporting only 3 [27] and a second reporting 7 cases [28], compared to 650 in Merseyside. The other study reported a public health cost per case of £3,155 (2012 GBP) for 40 cases [20], similar to our finding. Many public health interventions to contain and manage outbreaks of measles infection will be wide-reaching and with a large public health cost (e.g. identifying vaccination status of residents and healthcare workers in the community), but these activities will have the same burden whether a small or large number of cases is reported.

The total number of contacts traced plays a large role in the public health response to an outbreak and therefore to related public health costs. In the described outbreak attempts were made to identify all contacts during the early stages (1<sup>st</sup> February to 23<sup>rd</sup> March 2012). During this period, for every confirmed case there were approximately 16 potential contacts where public health risk assessment was undertaken. Although this has large workload and cost implications, the significant public health costs incurred mainly relate to follow-up procedures of administering prophylactic treatment and catch-up vaccinations to close contacts.

We were unable to compare the productivity costs of the Merseyside outbreak to those costs associated with other outbreaks as we were unable to find such accounts in the literature. This study therefore presents a new approach in estimating the total societal burden and economic cost of measles outbreaks by including estimates for productivity costs.

## **STRENGTHS AND LIMITATIONS**

### **LOSS OF PRODUCTIVITY CALCULATIONS**

We used wages to measure the loss of productivity caused by measles infection, though this is likely to be a conservative method and therefore the total cost of measles infection in the community is likely to be conservative also. We did not consider other possible sources of productivity loss such as the impact on an individual's leisure time and other activities not directly related to wages lost. Assigning a monetary value to these items is extremely difficult to do and we therefore excluded them from our analysis.

We used the most recent data from Thorington et al. (2014) [12] on the societal impact of measles infection to estimate the loss of productivity associated with measles in the household. This study used data from 203 individuals with confirmed measles to report on the proportion of individuals absent from work or school due to infection or infection in their household, as well as the distribution of the duration of that absence.

#### IMPLICATIONS OF INCREASING COVERAGE IN UNAFFECTED AREAS

Our analysis does not account for cases that were imported from outside the geographical study area that could seed future measles outbreaks if they too do not increase vaccination coverage above the threshold for herd immunity. We did not take into account the additional cost of increasing vaccination coverage in areas outside of the Merseyside area, thereby potentially underestimating the total cost of reaching a situation where future measles outbreaks can be avoided completely, as seeding from external populations is always likely to occur if measles is present within the United Kingdom. Indeed, Liverpool as a major metropolitan area of the north west region of England attracts commuters and tourists from many parts of the country, therefore the future seeding of a new measles epidemic could occur if an infected individual visits Merseyside from areas of low vaccination coverage. It is possible that our comparison of the costs of outbreak management and containment to the cost of outbreak prevention through vaccination could be heavily impacted by also including the cost of vaccination in a wider geographical area.

#### MORE CONSULTATIONS WITH ORGANISATIONS

The authors of the initial costing report consulted with staff from the largest NHS Trusts to obtain activity and cost data related to measles treatment and public health activities carried out during the course of the epidemic, but such consultations did not take place with staff from the smaller NHS Trusts in the area. As a result, the cost of activity in these smaller Trusts were estimated from the costs provided by the larger Trusts. Whilst this was a reasonable assumption to make in order to facilitate the prompt analysis and reporting of the initial costs of the first few months of the epidemic, the overall estimate of the total cost of the epidemic would have been improved with additional consultations and data from all Trusts that responded to the epidemic.

#### UNDERESTIMATING THE TOTAL COST TO ACHIEVE HERD IMMUNITY

In estimating the total cost required to achieve the herd immunity threshold for MMR vaccination coverage in the area we assumed that the relevant cost items were both the number of vaccines required to be administered plus the necessary administration costs. However, strongly vaccine-hesitant parents and guardians may require additional resources to convince them of the benefits of vaccination in order for them to consent to vaccination for their children.

At the time of the outbreak in Merseyside there were many parents and guardians who had not vaccinated their children due to wrongly-held beliefs concerning vaccine safety and efficacy, preference for vaccination alternatives and other worries [29]. Those parents and guardians that were actively anti-vaccine (i.e. those parents and guardians who did not want to vaccinate as opposed to

the parents and guardians who forgot or had accessibility issues) may not have responded to pro-vaccine messages. These messages may have even caused a recognised “backfire effect”, where vaccine skeptics with a negative opinion on vaccination grow even stronger in their dislike or mistrust of vaccinations [30-32]. Therefore, it is likely that these individuals would require additional resources in order to convince them of the benefits of MMR vaccination for prevention of measles infection.

Horne et al. (2015) describe a method to counter anti-vaccination attitudes in parents and guardians [33]. Participants of their study were given three pieces of information from the CDC website that would address their belief that measles infection was not a cause for concern. This intervention outperformed a similar intervention where parents and guardians read information from the CDC website that explained the lack of a link between the MMR vaccination and autism. McHale et al. (2015) reported that a majority of vaccine-hesitant parents and guardians in the Merseyside area did not vaccinate their children because of fear that the vaccine may cause autism [29], but Horne et al. (2015) show that correcting this incorrect belief is not as effective as replacing it with new information, analogous to the intervention provided by Lewandowsky et al. (2012) [34].

It is unclear if this intervention could be applied to parents and guardians during a GP consultation, in which case the additional cost to vaccinate sufficient children to reach the herd immunity threshold should include a GP consultation for each child in a household with vaccine-hesitant parents and guardians (£36 in 2012 [21]). If not, then additional educational and outreach programmes would need to be commissioned in order to reach this cohort.

## **POLICY IMPLICATIONS**

### **INVESTMENT IN PREVENTION**

Investment in childhood vaccination programmes will be undermined if the threshold for herd immunity in the local community is not achieved. The cost of containing and managing a measles outbreak in Merseyside is substantial, and a more cost-effective intervention to reduce the impact of such outbreaks already exists in the form of the MMR vaccination programme. It is vital that public health officials continue to commission and develop the MMR vaccination programme to achieve a level of vaccination coverage that will prevent future outbreaks of measles if both unwanted and high expenditure on treatment and associated public health and productivity costs are to be avoided.

Data from the Health & Social Care Information Centre for 2013-14 show that MMR vaccination coverage still falls short of the herd immunity threshold of 95% in Liverpool [35]. Although 96.8% of children were vaccinated with one MMR dose by the time of their fifth birthday, the requirement for two doses was only achieved by 90.9%. Additional resources may be required by public health

organisations tasked with increasing MMR vaccination coverage to reduce the potential impact of future measles epidemics in the area.

The outbreak in Merseyside could have been much larger and had a greater total burden of disease than the 650 confirmed cases seen in 2012-13. Many children had not received both doses of the MMR vaccination for which they were eligible, so it is very likely that an outbreak larger than that seen could have occurred, arguably with greater costs in terms of direct healthcare, direct public health and the loss of productivity. It also stands to reason that whilst MMR vaccination coverage in the area is still below the herd immunity threshold, such a larger outbreak could occur. The estimated cost to achieve the herd immunity threshold was just 4.2% that of the total cost of the outbreak, and this cost in additional vaccinations administered would also prevent such a larger outbreak as discussed.

#### USE OF RESOURCES DURING THE OUTBREAK

84.6% of the total cost of the outbreak was not spent on direct healthcare for individuals with confirmed measles or potential cases of measles. 40.1% of the cost was borne by the direct public health response and 44.5% of the cost was borne by the community through the estimated loss in productivity.

Although a number of individuals with confirmed measles were hospitalised with some measles-related complications, there were no measles-related deaths nor serious complications such as optic neuritis or subacute sclerosing panencephalitis as a result of the outbreak. It is unclear how the costs attributed to direct healthcare costs would have been influenced in the event of a measles-related death or serious complications from infection in the community, but it is likely that additional costs would be borne by the secondary care organisations and their commissioners. It is also likely that the extensive, timely public health actions undertaken coupled with the already high MMR vaccination coverage reduced the risk of larger outbreaks sufficiently that such major complications were not seen in hospitals. Complications such as encephalitis (£20,887 per admission), pneumonia (£9,798 per admission) and otitis media (£3,057 per admission [36]) were not observed but would have substantially increased direct healthcare costs if they had occurred. Furthermore, conditions such as subacute sclerosing panencephalitis which cost £6,217 per admission [36] may take many years to develop, eventually requiring many follow-up visits for specialist care, support, and longer period of home-care, and therefore the treatments costs associated with the outbreak may increase if assessed over a longer period than this analysis.

It is also unclear how cost-effective the expenditure on public health programmes and activities was during the outbreak without a comparison to another outbreak with less direct public health



expenditure. However, the impact of key public health messages on preventative vaccination cannot be underestimated. We estimated that an additional investment of £1 in preventative vaccination over the previous five years in the community would have saved £23 in costs related to the outbreak, had the herd immunity threshold been achieved.

## FUNDING

This work was funded by a Career Development Fellowship supported by the National Institute for Health Research (grant number NIHR-CDF-2011-04-019). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. The original costing study was commissioned from ICF by HPA (PHE predecessor organisation).

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## **Chapter 9 - Discussion and identifying areas for further research**

The strengths and limitations of each study have been discussed in the previous chapters. We present a brief summary of the main findings of each study before proposing future directions for research in this field.

### **A SUMMARY OF THE KEY FINDINGS AND THEIR IMPLICATIONS FOR PUBLIC HEALTH POLICY**

We established that the wide-ranging problems involved in estimating child- and adolescent health utilities have not been solved, though progress has been made in developing new child-specific instruments to obtain QALYs for a variety of conditions in these age groups. With that, we successfully described the health-related quality of life loss due to both seasonal influenza in primary schools and measles infection nationwide. We also reported on the social and economic impact of both diseases – seasonal influenza outbreaks in primary schools and the impact at home; and measles outbreaks nationwide.

We also established that the new seasonal influenza vaccination programme in England that offers an annual live-attenuated vaccine to school-children is only likely to provide the most benefit when rolled-out across both primary- and secondary school age groups. Finally, at the community level it is important that public health organisations strive to achieve homogeneous vaccination coverage within all schools in the targeted geographic location as schools failing to achieve the same vaccination coverage as other schools in the area can provide a sufficiently-sized pool of susceptible individuals to maintain community-based seasonal influenza transmission and outbreaks.

### **ESTIMATING HEALTH UTILITIES AND HEALTH-RELATED QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS**

There is extensive variation in the methods used to estimate health utilities in the paediatric population, and still no consensus on the use of proxy-reporting to estimate health utilities in children and adolescents.

There is an over-reliance on adult-specific methods and instruments that had been administered to the paediatric population to estimate health utilities (in agreement with Kromm et al. (2012) [1]), as well as very little discussion on missing questionnaire data.

Ten years after the Griebisch et al. (2005) review [2] we reported on the development of new child- and adolescent-specific instruments to estimate health utilities in the paediatric population, such as

the EuroQol EQ-5D-Y [3] or the CHU-9D [4]. However, the task of paediatric health utility estimation is still not standardised and the absence of a recommended instrument to use in these investigations from a body such as the National Institute for Health and Clinical Excellence (NICE) means that researchers in this field lack a clear way forward in resolving these issues and standardising the estimation of health utilities in children and adolescents.

#### **THE SOCIAL AND ECONOMIC IMPACT OF SEASONAL INFLUENZA OUTBREAKS IN PRIMARY SCHOOLS**

We reported on the socio-economic impact of the illness in terms of the total loss of productivity due to illness, using the mean absence from school for children; mean total time off work for primary caregivers; and the mean QALY-loss per infected individual. We also reported on the costs incurred by families during a child's infectious period.

The proportion of parents and guardians who stated that they would be willing to accept an annual seasonal influenza vaccination for their children was greater than the reported school-based uptake in primary schools in England during the 2014-15 influenza season (81.6% vs. 56.8%) [5]. These figures suggest that a minimum of 18.4% of parents and guardians face some form of non-attitudinal barrier that prevents their children from participating in school-based vaccination programmes.

This study highlights the importance of an effective seasonal influenza vaccination programme in primary schools. A programme like the current seasonal influenza vaccination programme in England can have a direct impact on those children vaccinated in reducing the risk of illness, and a substantial indirect impact in preventing disruption at home caused absence from work for parents and guardians required to look after their children during their illness. The indirect impact would also extend to preventing many parents and guardians incurring out-of-pocket expenses during this illness. Though our study did not measure the impact of secondary transmission in the household, it is important to note that seasonal influenza vaccination for schoolchildren can prevent secondary household transmission that would otherwise have a significant impact at home [6].

#### **MATHEMATICAL MODELLING OF NATIONWIDE SEASONAL INFLUENZA VACCINATION PROGRAMMES**

We established that a vaccination programme focused solely on either primary or secondary schools would not eliminate the potential for sustained influenza transmission, even at the highest possible levels of coverage. However, homogeneous vaccination across both school groups would effectively eliminate nationwide transmission at 66% coverage. The most cost-effective vaccination strategy would see 48% vaccination coverage in primary schools and 34% coverage in secondary schools. We've previously discussed the importance of an effective seasonal influenza vaccination programme

in primary schools and this mathematical modelling study reports the importance of ensuring that the programme continues its increased roll-out to all school age groups, particularly to secondary schools once all primary school age groups are included in the programme.

An effective vaccination programme extended to secondary schools would not only be cost-effective for the healthcare provider in England but also of substantial benefit to the wider population in terms of a reduction of school absence, work absence and out-of-pocket expense for parents and guardians even if only the measured benefits to parents and guardians of children in primary schools is taken into account.

The reported coverage achieved during recent pilots and early stages of the roll-out of the vaccination programme indicate relatively high coverage can be achieved in primary schools [5, 7], though it is likely to fall short of the coverage required in both primary and secondary schools to effectively eliminate nationwide transmission. The reasons for non-participation in the programme were not studied, but if our study in primary schools is representative of the wider population then policy makers seeking to increase coverage should concentrate on parents' and guardians' misunderstanding of the risks related to influenza infection as well as concerns over vaccine safety.

#### **MATHEMATICAL MODELLING OF SEASONAL INFLUENZA VACCINATION PROGRAMMES AT THE COMMUNITY LEVEL WITH FURTHER HETEROGENEITY IN COVERAGE**

With results similar to those reported in Chapter 5, a targeted vaccination policy in either primary or secondary schools alone would not be sufficient to eliminate seasonal influenza transmission in the community. However, a homogeneous policy with 47.8% coverage in both primary and secondary school groups would eliminate transmission.

An increase in the number of low-coverage schools in the metapopulation resulted in an increase in the expected mean final size of epidemics. However, a single low-coverage primary school in the metapopulation did not increase the expected final size of epidemics, though a single low-coverage secondary school would result in larger seasonal influenza epidemics due to the relative size of a secondary school to a primary school.

Heterogeneity by design in a vaccination programme was unable to reduce the total burden of disease in the metapopulation beyond that of an equivalent homogeneous vaccination policy. Indeed, several combinations of coverage levels that used heterogeneity in uptake underperformed in reducing the total burden of disease when compared to the equivalent homogeneous coverage policy. This study

reinforced the importance of extending the seasonal influenza vaccination policy in England to both primary and secondary school groups, not just targeting primary schools.

This study also emphasised the importance of maintaining homogeneous vaccination coverage in an effective seasonal influenza vaccination programme administered in schools. We established that low-coverage schools in the community cannot be compensated for by increasing coverage in already high-coverage schools, so policy makers should have contingency plans to increase coverage in low-coverage schools.

#### **THE SOCIAL IMPACT OF MEASLES INFECTION, IN PARTICULAR ITS IMPACT ON HEALTH-RELATED QUALITY OF LIFE**

Measles infection was associated with a substantial mean loss HRQoL per individual; in addition to a long absence from work or school for 63.1% of those infected and a long absence from work for the primary caregivers of those infected requiring a primary caregiver during their infection. Measles infection was also associated with a substantial societal burden in terms of both primary and tertiary care use.

This study was the first estimation of the impact of measles infection on health-related quality of life. The results from this study can be used to inform cost-utility analyses of new interventions designed to prevent or mitigate measles outbreaks in the community.

Another key result arising from this investigation was the suitability of using the new EuroQol EQ-5D proxy questionnaire for those individuals aged under 7 years. 70 of these questionnaires were returned from individuals with confirmed measles but only 20 (28.6%) of them included all the information required to estimate the health-related quality of life impact of measles infection, with the majority (70%) of these returned questionnaires missing a response to the EQ-5D item detailing the impact of infection on the individual's ability to continue to self-care. As discussed in Chapter 7, this question and others on the EQ-5D proxy questionnaire may not be appropriate for the age group targeted in the investigation. This result was also picked-up in the systematic review of all instruments and methods used to estimate health utilities in children and adolescents (Chapter 3), as another example of the overreliance of adult-specific measures being used to solicit health utilities from the paediatric population. We recommended that EuroQol revisit the EQ-5D proxy instrument and develop a new instrument based on EQ-5D that is appropriate for young children.

Another important finding from this study was the impact of measles infection at home. In a 2015 study that reported on the reasons for non-participation in measles vaccination programmes in Merseyside, several respondents claimed that additional information from the healthcare services

that demonstrated the severity of measles infection would have been useful in persuading them to vaccinate their child [8]. Informing parents and guardians of the impact that measles infection will have both on the health of their children and the day-to-day life at home during any infection may therefore be helpful in increasing participation in MMR catch-up campaigns.

#### **THE ECONOMIC IMPACT OF MEASLES OUTBREAKS IN THE COMMUNITY**

The measles outbreak in Cheshire and Merseyside in 2012 and 2013 is estimated to have incurred substantial costs to the community, much higher than previous studies on economic impact of other outbreaks have suggested, but we included a wider range of costs using a societal perspective so this is unsurprising.

The cost of achieving 95% MMR vaccination coverage in the region over the previous 5 years is estimated to be £182,909, based on a cost-per-dose of vaccine stock, logistics and administration. This represents just 4.2% of the total cost of the outbreak and means that every £1 spent on prevention could have saved £23 in resources used to control the outbreak if the 95% coverage target had been met.

This study emphasised the importance of adherence to a well-funded and effective preventative vaccination programme. The economic impact of measles outbreaks in the community of Cheshire and Merseyside was substantial, whilst both a very effective vaccine and well-funded vaccination programme exist. Achieving the herd protection vaccination threshold of 95% MMR coverage homogeneously across all areas of Cheshire and Merseyside would have enormous benefits to the local population, in terms of both health benefits in prevented measles cases and in economic terms also. It is important for policy makers to note that whilst local MMR coverage does not exceed 95%, the risk of sustained community-wide measles outbreaks remains.

#### **IDENTIFYING AREAS FOR FURTHER RESEARCH**

##### **ESTIMATING HEALTH UTILITIES AND HEALTH-RELATED QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS**

CLARITY ON THE MOST SUITABLE INSTRUMENTS FOR ESTIMATING HEALTH UTILITIES IN THE PAEDIATRIC POPULATION IS REQUIRED

There is increased emphasis on the need for a well-sourced cost-effectiveness analysis in the process of adopting a new healthcare technology or intervention. A lack of suitable tools available to researchers to properly assess the potential health benefits of that new healthcare technology is a stumbling-block to its adoption. Policy makers and administrative bodies such as NICE should develop



suitable protocols for cost-effectiveness analyses that involve children and adolescents, including the use of an instrument that accurately estimates health utilities in this group.

#### EQ-5D-Y NEEDS A TARIFF FOR CHILD HEALTH PREFERENCES

The EuroQol EQ-5D-Y classification system is a commonly-used method of obtaining utility weights from children. The protocol for use is well established as the child-friendly version of the EQ-5D mirrors this adult version in all but a minor re-wording of the questions. However, it still uses the same tariff as the adult version, which therefore implicitly assumes that child preferences for health are identical to adult preferences for health. Previous research has indicated that this assumption may not be valid [9-12]. For investigations into the health-related quality of life impact of both seasonal influenza and measles infection, we were able to administer an EQ-5D-Y to the children affected, facilitating an estimation of this impact. However, if the EQ-5D-Y tariff does not accurately reflect the health preferences of children then we may have misrepresented the impact of seasonal influenza and measles on the HRQoL of children.

Children and adolescents have previously reported utility weights through the Standard Gamble procedure (SG) successfully [10, 11], with Ratcliffe et al. (2011) also using a Best-Worst Scaling Discrete Choice Experiment (BWS DCE) [13] and comparing both responses and response rates of the SG and BWS DCE. The BWS DCE requires a respondent to compare two options using the best and worst attributes of each option and is reported to be easier to understand than the SG procedure for eliciting utility weights [13]. A tariff derived directly from children and adolescents could therefore be obtained for the EQ-5D-Y with a sufficiently large sample size of respondents.

#### THE DEVELOPMENT OF AN EQ-5D CLASSIFICATION SYSTEM FOR USE IN VERY YOUNG CHILDREN

The EQ-5D-Y was developed by adapting the wording of the existing EQ-5D questions to make a new classification system that was more acceptable to children [14], but keeping the same five dimensions of health that were evaluated in the original EQ-5D system. The EQ-5D proxy, however, may need the five dimensions re-evaluated to ensure that an EQ-5D-type measure is suitable for very young children. The study on the impact of measles infection demonstrated that the large proportion of missing responses for an individual's ability to self-care during illness may indicate that the dimension of self-care is not applicable to young children and may require removal or replacement with a different dimension of health.

Stevens (2010) identified eleven dimensions of health important for children in assessing their HRQoL through a series of face-to-face interviews, of which nine were later incorporated into the new CHU-9D classification system [4]. Children were individually asked about previously health problems they

had encountered, ensuring that both chronic and acute conditions were raised with each child. A discussion about how each identified health problem affected the children followed in terms of school work, health service resource use and absenteeism. Each interview sought to obtain the different consequences of the identified health problems, subsequently using each consequence in the development of the dimensions of health for the new classification system.

#### **THE SOCIAL AND ECONOMIC IMPACT OF SEASONAL INFLUENZA OUTBREAKS IN PRIMARY SCHOOLS**

##### **INCLUDE SECONDARY INFECTIONS IN HOUSEHOLD TO CAPTURE GREATER DISEASE BURDEN**

Our study to investigate the social and economic impact of seasonal influenza outbreaks in primary schools in England could only capture the impact of primary infections in the household. A survey sent at a later date with additional questions pertaining to any secondary infections within the household would have captured details on the wider impact of school-located outbreaks.

In order to understand the full impact of ILI infection at home, we need to include the possibility of secondary transmission within the household, with the household primary case assumed to be infection from the school-based outbreak. Neuzil et al (2002) reported 126 episodes of illness from secondary infection in a survey of 216 families with children attending schools in Seattle [15], so the burden of secondary infections is not likely to be insignificant.

To capture the impact of secondary infections in the household, a revised study would include the prompt distribution of follow-up questionnaires to parent and guardians who reported that their child was ill with ILI infection during the notified school outbreak. The questionnaire would be identical to those in the original questionnaire but framed to address illness in a member of the household, not necessarily a school-attending child.

Addressing the problem of secondary infections and their impact would help policy makers better understand the impact of seasonal influenza from a societal perspective. Secondary infections in the household are likely to increase the economic burden on that household, particularly if at least one of the secondary infections is either a caregiver or in employment. Our original study has only measured the impact of a primary case in a household where more than one case of ILI may have occurred.

##### **INCLUDE HRQOL MEASURES FOR CAREGIVERS DURING A CHILD'S ILLNESS**

The true impact of ILI infection in the household should also include the impact of the infection of the primary case on the HRQoL in other household members. Prosser et al. (2015) measured the impact of chronic illness on other household members and found this impact to be not insignificant [16]. Though the impact of chronic illness in the household would be different to the impact of short-term

acute illness, the assumption that this illness only affects the primary case in the household is likely to miss any impact felt by other household members, however small. Indeed, if measuring HRQoL using the EuroQol EQ-5D, the dimensions of health relating to usual activities and anxiety may well be sensitive to change for a caregiver during their child's illness through ILI.

Any successful interventions to avoid ILI infection being introduced to the household would avoid all potential loss of HRQoL in caregivers for the primary case. Therefore, this potential impact on HRQoL for caregivers should be quantified.

#### DAILY HRQoL MEASUREMENTS

When calculating the loss of HRQoL for each individual with ILI we assumed that health utility would fall linearly with time from baseline to the lowest health utility on the worst day, then it would recover linearly with time until the last day of infection, at which point it returns to the baseline level. This assumption has been used successfully in the past to measure the impact on HRQoL of H1N1v pandemic influenza [17], but the full nature of the loss of HRQoL deserves investigation.

We measured health utility using the EuroQol EQ-5D twice during infection. Intermediate measurements between around the time of the worst day of infection would provide further data to understand the magnitude of the loss of HRQoL by challenging the assumption of linear reduction and recovery. Our assumption of the shape of the polygon plotted when using the vertices at the two baseline measurements and the worst day of infection was that of a triangle. However, if the health utility experienced on the worst day of infection is felt for a longer period than one day then this polygon would be a trapezium and would increase the area of the shape of the assumed polygon representing the loss of HRQoL.

Some ways to fully understand the shape of the polygon representing the loss in HRQoL would be through challenge studies with volunteers willing to be infected with ILI and to have their period of infection monitored by completing daily EQ-5D measurements, or through a prospective cohort recruited in a similar fashion to that of the annual Flusurvey [18] with daily HRQoL measurements taken during periods of illness. Enrolling individuals at school who have ILI to complete daily EQ-5D measurements would be very difficult to administer.

#### EXTENDING THE STUDY TO INCLUDE SECONDARY SCHOOLS AND BOARDING SCHOOLS

Our study was originally intended to reach all primary and secondary schools that reported a suspected ILI outbreak during the 2012-13 and 2013-14 influenza seasons. A combination of the late introduction of the study during the first influenza season and the reduced influenza activity during

the second resulted in a small sample size consisting of primary schools exclusively. If it were possible to run the study again it would be important to capture the potential impact of ILI in secondary schools and boarding schools as well, thereby obtaining sufficient data to report the impact of ILI in the general school population.

Brousseau et al. (2015) evaluated the impact of influenza vaccination on age-specific respiratory disease incidence in children attending private boarding schools in England during 2013-14 [19]. They recruited 43 schools consisting of 14,776 pupils by working in collaboration with the Medical Officers of Schools Association (MOSA), asking the head nurse of each MOSA school to complete a weekly online survey about the number of respiratory illnesses in pupils. Though this study evaluated the impact of influenza vaccination, rather than the impact of influenza infection, it highlights a new method of identifying those schools with ILI epidemics during the influenza season.

Both MOSA and PHE have an existing long-standing relationship to manage a school-based surveillance programme in boarding schools. Using the same protocol as the Brousseau et al. (2015) study to identify respiratory illnesses in pupils, an adapted questionnaire could be delivered to those pupils with illness attending the boarding school in order to assess the impact of illness on their routine. This impact would be limited to HRQoL and attendance in classes, as the impact on the wider family would not be applicable as the children are not in the household. However, given that the impact of influenza vaccination in boarding schools has already been measured in terms of a reduction of ILI in pupils (RR 0.46, 95% CI: 0.28-0.76, [19]) then additional data on the impact of ILI infection on a pupil's HRQoL as well as a societal measure such as their loss of productivity would give public health teams sufficient information to present to vaccine hesitant parents in order to increase vaccination coverage at boarding schools.

## **MATHEMATICAL MODELLING OF NATIONWIDE SEASONAL INFLUENZA VACCINATION PROGRAMMES**

### **MODELLING THE TIMING OF SEASONAL VACCINATION**

One assumption in our model was that all vaccinations are administered before the beginning of seasonal influenza outbreaks. Though this assumption was useful in simplifying the model, it may not bear resemblance to vaccination attitudes of individuals eligible for seasonal influenza vaccination.

Vaccine stocks are delivered to GP practices, pharmacies and to Public Health England central stocks from September each year, but vaccination for seasonal influenza continues through winter until February [20]. Vaccination coverage does not reach its maximum before the beginning of nationwide influenza outbreaks, nor does vaccination uptake increase linearly with time during the winter period (Figure 9.1).

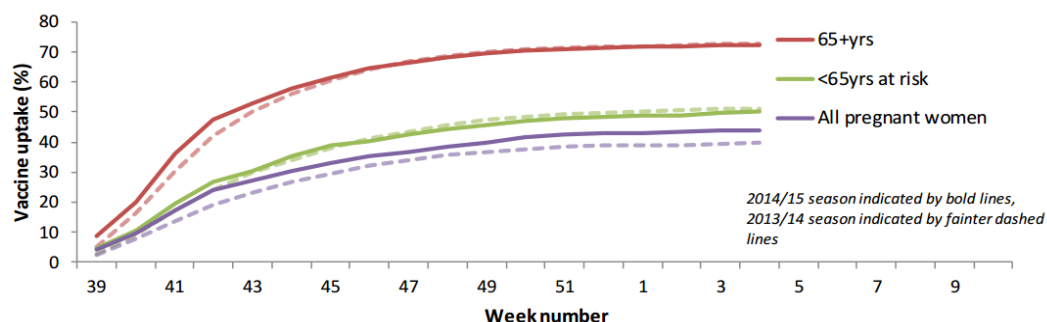


Figure 9.1 - Cumulative weekly influenza vaccine uptake by target group in England

Figure credit: [21].

Improvements to the model would include a time-dependent vaccination coverage parameter for each population group eligible for the seasonal influenza vaccine. In addition to including time-dependent coverage, the vaccination coverage parameter should account for the time needed between vaccination administration and the delay between immunity onset. Baguelin et al. (2013) assumed coverage increased at regular intervals during the influenza season [22], but additional data from vaccination uptake surveillance programmes would inform this further.

Public Health England releases weekly national influenza reports during the influenza season and these weekly reports include weekly vaccination coverage data. Baguelin et al. (2012) assumed that the time delay between vaccination administration and immunity onset was two weeks [23], though this estimate could be improved with data from challenge studies.

#### MODELLING REACTIVE VACCINATION DECISIONS

Data gathered from primary schools that reported a suspected ILI outbreak during the 2012-13 and 2013-14 influenza seasons suggest that parents or guardians of children attending schools with recent outbreaks are keen to accept the offer of seasonal influenza vaccination, but uptake data from the 2013-14 pilot study in six primary schools suggest that the willingness to accept a vaccine does not equate to high vaccination uptake [7]. The intention to study the difference between a willingness to vaccinate and achieved vaccination coverage was discussed in Chapter 4, but the high proportion of parents and guardians reporting a willingness to vaccinate their children against seasonal influenza may have been influenced by the recent suspected ILI outbreak at their child's school. This begs the question of how many decisions to vaccinate are influenced by recent local ILI or influenza outbreaks.

It is not clear from the uptake data reported in Figure 9.1 if any weekly increase in vaccination coverage is due to reports of local outbreaks – such detail on local uptake is lost in the reporting of

national uptake figures. However, if data on vaccine decisions were gathered during the influenza season at the time of vaccine administration then the impact of local outbreaks on the decision to vaccinate could be studied. A spatially explicit model could account for a possible increase in local vaccination uptake due to localised influenza outbreaks.

#### STAGGERED DELIVERY OF VACCINES

We've previously discussed modelling time-dependent vaccination uptake, but vaccine programmes may have time-dependent delivery and administration of vaccines to different targeted groups. Rather than administering vaccines to all targeted groups simultaneously, it may be logistically easier and more cost-effective to administer vaccines to different targeted groups one-after-another [24]. Therefore, if simultaneous delivery during one influenza season to both primary and secondary school groups is unfeasible, it is sensible to explore whether primary or secondary schools should be offered the vaccination first, as well as the wider issue of vaccinating healthy children before or after risk groups. Such a scenario would require a model to account for the increase in vaccination coverage as the influenza season progresses.

#### **MATHEMATICAL MODELLING OF SEASONAL INFLUENZA VACCINATION PROGRAMMES AT THE COMMUNITY LEVEL WITH FURTHER HETEROGENEITY IN COVERAGE**

##### MODIFYING THE MODEL FOR OTHER METAPOPOPULATIONS, WITH VACCINE UPTAKE MODELLED USING DEMOGRAPHIC FACTORS

Our model of heterogeneous vaccination coverage in the community investigated the impact of heterogeneous seasonal influenza vaccination coverage at the school-level. However, at a national level there is sufficient evidence to suggest that heterogeneities in coverage will be seen based on the implementation of different vaccine-administration methods [5, 7]; level of deprivation and urban/rural areas [25]; and the different educational or promotional material released by the healthcare and education authorities [26]. Our metapopulation model was unable to address this issue, but we can use it to propose the basis for a new model that may assist in answering the question of nationwide coverage heterogeneities.

Green et al. (2015) used vaccination coverage data in England from the first year of the roll-out phase of the new JCVI influenza vaccination programme and modelled vaccine uptake using collected demographic factors [27]. Factors including ethnicity, deprivation and religious beliefs were important factors in determining vaccine uptake. The data were aggregated by clinical commissioning group (CCG) and Public Health England Region. Data for those individuals aged 2 and 3 years old were available for the whole country, whilst data for those aged 4-11 years old were available for the six pilot sites administering vaccinations in schools.

Data on the demographic factors for those individuals receiving their seasonal influenza vaccination at their GP practice were available to Green et al., aggregated at GP practice level. With each GP practice assigned to a CCG covering a discrete geographical area, it is possible to build a patch-structured metapopulation model of the CCGs in England, each with estimated vaccine coverage. This spatially-structured model could then be used to simulate seasonal influenza epidemics in England, subsequently providing Public Health officials with information on where best to focus their efforts on reducing vaccine coverage heterogeneity.

In addition, demographic factors on the individuals aged 4-11 years old that received their vaccination in schools participating in the pilot study could be extrapolated to cover England and estimate uptake at CCG level using demographic factors for 4-11 year olds in each CCG. An influenza transmission model within a structured metapopulation model with 211 CCGs would be computationally expensive to execute, so the merits of a stochastic model versus a simpler deterministic model would need to be established during this project. This extrapolation, however, will increase the uncertainty in predicted coverage level for each CCG as the original sample size is very small. As the roll-out of the new seasonal influenza vaccination coverage continues, additional demographic data can be modelled with uptake in each CCG to improve the model.

Studies to map or predict vaccination uptake have been conducted on a variety of different vaccinations in different countries. Coverage of seasonal influenza vaccination programmes has been studied in the United Kingdom [25], Kenya [28], Japan [29] and the United States [30], modelling coverage with socio-economic and demographic factors (Figure 9.2).



*Figure 9.2 - Influenza vaccination and socio-economic factors for (top) 2010-11 and (bottom) 2011-12 in North Carolina, USA*

Figure credit: [30].

In addition, several studies have modelled vaccination coverage for pandemic influenza [31], MMR [32-34] and the regular childhood vaccination schedule in New Zealand [35], all with various socio-economic and demographic indicators. Spatially-explicit metapopulation models using these data could be implemented to model the potential burden of disease for each setting, to better inform the allocation of resources for vaccination programmes.

#### **THE SOCIAL AND ECONOMIC IMPACT OF MEASLES OUTBREAKS**

##### **DAILY HRQoL MEASUREMENTS**

In estimating health utilities and the total burden of disease for measles in England during 2012-13 we assumed that HRQoL would fall linearly with time until a minimum at the worst day of infection, after which the HRQoL of the individual will increase linearly with time until returning to the baseline level after symptoms have gone.

We proposed measuring HRQoL daily through an individual's infection with influenza, and here we propose to do the same for measles infection. The daily impact on HRQoL of measles infection was assumed to decline and recover linearly but this assumption should be challenged by the



administration of additional questionnaires to individuals with measles. Successfully estimating the loss of HRQoL through QALYs and QALDs would result in a more accurate estimation of the total burden of disease due to measles infection.

#### COST-UTILITY ANALYSES OF PREVENTATIVE OR REACTIVE INTERVENTIONS FOR MEASLES OUTBREAKS

To our knowledge, our study to estimate the impact of measles infection in terms of QALYs using a validated health-state instrument was the first attempt to do so. Information on the estimated QALY-loss caused by acute infectious disease is important for cost-utility analyses of interventions designed to prevent or manage outbreaks of those infectious diseases. Previous cost-effectiveness analyses have been able to estimate the cost to prevent each measles case in an outbreak [36-40], but now a suitable transmission model linked to an economic analysis using QALYs to estimate potential health benefits through case prevention will facilitate the calculation of the cost-per-QALY ratio.

#### **THE WIDER PICTURE: THE CHALLENGES FOR PUBLIC HEALTH OF VACCINE-PREVENTABLE OUTBREAKS OF INFLUENZA AND MEASLES**

##### **ERADICATION OF MEASLES**

The World Health Organisation aims to achieve elimination of measles infection in at least five WHO regions by the end of the year 2020 [41]. Measles remains a leading cause of morbidity and mortality for children around the world, despite the availability of an effective and ineffective vaccine against the disease and a 73% decline in worldwide annual incidence between 2000-2014 [42].

In 2013 the WHO's Strategic Advisory Group of Experts (SAGE) on Immunisation warned that several WHO regions were unlikely to meet their 2015 elimination goals for both measles and rubella. The outbreaks of measles in the United States and Europe in 2012-14, due to declining MMR vaccination uptake in the late 90s and early 00s, were likely a contributor to this warning. Areas of the world plagued by conflict, including Iraq, Syria and Sudan, reported measles outbreaks throughout 2014, demonstrating the difficulties in meeting this worldwide target of elimination [43].

The eradication programme faces significant challenges: at the national and local level, individuals still face barriers to measles vaccination for many reasons [44], and clusters of unvaccinated individuals can trigger far-reaching outbreaks in the community [45-47], the impact of which has been described in Chapter 7 and Chapter 8 of this thesis.

Increasing the demand for the measles vaccine at the national and local level can be achieved by improving the quality of the vaccine supply [48], advocacy undertakings with parents and guardians

responsible for making vaccine decisions [49], and increasing the awareness of the dangers of measles infection in the minds of the general public [50]. Effective public health campaigns making use of clear educational messages are required to address the misplaced scepticism towards the measles vaccine and to accept vaccination to protect both their children and the wider community.

#### THE CONTRIBUTION OF THIS THESIS

Global disease eradication programmes depend on the success of the constituent national disease eradication programmes, which in turn rely on successful local and community-wide public health campaigns and engagement activities to increase awareness of both the dangers of infection and socio-economic burden of disease as well as the benefits of vaccination.

The importance of a well-resourced preventative vaccination programme was outlined in Chapter 8, comparing the total economic burden of a local measles outbreak to the total estimated cost of achieving herd protection. The economic burden of sustained community-wide measles transmission was much larger than the estimated total cost of achieving herd protection through an existing vaccination programme. This analysis demonstrates the necessity for continued investment in vaccination programmes and increased support for commissioning public health campaigns designed to increase participation in vaccination programmes.

In addition to the importance of a measles vaccination programme from the perspective of public health organisations and the wider community, this thesis offers additional detail on the individual burden of disease through the reported results in Chapter 7. Taken together, the results from both chapters should support public health organisations in making a very compelling case for renewed vigour in further commissioning and support for the MMR vaccination programme, whilst individuals not currently reached by this programmes have additional information on the impact of measles infection that should increase demand for the vaccine.

The contribution of well-resourced and far-reaching national vaccination programmes to a global measles eradication programme cannot be underestimated. It is the pockets of low-vaccination coverage distributed across different countries that continue to periodically revive large-scale outbreaks, so it is therefore of the utmost importance that individuals in these communities are fully engaged with local public health organisations and their vaccination programmes to reduce the potential for further future outbreaks.

## **PUBLIC HEALTH CHALLENGES WITH SEASONAL INFLUENZA**

In 2011 the ECDC identified several challenges in increasing engagement with seasonal influenza vaccination programmes in European countries [51]:

- Communication
- Doubts on vaccine safety and effectiveness
- Involvement of healthcare workers in the programmes

Vaccination coverage in Europe for seasonal influenza is heterogeneous but can be high in some targeted groups in several countries – indeed, both The Netherlands and the UK achieved over 75% coverage in the elderly population in 2012-13 [52]. However, many other countries still experience significant challenges to increase coverage in their targeted risk groups. These challenges include a lack of awareness of influenza; a lack of education on the disease; a gap in trust towards public health authorities; a lack of adequate advice from those healthcare services with which the population is engaged; and unclear messages from new media sources that may also promote anti-vaccination attitudes [51, 53].

Many studies have previously concluded that increased engagement with primary care services can increase vaccination coverage in both high-risk groups [54] and the general population as a whole [55], with strategies that use outreach programmes and reminder systems proving to be the most effective. An effective communication strategy in the primary care setting can help overcome the barriers to vaccination programme engagement caused by issues in communication. Public health efforts to address misconceptions about vaccine safety and effectiveness are crucial to improving the public's understanding of the benefits of seasonal influenza vaccination, particularly among minority groups [56], parents of children eligible for childhood vaccination programmes [57] and university students [58]. Engagement with healthcare workers is essential, and this requires a thorough understanding of the motivators for healthcare workers to consent to seasonal influenza vaccination. These motivators primarily concern the personal benefit of vaccination, highlighted in this thesis, rather than indirect benefits that may be experienced by the healthcare workers' patients [59].

## **THE CONTRIBUTION OF THIS THESIS**

This thesis reported on the importance of maintaining the current planned roll-out of the childhood seasonal influenza vaccination programme (Chapter 5) whilst targeting consistent coverage levels in the community (Chapter 6) and both the social and economic impact of influenza infection that should

be used to inform parents and guardians of the importance of the participation of their children in the childhood seasonal influenza vaccination programme (Chapter 4). Both Chapter 5 and Chapter 6 should inform public health organisations of the significance of maintaining good vaccination coverage in the community, it is the results from Chapter 4 that may assist the ECDC in tackling the challenges identified to increase engagement in these vaccination.

The results from Wooten et al. (2012) on concerns over vaccine safety and efficacy acting as a barrier to engagement with seasonal influenza vaccine programmes were reiterated in this thesis [56]. Addressing these issues with well-publicised vaccination campaigns that inform the population of the efficacy of vaccines can address this issue [26], though an important component of any such campaign is a warning of the dangers of infection to counter anti-vaccine or vaccine hesitant attitudes [50], which the results of Chapter 4 can inform. Communicating the risks posed by infection of vaccine-preventable diseases can have significant changes in vaccination intentions. Communicating the risk of infection in terms of the severity of illness in addition to the socio-economic impact at home through media outlets would ensure that this message has its widest possible reach [60].

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