PRISMA 2009 Checklist

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

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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

STUDY PROTOCOL

The Impact of Infectious Disease Outbreaks in Schools

Version: V3.7 26th September 2013

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ABBREVIATIONS

EQ-5D	EuroQol 5D three-level health-related quality of life measure
PHE	Public Health England
HPT	Health Protection Team, PHE centre
HRQoL	Health-related quality of life
JCVI	Joint Committee on Vaccination and Immunisation
LSHTM	London School of Hygiene and Tropical Medicine
NICE	National Institute for Health and Clinical Excellence
QALY	Quality-adjusted life years
FES	Field Epidemiology Services, Victoria

SUMMARY FOR THE LAY PERSON

The 2009 H1N1 influenza pandemic sparked debate on what public health interventions are most appropriate for dealing with infectious disease outbreaks occurring within schools. The discussion of the impact of school closures or other measures must be informed with knowledge of the wider consequences of these outbreaks, including all clinical and financial effects in those communities involved.

If children cannot attend school through illness or school closure the families affected may need to alter their work and social arrangements to ensure that those children are supervised during their time at home. These actions can be disruptive and may have financial implications if parents or guardians must temporarily stop working.

Other actions can be disruptive such as hiring professional childcare assistance, asking for childcare assistance from friends and relatives, organising and travelling to medical appointments for the child, rescheduling or cancelling evening and weekend activities and other such arrangements. Some of these may involve additional costs for the families to bear and the disruption may impact on the health and wellbeing of the parents, guardians or caregivers.

Earlier this year (2012) the JCVI recommended that all children aged between 2-17 years should receive an annual vaccination for influenza, the same vaccination that is currently given to people aged 65 years and over [1]. Vaccinating school children might reduce the impact of an influenza epidemic by protecting children from both acquiring and then spreading influenza. The vaccination programme would help families by ensuring that school closures are less likely in the future and avoid the potential disruption at home experienced by families with children who're absent from school with illness. Further information about this disruption and related costs for the families involved would help policy-makers in their discussions on the merits of the proposed vaccination programme.

This study seeks to describe the impact of infectious disease outbreaks in schools as felt by the families of the children directly affected in terms of costs and disruption in the household. We will also assess the effect that the child's illness has on the child too, providing data that may be used in further modelling and simulation studies.

Background

Infectious disease outbreaks in schools will have an economic impact in the community. 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. 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. 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. This study looks to address the lack of data on societal costs by asking parents affected by a school outbreak how an illness in their family influenced life at home.

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. Understanding the potential heterogeneity in the uptake of the offered vaccinations will help the healthcare authorities evaluate the cost-effectiveness of the proposed programme.

QALY-loss assessment associated with infectious disease outbreaks can be examined by employing HRQoL measures aimed at patients infected. The measure recommended by NICE is the EQ-5D, a questionnaire that divides life into five dimensions of three levels - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This questionnaire has also been used in children to examine their health and inform cost-utility analyses for interventions 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. 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.

PRIMARY OBJECTIVE

In describing the burden of influenza-like-illness outbreaks in schools on families and the community we wish to

- study parents'/guardians' childcare seeking behaviour for hypothetical school closures

- describe childcare arrangements for parents/guardians whose children were ill during school outbreaks

- describe the logistical problems concerning cancelled or rescheduled work and social arrangements for parents/guardians whose children were ill during school outbreaks

- evaluate the total cost of the outbreaks from the perspective of the affected families

- quantify the temporary deterioration of health for the children who were ill during the outbreak for the purpose of a cost-utility analysis and for potential future modelling studies

SECONDARY OBJECTIVE

In light of the recommendation from the JCVI to offer an annual influenza vaccination to all children in schools and preschools, we wish to study parents'/guardians' attitudes to the recommendation. Specifically

- their knowledge of the recent recommendation for an updated influenza vaccination programme

- their attitude to this programme

- will they accept the offer of annual influenza vaccination for their children as part of the programme?

METHODS

STUDY DESIGN

This is a prospective, observational cross-sectional study. This study will focus on parents whose children attend schools where an infectious disease outbreak has recently occurred. We will ask them to complete online questionnaires designed to help us understand the arrangements that families make to minimise the impact at home due to an outbreak in their children's schools. These questions will examine all paid and unpaid time taken off work to supervise children as well as the total cost to the both the family and others and logistical problems faced by families arranging childcare during the child's illness.

We will also investigate the temporary deterioration of health for the children who're ill. The questionnaires will include age-specific questions that facilitate the calculation of health-utilities, both during the worst day of the child's illness and a background utility for their normal health state several

weeks after the infection has ended. These health-utilities will be used to calculate QALYs lost during the outbreak for the affected population to use in future modelling studies and cost-utility analyses.

We will ask all parents to respond to a questionnaire to examine how parents would react to a hypothetical school closure – questions will propose school closures for three different lengths of time (one day, one week and four weeks), inviting participants to select their preferred methods of childcare in these scenarios where appropriate. 10-point Likert scales will let parents or guardians describe the potential disruption for the school closures over the three different lengths of time.

Further questions will examine the arrangements made for childcare for those parents whose children were ill during the outbreak. These questions will focus on how many people were required for the childcare arrangements for the duration of the illness, how many of those people took paid (i.e. used some of their allowance of annual leave) and/or unpaid days off from work and a total additional cost estimate for the parents referring to childcare, medicines, travel, etc. These questions will be sent to all parents whose children attend schools where outbreaks have occurred, including those whose children have been absent from school due to illness and will receive the questionnaire previously mentioned.

We will use children-specific HRQoL measures to quantify the QALY-loss for those children who fall ill during the outbreak. A child-friendly version of the EQ-5D measure (known as EQ-5D-Y) has modified questions so that they're pitched at the appropriate reading ability and can be answered with the assistance of the parent if necessary. For children who will not be able to answer the EQ-5D-Y will receive an EQ-5D-Y proxy version, to be answered by the parents on behalf of the child.

When considering the impact on the quality of life for the primary caregivers we will use both the EQ-5D questionnaire to quantify their temporary deterioration in health and a questionnaire that explores the logistical problems concerning illness for a child in the family. This will consider cancelled or rescheduled work and social arrangements, additional travelling to medical appointments for the child and any missed medical appointments for the parents or other family members. We wish to understand the impact on the primary caregivers both quantitatively and qualitatively.

The questionnaires that will be employed are:

Children

i) HRQoL for those directly affected by the outbreak

ii) Children attending secondary schools will receive the EQ-5D-Y. Children attending primary schools will receive the EQ-5D proxy version.

Adults

i) Response to a hypothetical school closure to all parents or guardians of children where an outbreak has occurred. This questionnaire will propose three scenarios for potential school closures – closure for one day, one week and four weeks, and will ask for the parents' or guardians' preferred arrangements for childcare in each scenario. We will also ask how much parents or guardians are willing to pay per day for childcare assistance, to enable them to attend work as normal during a school closure. 10-point Likert scales will ask parents or guardians to assess how disrupting the potential closures would be for them.

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) Questions will be asked for the parents or guardians to state their knowledge of the proposed programme and their attitudes towards it, including whether or not they would accept the offer of an annual influenza vaccination.

iv) Economic burden of the outbreak for those directly affected through their children's illness. Questions will be asked to quantify both direct and indirect costs of an outbreak within a school. Healthcare-seeking behaviour for parents or guardians of ill children will be examined along with the number of people involved in providing childcare. We will ask for the number of both paid and unpaid days off work needed to provide childcare from anyone who helped the parents or guardians. Finally we will ask for an estimate of the costs involved in providing this childcare from the perspective of the family.

RECRUITMENT METHOD

A local HPT in England will receive notification from a school of an outbreak. If the Head Teacher agrees, their contact details will be passed to the researchers at LSHTM so that a full discussion of the study can take place at a later time between the school and LSHTM. The local HPT will act as facilitator by sending the contact details to LSHTM. These details will be collected in a pro forma then sent to LSHTM via email.

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

If the school agrees to participate in the study then LSHTM will send the links to the online questionnaires to the school within one week of the notification. The links consist 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 need 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 will help facilitate participation of schools in this study. Because QALYs should be gathered as quickly as possible during an outbreak it is essential that the study packs are sent to the school soon after the notification of an outbreak. If schools can be recruited shortly after notification then this process is easier than if LSHTM approached schools separately without HPT involvement, perhaps weeks after notification was sent to the local HPT.

Without FES and HPT involvement in this study we would struggle to recruit sufficient schools to the study. Once a school has notified the HPT of the outbreak and expressed an interest in participating then the management of the schools involvement will be the responsibility of LSHTM who will invite 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 will be agreed in future 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

SAMPLE SIZE

A previous study using EQ-5D to examine the burden of H1N1 pandemic influenza [2] distributed HRQoL questionnaires to 655 patients. 287 responses were returned (43.8%), of which 160 had complete HRQoL data (55.7% of returned responses).

We wish to test that the temporary deterioration in HRQoL caused by influenza is greater than 0. The previous study on this matter reported a mean QALY-loss of 0.008 and the standard deviation of the measurement is 0.01. Using the values of the mean and standard deviation in conjunction with our plan for a 95% confidence interval and power of 80% we need a returned and successfully completed minimum sample of 24 questionnaires across all schools recruited to the study for meaningful results in the HRQoL analysis.

Assuming a response rate of 20 – 40% with 50% of these successfully completed for the purpose of calculating HRQoL loss, we must distribute a minimum of 120 – 240 questionnaires. If we can successfully recruit 5 schools to the study then we need to distribute 24 – 48 questionnaires to each school. Our plan, however, is to distribute several hundred questionnaires to each school as we cannot guarantee how many schools will be affected by an ILI outbreak during this flu season, or the flu season of next year.

However, to achieve a representative sample of the population of school-age children and their parents or guardians we must sample from a total population of 2,957,600 school-age children (ONS mid-2011 estimates) in the geographical area of interest. Assuming that 5 schools are successfully recruited to the study and a return rate of 20 – 40%, to achieve a result within 5% of the population value for the metrics of interest (time off work, willingness-to-pay for childcare, potential vaccine uptake, etc.) we must sample 615 – 1,230 families in total. Split across 5 clusters of equal size, this gives a total of 123 – 246 per school. This is more than the minimum number of responses needed for a meaningful result in the HRQoL analysis, therefore a sample size that facilitates useful results in all aspects of our study.

DELIVERY METHOD AND FOLLOW-UP

Online questionnaires will be sent by LSHTM to the schools in bulk within one week of the notification to the local HPT (delivery to participating boarding schools will be made within two weeks of notification). Head Teachers will email the links to parents or guardians at their convenience. Patient consent will be implied through the return of a completed questionnaire.

Parents or guardians who do not respond to the questionnaire will not be followed-up. Schools that choose not to participate in the study will not be followed-up. Schools that experience a low rate of return for the questionnaires will not be followed-up.

FINANCIAL INCENTIVES

No financial incentives will be given.

LANGUAGES

The questionnaires will only be available in English.

DATA MANAGEMENT

The final data files (as a csv file) will be stored as a Google Doc spreadsheet accessible only to Dominic Thorrington, the primary investigator based in LSHTM. The Google Doc spreadsheet will be downloaded to a secure network drive for analysis once data collection has ceased. Only the investigators based in LSHTM will have access to this file. No identifiable data will be returned on the questionnaires.

COLLECTED OUTCOME VARIABLES

The following information will be obtained from the sources listed below:

- Local HPT
    - Date of outbreak notification
    - Name of school reporting the outbreak
    - Address of school
    - Contact details for the Head Teachers
- Parents or guardians and children
    - See appendix A for the links to the online questionnaires.

SEVERITY BIAS

The most severe cases are perhaps more likely to respond, introducing a bias towards severe disease in our sample. In this scenario the health utilities obtained from the EQ-5D classification system may overestimate the impact of the outbreak on the children's health.

Data analysis

The key stages of data analysis will be:

- Cleaning the data
- Imputation of missing data
- Regression analysis

The data are likely to be clustered at school-level. This can be confirmed by testing for correlation between the data of each school. A suitable regression analysis that takes into account the potential clustered nature of the data will be a random effects regression model, assuming that the data within each cluster are dependent to a degree.

Our alternative options in this analysis are:

1) Ignore any clustering
2) Reduce clusters to independent observations
3) Use a fixed effects regression model

Option 1 is unsuitable. Option 2 reduces the number of observations to the number of schools recruited, which may be few. Option 3 leaves us with a model where the fixed effects apply only to our sample, rather than representative of the population that we wish to survey.

All data analysis will be done by Ken Eames and Dominic Thorrington at LSHTM.

Validation

Responses will be checked for internal consistency.

Dissemination of results

The results of this study will be submitted as a peer-reviewed publication (journal to be determined).

Ethical considerations

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 does

not have such approval to collect data on the financial burden suffered by families affected by the outbreak.

No identifiable data will be collected from parents or children in this study.

COLLABORATORS

- **Ken Eames** (Lecturer, London School of Hygiene and Tropical Medicine, London)
- **Dominic Thorrington** (PhD student, London School of Hygiene and Tropical Medicine, London)
- **Helen Maguire** (Consultant Medical Epidemiologist, Public Health England, London)
- **Sooria Balasegaram** (Consultant Medical Epidemiologist, Public Health England, London)
- **Anand Fernandes** (Consultant in Health Protection – Public Health England, Wessex Centre)
- **David Hagen** (Regional Influenza Lead – Public Health England, South East)
- **Eamonn o'Moore** (Consultant in Communicable Disease Control – Public Health England, London)
- **Anita Turley** (Regional Influenza Lead – Public Health England, London)

KE will be responsible for the overall management of the project and DT for all data analysis. The questionnaire was finalised in collaboration between KE, DT, HM and SB.

All authors will contribute to the writing of publications.

All data and materials generated during the study will remain the property of LSHTM.

TIMETABLE

Year	Month	Goal	Lead
2013	September	Ethics committee approval	KE, DT
2013-14	September - February	Recruitment of schools, data analysis and writing of manuscript	KE, DT, PHE
2014	March - May	Submission manuscript to journal	KE, DT

COSTS

As there will be no postage costs in the modified study, there will be no cost to LSHTM or LSHTM researchers for this study.

REFERENCES

1. Joint Committee on Vaccination and Immunisation (2012) Position statement on the annual influenza vaccination programme. Accessed 22 August 2014. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf.
2. van Hoek AJ, Underwood A, Jit M, Miller E and Edmunds WJ (2011) The impact of pandemic influenza h1n1 on health-related quality of life: A prospective population-based study. PLoS ONE, **6**(3): p. e17030.

QUESTIONNAIRES USED TO GATHER DATA FOR CHAPTER 4

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Public Health England

London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT

Tel: (UK) 020 7927 2247
E-mail: Dominic.Thorrington@lshtm.ac.uk

5th February 2014

Dear Parents or Guardians,

Survey on the impact of infectious disease outbreaks in schools on health and childcare

Recently there was an outbreak of an illness similar to flu at your child's school. For this reason we'd like to invite you to take part in an important study of the impact that infectious disease outbreaks in schools have on pupils and parents or guardians.

Why is the study being done?

The impact of outbreaks in schools can be felt in many ways – the impact on the children's health, the impact on the health of parents or guardians whose children's health suffers, additional childcare costs for families involved and disruption in the workplace. At the moment we don't know the full extent of this impact. This survey will help us understand these issues and find the best ways to prepare for them.

What information will be collected?

We would like to ask you about how you would arrange childcare in the event of your child's school closing on the next school day. How parents or guardians would arrange this childcare at short notice is important in helping us understand the possible disruption to your usual routine at home. We would also like to ask you about your attitude to vaccinations for your child. If your child was ill during the recent outbreak we would like to ask about their illness and how it affected you.

Do we have to take part?

No – it is entirely up to you and your child whether you take part or not. If you and your child do not want to take part then you do not need to return the questionnaire and you don't need to give a reason why.

What will I have to do to take part?

Please complete the questionnaire sent in this envelope then return them in the prepaid envelope to the London School of Hygiene and Tropical Medicine. You do not need to put a stamp on the envelope. Alternatively, the questionnaire can be completed online at http://bit.ly/1fhbIOz but please only complete the questionnaire once—either on paper on online.

How long will it take?

It should take no longer than 10 minutes to complete the questionnaire.

What will my child have to do to take part?

We have enclosed separate questions for you to answer with your child if they were ill during the recent outbreak. Please ask them if they want to take part. If they would like to take part then please complete the questions with them before returning everything together in the prepaid envelope. You and your child should not fill in these separate questions if they were not ill during the outbreak.

We do hope that you can help us. If you have any questions about this survey then you can contact us using the details listed at the top of this letter.

Yours sincerely,

Dominic Thorrington
PhD student
London School of Hygiene and Tropical Medicine

Dr. Ken Eames
Lecturer
London School of Hygiene and Tropical Medicine

Public Health England

Questionnaire for all parents or guardians

Details about you and your child

What is the name of your child's school? ☐

How old is your child? ☐ What school-year is your child in? ☐

What is your child's gender? (Please circle) Male / Female

What is your current family status? (Please tick one) Single parent ☐ Two parent family ☐

What is your current employment status?		If applicable, what is your partner's current employment status?	
Full-time employment ☐	Unemployed ☐	Full-time employment ☐	Unemployed ☐
Part-time/Casual/ Shift employment ☐	Retired ☐	Part-time/Casual/ Shift employment ☐	Retired ☐
Self-employed ☐	Student ☐	Self-employed ☐	Student ☐

Childcare arrangements if your child's school had to be closed in future outbreaks

We'd like to know what childcare arrangements you would consider if your child's school was closed for different periods of time, starting on the next school day. These different periods are one day, one week and four weeks.

We'd like to know what would be your **one main option**, then what other arrangements you might also consider, if any—**as many as you would like**. Please tick the boxes in the table below. We've completed an example to help.

Who would look after your child if school was closed?	Example		One day		One week		Four weeks	
	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)
A parent	☑	☐	☐	☐	☐	☐	☐	☐
An other family member	☐	☐	☐	☐	☐	☐	☐	☐
A friend	☐	☐	☐	☐	☐	☐	☐	☐
My child is able to stay at home alone	☐	☐	☐	☐	☐	☐	☐	☐
I'd pay for someone to look after my child	☐	☑	☐	☐	☐	☐	☐	☐
I don't know	☐	☐	☐	☐	☐	☐	☐	☐
Other (Please state below)	☐	☐	☐	☐	☐	☐	☐	☐

☐

With the options you've chosen above, would anyone need to take any time off work?

	Example		One day		One week		Four weeks	
	Main option	Other options	Main option	Other options	Main option	Other options	Main option	Other options
Yes	☑	☐	☐	☐	☐	☐	☐	☐
No	☐	☑	☐	☐	☐	☐	☐	☐

How disruptive would school closures be to your normal routine at home? On a scale of 0 to 10 with 0 meaning 'Not disruptive' and 10 meaning 'Very disruptive', please mark on the lines for each time period.

One day	One week	Four weeks
Not disruptive → Very disruptive	Not disruptive → Very disruptive	Not disruptive → Very disruptive
0 5 10	0 5 10	0 5 10

Please turn over →

Public Health England

Questionnaire for all parents or guardians (continued)

Do you consider your child to be old enough to stay at home unsupervised for many hours, such as when other family members are working/studying? (Please circle) Yes / No

If you needed to pay for someone to look after your child, how much would you expect to pay per day? £

Vaccinations

We'd like to know about your attitude to vaccination for your child.

If an annual flu vaccination was offered to all school children, like the flu vaccination that is available for older people and other at-risk groups, would you accept the offer? (Please circle) Yes / No

If you **would** accept the vaccine, would you prefer for the vaccine to be given to your child at school or at your local GP surgery? (Please tick one)

- At my child's school ☐
- At my local GP surgery ☐
- No preference ☐

If you **would not** accept the vaccine, please select as many of the options below as you wish to say why not : (Please tick)

- It is better to build your own natural immunity ☐
- I doubt that the vaccine is effective ☐
- Influenza is a minor illness ☐
- My child is unlikely to get influenza ☐
- Other (please state below) ☐
- I believe that the vaccine causes influenza ☐
- I am worried that the vaccine is not safe ☐
- I don't like my child having vaccinations ☐
- No particular reason ☐

Was your child ill during the recent outbreak at their school? (Please tick one)

- No ☐ → Please STOP HERE and return this questionnaire in the stamped addressed envelope provided
- Yes ☐ → Please continue the questionnaire

Did your child have any of the following symptoms during their illness? (Please tick all that apply)

- ☐ Fever
- ☐ Chills
- ☐ Runny or blocked nose
- ☐ Sneezing
- ☐ Sore throat
- ☐ Cough
- ☐ Shortness of breath
- ☐ Headache
- ☐ Muscle/Joint pain
- ☐ Chest pain
- ☐ Feeling tired or exhausted (malaise)
- ☐ Loss of appetite
- ☐ Coloured sputum/phlegm
- ☐ Watery, bloodshot eyes
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhoea
- ☐ Stomach ache
- ☐ Other

Please turn over only if your child was ill during the recent outbreak →

Public Health England

Questionnaire for children who were ill during the outbreak

Questions about your child's illness

For how many days was your child ill during the outbreak? ____ days

Has your child recovered from their illness yet? (Please circle) Yes / No

On which date did your child's illness start? (DD / MM / YYYY) ____ / ____ / ____

Because of your child's illness how many times did you contact any of the following?
(Please list the number of times for all that apply)

Phone or email NHS Direct / NHS 24 / NHS Choices		Hospital A&E department (including out of hours service)	
Phone or email GP - response from the receptionist			
Phone or email GP - response from the GP / Nurse		Other medical services	
Visit (face-to-face) a GP or nurse			

Childcare arrangements if your child was absent from school with illness

Was your child absent from school due to illness during the outbreak? (Please circle) Yes / No

If your child was not absent from school then please go straight to the Costs below this section

For how many days was your child absent from school with illness? ____ days

If your child has been absent from school, are they still absent from school with illness? (Please circle) Yes / No

How many different people looked after your child during their absence? ____

Please list how many different people looked after your child from the groups below. Please also state the total number of days they looked after your child, then the total number of paid and unpaid days off work (if any) for each group

	Number of people	Total number of days looking after your child	Total number of PAID days off work	Total number of UNPAID days off work
Parents/Guardians				
Other family member				
Friends				
Child minders				
Other (Please state)				

Costs

Please give an estimate of the total extra cost to yourself and to anyone else involved in looking after your child during their illness. These costs may include loss of wages due to days off work, extra travel costs, medicines, cost of any childcare arrangements, etc. (Please tick one box from each column)

	Cost to yourself	Cost to others involved
£0	☐	☐
£1 to £50	☐	☐
£51 to £100	☐	☐
£101 to £150	☐	☐
£151 to £200	☐	☐
£201 to £250	☐	☐
Over £250	☐	☐

Please turn over →

Public Health England

Questionnaire for children who were ill during the outbreak

We'd like to ask you about how your child's illness affected their health. Please complete the questions below relating to how they felt on the worst day of your their illness, then how they're feeling today.

Describing the child's health ON THE WORST DAY

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think the child would mark to describe his/her own health ON THE WORST DAY if he/she were able to do so.

Mobility *(walking about)*
- He/she had no problems walking about ☐
- He/she had some problems walking about ☐
- He/she had a lot of problems walking about ☐

Looking after myself
- He/she had no problems washing or dressing him/herself ☐
- He/she had some problems washing or dressing him/herself ☐
- He/she had a lot of problems washing or dressing him/herself ☐

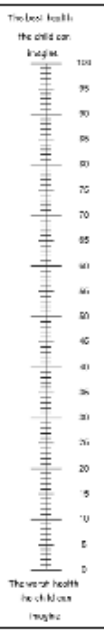
Usual activities *(e.g. work, study, housework, family or leisure activities*
- He/she had no problems doing his/her usual activities ☐
- He/she had some problems doing his/her usual activities ☐
- He/she had a lot of problems doing his/her usual activities ☐

Having pain or discomfort
- He/she had no pain or discomfort ☐
- He/she had some pain or discomfort ☐
- He/she had a lot of pain or discomfort ☐

Feeling worried, sad or unhappy
- He/she was not worried, sad or unhappy ☐
- He/she was a bit worried, sad or unhappy ☐
- He/she was very worried, sad or unhappy ☐

How good was the health of the child ON THE WORST DAY?

- We would like to know how good or bad you think the child would rate his/her own health on the WORST day
- This line is numbered from 0 to 100
- 100 means the best health the child can imagine
- 0 means the worst health the child can imagine
- Please, mark an X on the line that shows how good or bad the child would rate his/her health was on the WORST day



Describing the child's health TODAY

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think the child would mark to describe his/her own health TODAY if he/she were able to do so.

Mobility *(walking about)*
- He/she has no problems walking about ☐
- He/she has some problems walking about ☐
- He/she has a lot of problems walking about ☐

Looking after myself
- He/she has no problems washing or dressing him/herself ☐
- He/she has some problems washing or dressing him/herself ☐
- He/she has a lot of problems washing or dressing him/herself ☐

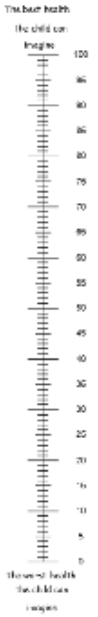
Usual activities *(e.g. work, study, housework, family or leisure activities*
- He/she has no problems doing his/her usual activities ☐
- He/she has some problems doing his/her usual activities ☐
- He/she has a lot of problems doing his/her usual activities ☐

Having pain or discomfort
- He/she has no pain or discomfort ☐
- He/she has some pain or discomfort ☐
- He/she has a lot of pain or discomfort ☐

Feeling worried, sad or unhappy
- He/she is not worried, sad or unhappy ☐
- He/she is a bit worried, sad or unhappy ☐
- He/she is very worried, sad or unhappy ☐

How good is the health of the child TODAY?

- We would like to know how good or bad you think the child would rate his/her health TODAY
- This line is numbered from 0 to 100
- 100 means the best health the child can imagine
- 0 means the worst health the child can imagine
- Please, mark an X on the line that shows how good or bad you think the child would rate his/her health TODAY



Please now return the questionnaire in the prepaid envelope provided

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Public Health England

London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT

Tel: (UK) 020 7927 2247
E-mail: Dominic.Thorrington@lshtm.ac.uk

19 September 2013

Dear Parents or Guardians,

Survey on the impact of infectious disease outbreaks in schools on health and childcare

Recently there was an outbreak of an illness similar to flu at your child's school. For this reason we'd like to invite you to take part in an important study of the impact that infectious disease outbreaks in schools have on pupils and parents or guardians.

Why is the study being done?

The impact of outbreaks in schools can be felt in many ways – the impact on the children's health, the impact on the health of parents or guardians whose children's health suffers, additional childcare costs for families involved and disruption in the workplace. At the moment we don't know the full extent of this impact. This survey will help us understand these issues and find the best ways to prepare for them.

What information will be collected?

We would like to ask you about how you would arrange childcare in the event of your child's school closing on the next school day. How parents or guardians would arrange this childcare at short notice is important in helping us understand the possible disruption to your usual routine at home. We would also like to ask you about your attitude to vaccinations for your child. If your child was ill during the recent outbreak we would like to ask about their illness and how it affected you.

Do we have to take part?

No – it is entirely up to you and your child whether you take part or not. If you and your child do not want to take part then you do not need to return the questionnaire and you don't need to give a reason why.

What will I have to do to take part?

Please complete the questionnaire sent in this envelope then return them in the prepaid envelope to the London School of Hygiene and Tropical Medicine. You do not need to put a stamp on the envelope.

How long will it take?

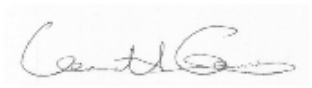
It should take no longer than 10 minutes to complete the questionnaire.

What will my child have to do to take part?

We have enclosed separate questions for your child to fill in if they were ill during the recent outbreak. Please ask them if they want to take part. If they would like to take part then please let them complete the questions before returning everything together in the prepaid envelope. Your child should not fill in the questionnaire if they were not ill during the outbreak.

We do hope that you can help us. If you have any questions about this survey then you can contact us using the details listed at the top of this letter.

Yours sincerely,



Dominic Thorrington
PhD student
London School of Hygiene and Tropical Medicine

Dr. Ken Eames
Lecturer
London School of Hygiene and Tropical Medicine

Public Health England

Questionnaire for all parents or guardians

Details about you and your child

What is the name of your child's school? ☐

How old is your child? ☐ What school-year is your child in? ☐

What is your child's gender? (Please circle) Male / Female

What is your current family status? (Please tick one) Single parent ☐ Two parent family ☐

What is your current employment status?				If applicable, what is your partner's current employment status?			
Full-time employment	☐	Unemployed	☐	Full-time employment	☐	Unemployed	☐
Part-time/Casual/ Shift employment	☐	Retired	☐	Part-time/Casual/ Shift employment	☐	Retired	☐
Self-employed	☐	Student	☐	Self-employed	☐	Student	☐

Childcare arrangements if your child's school had to be closed in future outbreaks

We'd like to know what childcare arrangements you would consider if your child's school was closed for different periods of time, starting on the next school day. These different periods are one day, one week and four weeks.

We'd like to know what would be your **one main option**, then what other arrangements you might also consider, if any—**as many as you would like**. Please tick the boxes in the table below. We've completed an example to help.

Who would look after your child if school was closed?	Example		One day		One week		Four weeks	
	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)	Main option (tick one)	Other options (tick any others)
A parent	✓	☐	☐	☐	☐	☐	☐	☐
An other family member	☐	☐	☐	☐	☐	☐	☐	☐
A friend	☐	☐	☐	☐	☐	☐	☐	☐
My child is able to stay at home alone	☐	☐	☐	☐	☐	☐	☐	☐
I'd pay for someone to look after my child	☐	✓	☐	☐	☐	☐	☐	☐
I don't know	☐	☐	☐	☐	☐	☐	☐	☐
Other (Please state below)	☐	☐	☐	☐	☐	☐	☐	☐

☐

With the options you've chosen above, would anyone need to take any time off work?

	Example		One day		One week		Four weeks	
	Main option	Other options	Main option	Other options	Main option	Other options	Main option	Other options
Yes	✓	☐	☐	☐	☐	☐	☐	☐
No	☐	✓	☐	☐	☐	☐	☐	☐

How disruptive would school closures be to your normal routine at home? On a scale of 0 to 10 with 0 meaning 'Not disruptive' and 10 meaning 'Very disruptive', please mark on the lines for each time period.

One day	One week	Four weeks
Not disruptive — Very disruptive	Not disruptive — Very disruptive	Not disruptive — Very disruptive
0 5 10	0 5 10	0 5 10

Please turn over →

Public Health England

Questionnaire for all parents or guardians (continued)

Do you consider your child to be old enough to stay at home unsupervised for many hours, such as when other family members are working/studying? (Please circle) **Yes / No**

If you needed to pay for someone to look after your child, how much would you expect to pay per day? **£**

Vaccinations

We'd like to know about your attitude to vaccination for your child.

If an annual flu vaccination was offered to all school children, like the flu vaccination that is available for older people and other at-risk groups, would you accept the offer? (Please circle) **Yes / No**

If you **would** accept the vaccine, would you prefer for the vaccine to be given to your child at school or at your local GP surgery? (Please tick one)

- ☐ At my child's school
- ☐ At my local GP surgery
- ☐ No preference

If you **would not** accept the vaccine, please select as many of the options below as you wish to say why not : (Please tick)

- ☐ It is better to build your own natural immunity
- ☐ I doubt that the vaccine is effective
- ☐ Influenza is a minor illness
- ☐ My child is unlikely to get influenza
- ☐ Other (please state below)
- ☐ I believe that the vaccine causes influenza
- ☐ I am worried that the vaccine is not safe
- ☐ I don't like my child having vaccinations
- ☐ No particular reason

Was your child ill during the recent outbreak at their school? (Please tick one)

- ☐ No → Please STOP HERE and return this questionnaire in the stamped addressed envelope provided
- ☐ Yes → Please continue the questionnaire

Did your child have any of the following symptoms during their illness? (Please tick all that apply)

- ☐ Fever
- ☐ Chills
- ☐ Runny or blocked nose
- ☐ Sneezing
- ☐ Sore throat
- ☐ Cough
- ☐ Shortness of breath
- ☐ Headache
- ☐ Muscle/Joint pain
- ☐ Chest pain
- ☐ Feeling tired or exhausted (malaise)
- ☐ Loss of appetite
- ☐ Coloured sputum/phlegm
- ☐ Watery, bloodshot eyes
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhoea
- ☐ Stomach ache
- ☐ Other

Please turn over only if your child was ill during the recent outbreak →

Public Health England

Questionnaire for children who were ill during the outbreak

Questions about your child's illness

For how many days was your child ill during the outbreak? ____ days

Has your child recovered from their illness yet? (Please circle) Yes / No

On which date did your child's illness start? (DD / MM / YYYY) ____ / ____ / ____

Because of your child's illness how many times did you contact any of the following?
(Please list the number of times for all that apply)

- Phone or email NHS Direct / NHS 24 / NHS Choices ☐
- Phone or email GP - response from the receptionist ☐
- Phone or email GP - response from the GP / Nurse ☐
- Visit (face-to-face) a GP or nurse ☐
- Hospital A&E department (including out of hours service) ☐
- Other medical services ☐

Childcare arrangements if your child was absent from school with illness

Was your child absent from school due to illness during the outbreak? (Please circle) Yes / No

If your child was not absent from school then please go straight to the Costs below this section

For how many days was your child absent from school with illness? ____ days

If your child has been absent from school, are they still absent from school with illness? (Please circle) Yes / No

How many different people looked after your child during their absence? ____

Please list how many different people looked after your child from the groups below. Please also state the total number of days they looked after your child, then the total number of paid and unpaid days off work (if any) for each group

	Number of people	Total number of days looking after your child	Total number of PAID days off work	Total number of UNPAID days off work
Parents/Guardians				
Other family member				
Friends				
Child minders				
Other (Please state)				

Costs

Please give an estimate of the total extra cost to yourself and to anyone else involved in looking after your child during their illness. These costs may include loss of wages due to days off work, extra travel costs, medicines, cost of any childcare arrangements, etc. (Please tick one box from each column)

	Cost to yourself	Cost to others involved
£0	☐	☐
£1 to £50	☐	☐
£51 to £100	☐	☐
£101 to £150	☐	☐
£151 to £200	☐	☐
£201 to £250	☐	☐
Over £250	☐	☐

Please turn over →

Public Health England

Questionnaire for children who were ill during the outbreak

We'd like to ask you about how your child's illness affected their health. Please help them to answer the questions below relating to how they felt on the worst day of your their illness, then how they're feeling today.

Describing your health for the WORST DAY of your illness

Under each heading, mark the ONE box that best describes your health for the WORST day.

Mobility *(walking about)*
- I had no problems walking about ☐
- I had some problems walking about ☐
- I had a lot of problems walking about ☐

Looking after myself
- I had no problems washing or dressing myself ☐
- I had some problems washing or dressing myself ☐
- I had a lot of problems washing or dressing myself ☐

Usual activities *(e.g. work, study, housework, family or leisure activities*
- I had no problems doing my usual activities ☐
- I had some problems doing my usual activities ☐
- I had a lot of problems doing my usual activities ☐

Having pain or discomfort
- I had no pain or discomfort ☐
- I had some pain or discomfort ☐
- I had a lot of pain or discomfort ☐

Feeling worried, sad or unhappy
- I was not worried, sad or unhappy ☐
- I was a bit worried, sad or unhappy ☐
- I was very worried, sad or unhappy ☐

How good was your health on the WORST DAY of your illness?

- We would like to know how good or bad your health was on the WORST day
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
- 0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health was on the WORST day

Describing your health TODAY

Under each heading, mark the ONE box that best describes your health TODAY.

Mobility *(walking about)*
- I have no problems walking about ☐
- I have some problems walking about ☐
- I have a lot of problems walking about ☐

Looking after myself
- I have no problems washing or dressing myself ☐
- I have some problems washing or dressing myself ☐
- I have a lot of problems washing or dressing myself ☐

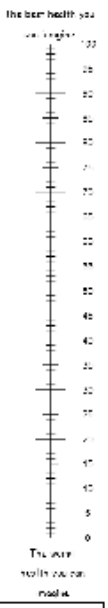
Usual activities *(e.g. work, study, housework, family or leisure activities*
- I have no problems doing my usual activities ☐
- I have some problems doing my usual activities ☐
- I have a lot of problems doing my usual activities ☐

Having pain or discomfort
- I have no pain or discomfort ☐
- I have some pain or discomfort ☐
- I have a lot of pain or discomfort ☐

Feeling worried, sad or unhappy
- I am not worried, sad or unhappy ☐
- I am a bit worried, sad or unhappy ☐
- I am very worried, sad or unhappy ☐

How good is your health TODAY?

- We would like to know how good or bad your health is TODAY
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
- 0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health is TODAY



Please now return the questionnaire in the prepaid envelope provided

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Public Health England

Health Protection Teams pro forma

Study on the impact of infectious disease outbreaks in schools

Please inform each notifying school of our study. Please complete the information in the box at the side of this notice.

The study is being conducted with the London School of Hygiene and Tropical Medicine. It is an important study as it will help us to understand the financial and health-related consequences of outbreaks in schools.

If the Head Teacher is willing to hear more about the study then Dominic Thorrington from the London School of Hygiene and Tropical Medicine will contact them shortly for a full discussion.

Note:
This study will not be conducted in special needs education establishments so please do not invite them to participate.

Please send all details to Dominic Thorrington and Ken Eames at the London School of Hygiene and Tropical Medicine:

Dominic.Thorrington@LSHTM.ac.uk
Ken.Eames@LSHTM.ac.uk

Date today
_____

Date of outbreak notification
_____

Name of school reporting the outbreak
_____

Address of school reporting the outbreak
_____
_____
_____
_____
_____

Name of Head Teacher
_____

Telephone number of Head Teacher
_____

Email address of Head Teacher
_____

Number of pupils
_____

R SCRIPTS FOR MATHEMATICAL MODELS USED IN CHAPTER 5

MAIN MODEL SCRIPT

```
#############################################################################################################
# Discrete time SEIR model
#
# Attempt 1: age-structured population, deterministic parameters, 1 patch
#          with age-heterogeneous vaccination coverage
#
# Dom Thorrington 28/02/2014
#############################################################################################################

datestamp <- 20150706

# For progress bar
#install.packages("tcltk")
#install.packages("tcltk2")
require(tcltk)
require(tcltk2)

# Set location
location <- 1  # 1 = Office
# 2 = Home

if (location==1){
  setwd("C:/Users/lsh337197/Dropbox/PhD guff/R stuff/Discrete time SEIR/31 patch/Project/4.0 Agg ext split sch/2.0 5 age groups/Deterministic/Targeting paper")
} else {
  setwd("C:/Users/Laptop/Dropbox/PhD guff/R stuff/Discrete time SEIR/31 patch/Project/4.0 Agg ext split sch/2.0 5 age groups/Deterministic/Targeting paper")
}

#############################################################################################################
# Prepare output file
#############################################################################################################

dataframerow <- 0
overestimate <- 1250        # upper limit of the number of rows in the dataframe
Epidemic_results <- data.frame(Simulation=rep(NA,overestimate),    # Record the simulation number for the conditions set
                      R0=rep(NA,overestimate),
                      privac=rep(NA,overestimate),
                      secvac=rep(NA,overestimate),
                      finalsize1=rep(NA,overestimate),
                      finalsize2=rep(NA,overestimate),
                      finalsize3=rep(NA,overestimate),
                      finalsize4=rep(NA,overestimate),
                      finalsize5=rep(NA,overestimate),
                      finalsize=rep(NA,overestimate),
                      Vaccinated1=rep(NA,overestimate),
                      Vaccinated2=rep(NA,overestimate),
                      Vaccinated3=rep(NA,overestimate),
                      Vaccinated4=rep(NA,overestimate),
                      Vaccinated5=rep(NA,overestimate),
                      stringsAsFactors=F)

# Start progress bar
masterpb <- winProgressBar(title="Running simulations", label="0% done", min=0, max=100, initial=0)

#############################################################################################################
# Run simulations to put final size into matrix
#############################################################################################################

# General parameters - R0, beta, etc.
source('Parameters.R')

timeseries_m    <- matrix(0, nrow = overestimate, ncol = nsteps)

for (LHS in 1:overestimate){
# for (privac in seq(from=0.00, to=1.00, by=0.01)){
#    for (secvac in seq(from=0.00, to=1.00, by=0.01)){

  privac <- 0.42
  secvac <- 0.42

  dataframerow <- dataframerow + 1
  Sys.sleep(0.1) # slow down the progress bar code for illustration purposes
  info <- sprintf("%f%% done", round(dataframerow/overestimate,2)*100)
  setWinProgressBar(masterpb, round(dataframerow/overestimate,2)*100, label=info)

# Uptake of vaccine according to new JCVI guidance
uptake_gen <- c(0,   # uptake of 0-3
            privac,   # uptake of 4-10   ***
            secvac,   # uptake of 11-16   ***
            0,   # uptake of 17-64
            0)   # uptake of 65+
```

```
# Overall coverage
vacc_coverage <- numeric(0)
for (i in 1:nage){
 vacc_coverage[i] <- c(1-((uptake_risk[i]*risk_groups[i])+(uptake_gen[i]*(1-uptake_risk[i]*risk_groups[i]))))
}

#############################################################################################################
# Setting population lists before model
#############################################################################################################

# Initialise population lists
S <- numeric(0) # Susceptible
E <- numeric(0) # Exposed
I <- numeric(0) # Infectious
R <- numeric(0) # Recovered
V <- numeric(0) # Effectively vaccinated
W <- numeric(0) # Vaccinated in total
A <- numeric(0) # Prior immunity through antibodies
N <- numeric(0) # S+E+I+R+V

#seed_age <- sample(1:nage,1,replace=T) # randomly choose age group to seed:
seed_age <- 2                    # seed the primary school age group

# Structure of infected population
I <- c(rep(0,nage))

I[seed_age] <- seed

# Structure of incubated population
E <- c(rep(0,nage))

# Structure of recovered population
R <- c(rep(0,nage))

# Structure of population with prior immunity
A <- round(ageSize* c(1-LHS_results$A1[LHS],   #0.7837
                      1-LHS_results$A2[LHS],   #0.8943
                      1-LHS_results$A3[LHS],   #0.9819
                      1-LHS_results$A4[LHS],   #0.9496
                      1-LHS_results$A5[LHS]))  #0.9736

# Structure of susceptible and vaccinated populations
for (i in 1:nage){
 W[i] <- round(ageSize[i]*(1-vacc_coverage[i]))          # All vaccinations
 V[i] <- round(ageSize[i]*(1-vacc_coverage[i])*vac_eff[i]) # All effective vaccinations
 S[i] <- ageSize[i] - V[i] - A[i]
}

# Remove the seed from S
S <- S - I

# Set up N
N <- S + E + I + R + V + A

#############################################################################################################
# Model
#############################################################################################################
age_timeseries   <- matrix(0, nrow = nage, ncol = nsteps)
timeseries_v     <- numeric()
Re <- matrix(ncol=nage,nrow=nsteps) # Matrix for effective reproduction number results

for (k in 1:nsteps){

 # Next generation stuff
 NGM <- contacts*beta*(1/gamma)*(1/ageSize)*S
 EVs <- eigen(NGM)
 Re[k,] <- EVs$values

 ########################################
 # Break criteria for stochastic fadeout
 ########################################

 break_criteria <- FALSE

 if ((sum(E)+sum(I))==0){       # Criteria is that no more individuals exist
  break_criteria <- TRUE        # in model to transmit infection further
 }

 if (break_criteria==TRUE){
  break
 }

 FoI  <- numeric(0)
 Case <- numeric(0)
 Infe <- numeric(0)
 Reco <- numeric(0)

 FoI <- (beta)*(contacts%*%(I/N))
```

```
 # Calculate Case, Infe and Reco
 for (i in 1:nage){
  if (S[i]>0){
   Case[i] <- S[i]*step*FoI[i]
  } else {
   Case[i] <- 0
  }
  if (E[i]!=0){
   Infe[i]<- E[i]*step*delta
  } else {
   Infe[i] <- 0
  }
  if (I[i]!=0){
   Reco[i] <- I[i]*step*gamma
  } else {
   Reco[i] <- 0
  }
 }

 # Calculate and execute movement between compartments
 S <- S - Case
 E <- E - Infe + Case
 I <- I - Reco + Infe
 R <- R + Reco

 # Time series for each age group
 age_timeseries[,k] <- I
 timeseries_v[k] <- sum(age_timeseries[,k])
}

##################################################################################################
# Final size statistics
##################################################################################################

# Final size
finalsize <- R/N
overallfinalsize <- sum(R)/sum(N)
timeseries_m[LHS,] <- timeseries_v

# Append results to the data frame
Epidemic_results[dataframerow,] <- c(dataframerow,
                        R0,
                        privac,
                        secvac,
                        finalsize[1],
                        finalsize[2],
                        finalsize[3],
                        finalsize[4],
                        finalsize[5],
                        overallfinalsize,
                        W[1],
                        W[2],
                        W[3],
                        W[4],
                        W[5])

#} # End privac
#} # End secvac
} # End LHS

##################################################################################################
# Export the created data frame and close progress bar
##################################################################################################

# write.table(Epidemic_results, row.names=F, col.names=T,
#           file=paste(datestamp, ", privac, Epidemic results output.csv", sep=""))

##################################################################################################
# Plots
##################################################################################################

# # Plot by age group
# plot(age_timeseries[1,]/ageSize[1],
#     type="o",
#     col=2,
#     lwd=5,
#     xaxt="n",
#     xlab="Time steps (days)",
#     ylab="Fraction infected",
#     ylim=c(0,1.1*max(c(age_timeseries[1,]/ageSize[1],
#                     age_timeseries[2,]/ageSize[2],
#                     age_timeseries[3,]/ageSize[3],
#                     age_timeseries[4,]/ageSize[4],
#                     age_timeseries[5,]/ageSize[5]))),
#     xlim=c(0,3650),
#     cex.main=1.5,
#     cex.axis=1.5,
```

```
#     cex.lab=1.5
#     #main=paste("1 patch deterministic model \nWith age-heterogeneous vaccination, total population of ",sum(ageSize),sep="")
#     )
# axis(1, at=c(1000,2000,3000), labels=c(100,200,300), cex.axis=1.5)
# lines(age_timeseries[2,]/ageSize[2],type="o",col=3,lwd=7)
# lines(age_timeseries[3,]/ageSize[3],type="o",col=4,lwd=5)
# lines(age_timeseries[4,]/ageSize[4],type="o",col=5,lwd=5)
# lines(age_timeseries[5,]/ageSize[5],type="o",col=6,lwd=5)
# legend("topright",
#       legend=c("0 - 3 years",
#                "4 - 10",
#                "11 - 16",
#                "17 - 64",
#                "65+"),
#       col=c(2,3,4,5,6),
#       bty="n",
#       lwd=8,
#       cex=1.5)


# # Plot overall time series
# plot(timeseries_m[1251,]/sum(ageSize),
#     type="o",
#     col="gray95",
#     lwd=5,
#     xaxt="n",
#     xlab="Time steps (days)",
#     ylab="Fraction infected",
#     ylim=c(0,1.1*max(timeseries_m)/sum(ageSize)),
#     xlim=c(0,3650),
#     cex.main=1.5,
#     cex.axis=1.5,
#     cex.lab=1.5
#     #main=paste("1 patch deterministic model \nWith age-heterogeneous vaccination, total population of ",sum(ageSize),sep="")
# )
# axis(1, at=c(1000,2000,3000), labels=c(100,200,300), cex.axis=1.5)
#
# for (i in 1251:2500){
#   lines(timeseries_m[i,]/sum(ageSize),type="l",col="gray90",lwd=8)
# }
# for (i in 251:1250){
#   lines(timeseries_m[i,]/sum(ageSize),type="l",col="gray80",lwd=8)
# }
# for (i in 2:250){
#   lines(timeseries_m[i,]/sum(ageSize),type="l",col="gray60",lwd=8)
# }
# lines(timeseries_m[1,]/sum(ageSize),type="l",col="black",lwd=8)
#
# legend("topright",
#       legend=c("Best fit",
#                "Best fitting 1%",
#                "Best fitting 5%",
#                "Best fitting 10%"),
#       col=c("black","gray60","gray80","gray90"),
#       bty="n",
#       lwd=8,
#       cex=1.5)

# # Plot calibrated parameter spread
# hist(LHS_results$A1[1:1250],
#     main="Susceptibility, 0-3 years",
#     xlab="Proportion of population susceptible",
#     ylab="",
#     col="orangered")
# hist(LHS_results$A2[1:1250],
#     main="Susceptibility, 4-10 years",
#     xlab="Proportion of population susceptible",
#     ylab="",
#     col="orangered")
# hist(LHS_results$A3[1:1250],
#     main="Susceptibility, 11-16 years",
#     xlab="Proportion of population susceptible",
#     ylab="",
#     col="orangered")
# hist(LHS_results$A4[1:1250],
#     main="Susceptibility, 17-64 years",
#     xlab="Proportion of population susceptible",
#     ylab="",
#     col="orangered")
# hist(LHS_results$A5[1:1250],
#     main="Susceptibility, 65+ years",
#     xlab="Proportion of population susceptible",
#     ylab="",
#     col="orangered")
#
# install.packages("GGally")
# install.packages("digest")
# install.packages("proto")
```

```
# install.packages("reshape2")
# install.packages("colorspace")
# install.packages("labeling")
#
# require(GGally)
# require(digest)
# require(proto)
# require(reshape2)
# require(colorspace)
# require(labeling)
#
# library(GGally)
# library(digest)
# library(proto)
# library(reshape2)
# library(colorspace)
# library(labeling)
#
# # Temporary re-labelling of columns in dataframe
# names(LHS_results)[5] <- "Preschool"
# names(LHS_results)[6] <- "Primary"
# names(LHS_results)[7] <- "Secondary"
# names(LHS_results)[8] <- "Adult"
# names(LHS_results)[9] <- "Elderly"
#
# # colfunc <- colorRampPalette(c("black", "red"))
# # colfunc(10)
#
# # Best 1% fit
# ggpairs(LHS_results[1:250,5:9],
#         diag=list(continuous="bar",params=c(binwidth = 0.013,col=2)),
#         title="Calibrated parameters, best 1%",
#         upper="blank",
#         lower=list(params=c(col="orangered")))
#
# # Best 5% fit
# ggpairs(LHS_results[1:1250,5:9],
#         diag=list(continuous="bar",params=c(binwidth = 0.013,col=2)),
#         title="Calibrated parameters, best 5%",
#         upper="blank",
#         lower=list(params=c(col="orangered")))
#
# # Best 10% fit
# ggpairs(LHS_results[1:2500,5:9],
#         diag=list(continuous="bar",params=c(binwidth = 0.013,col=2)),
#         title="Calibrated parameters, best 10%",
#         upper="blank",
#         lower=list(params=c(col="orangered")))
#
#
# # Re-labelling of columns in dataframe
# names(LHS_results)[5] <- "A1"
# names(LHS_results)[6] <- "A2"
# names(LHS_results)[7] <- "A3"
# names(LHS_results)[8] <- "A4"
# names(LHS_results)[9] <- "A5"

##################################################################################################
# Run economic evaluation
##################################################################################################

source('EconAnalysis.R')

##################################################################################################
# Update results .csv file
##################################################################################################

write.table(Epidemic_results, row.names=F, col.names=T,
          file=paste(datestamp, ", hom 5pc, Epidemic results output.csv", sep=""))

close(masterpb) # Close the master progress bar

# # Vaccinations vs. final size
# par(mfrow=c(2,1))
# plot(finalsize_data$consvac,finalsize_data$c_fs,
#      xlab="Vaccination coverage",
#      ylab="Overall final size",
#      pch=19,
#      col=9,
#      lwd=1,
#      cex.lab=1.3,
#      cex.axis=1.3)
# lines(finalsize_data$consvac,finalsize_data$c_fs,pch=19,col=9,lwd=10)
# lines(finalsize_data$privac,finalsize_data$p_fs,pch=19,col=3,lwd=10)
# lines(finalsize_data$secvac,finalsize_data$s_fs,pch=19,col=4,lwd=10)
# legend("topright",
#        legend=c("Both primary and secondary",
#                 "Primary school only",
```

```
#             "Secondary school only"),
#       col=c(9,3,4),
#       bty="n",
#       lwd=6,
#       cex=1.3)
#
# plot(finalsize_data$c_vacc,finalsize_data$c_fs,
#      xlab="Number of vaccinations",
#      ylab="Overall final size",
#      pch=19,
#      col=9,
#      lwd=1,
#      cex.lab=1.3,
#      cex.axis=1.3)
# lines(finalsize_data$c_vacc,finalsize_data$c_fs,pch=19,col=9,lwd=10)
# lines(finalsize_data$p_vacc,finalsize_data$p_fs,pch=19,col=3,lwd=10)
# lines(finalsize_data$s_vacc,finalsize_data$s_fs,pch=19,col=4,lwd=10)
# legend("topright",
#       legend=c("Both primary and secondary",
#             "Primary school only",
#             "Secondary school only"),
#       col=c(9,3,4),
#       bty="n",
#       lwd=6,
#       cex=1.3)
#
# # QALYs obtained per vaccination
# plot(QALYperVacc$consvac,QALYperVacc$c_QALYs_per_Vacc,
#      xlab="Vaccination coverage",
#      ylab="QALYs gained per vaccination",
#      pch=19,
#      col=9,
#      lwd=10,
#      cex.lab=1.5,
#      cex.axis=1.5)
# lines(QALYperVacc$consvac,QALYperVacc$c_QALYs_per_Vacc,pch=19,col=9,lwd=15)
# lines(QALYperVacc$privac,QALYperVacc$p_QALYs_per_Vacc,pch=19,col=3,lwd=15)
# lines(QALYperVacc$secvac,QALYperVacc$s_QALYs_per_Vacc,pch=19,col=4,lwd=15)
# abline(v=QALYperVacc$consvac[which.max(QALYperVacc$c_QALYs_per_Vacc)],col=9)
# abline(v=QALYperVacc$privac[which.max(QALYperVacc$p_QALYs_per_Vacc)],col=3)
# abline(v=QALYperVacc$secvac[which.max(QALYperVacc$s_QALYs_per_Vacc)],col=4)
# legend("topright",
#       legend=c("Homogeneous vaccination",
#             "Primary school only",
#             "Secondary school only"),
#       col=c(9,3,4),
#       lwd=6,
#       cex=1.5,
#       bg="white")
#
# # Comparing metrics using coverage
# options(scipen=10)
# par(mfrow=c(2,2))
# # 1 - Costs
# plot(CovComp$consvac[CovComp$consvac>0],(1/1000000)*CovComp$Cost_c[CovComp$consvac>0],
#      main="1 - Total costs",
#      xlab="Vaccination coverage",
#      ylab="Costs (£m)",
#      pch=19,
#      col=9,
#      lwd=7,
#      cex.lab=1.5,
#      cex.axis=1.5)
# lines(CovComp$consvac[CovComp$consvac>0],(1/1000000)*CovComp$Cost_c[CovComp$consvac>0],col=9,lwd=10)
# lines(CovComp$privac[CovComp$privac>0],(1/1000000)*CovComp$Cost_p[CovComp$privac>0],pch=19,col=3,lwd=10)
# lines(CovComp$secvac[CovComp$secvac>0],(1/1000000)*CovComp$Cost_s[CovComp$secvac>0],pch=19,col=4,lwd=10)
#
# # 2 - QALYs over baseline
# plot(CovComp$consvac[CovComp$consvac>0],CovComp$QALYs_c[CovComp$consvac>0],
#      main="2 - QALYs lost",
#      xlab="Vaccination coverage",
#      ylab="QALYs lost due to influenza",
#      pch=19,
#      col=9,
#      lwd=7,
#      cex.lab=1.5,
#      cex.axis=1.5)
# lines(CovComp$consvac[CovComp$consvac>0],CovComp$QALYs_c[CovComp$consvac>0],col=9,lwd=10)
# lines(CovComp$privac[CovComp$privac>0],CovComp$QALYs_p[CovComp$privac>0],pch=19,col=3,lwd=10)
# lines(CovComp$secvac[CovComp$secvac>0],CovComp$QALYs_s[CovComp$secvac>0],pch=19,col=4,lwd=10)
#
# # 3 - ICER
# plot(CovComp$consvac[CovComp$consvac>0],(1/1000)*CovComp$ICER_c[CovComp$consvac>0],
#      main="3 - ICER",
#      xlab="Vaccination coverage",
#      ylab="ICER (£thou)",
#      pch=19,
#      col=9,
```

```
#     lwd=7,
#     cex.lab=1.5,
#     cex.axis=1.5,
#     ylim=c(0,20))
# lines(CovComp$consvac[CovComp$consvac>0],(1/1000)*CovComp$ICER_c[CovComp$consvac>0],col=9,lwd=10)
# lines(CovComp$privac[CovComp$privac>0],(1/1000)*CovComp$ICER_p[CovComp$privac>0],pch=19,col=3,lwd=10)
# lines(CovComp$secvac[CovComp$secvac>0],(1/1000)*CovComp$ICER_s[CovComp$secvac>0],pch=19,col=4,lwd=10)
#
# # 4 - Deaths averted over baseline
# plot(CovComp$consvac[CovComp$consvac>0],CovComp$Deaths_c[CovComp$consvac>0],
#     main="4 - Deaths averted",
#     xlab="Vaccination coverage",
#     ylab="Deaths averted over baseline",
#     pch=19,
#     col=9,
#     lwd=7,
#     cex.lab=1.5,
#     cex.axis=1.5)
# lines(CovComp$consvac[CovComp$consvac>0],CovComp$Deaths_c[CovComp$consvac>0],col=9,lwd=10)
# lines(CovComp$privac[CovComp$privac>0],CovComp$Deaths_p[CovComp$privac>0],pch=19,col=3,lwd=10)
# lines(CovComp$secvac[CovComp$secvac>0],CovComp$Deaths_s[CovComp$secvac>0],pch=19,col=4,lwd=10)
#
#
# PSA charts
par(mfrow=c(2,2))

# 1 - Homogenous vaccination at 42%
plot(PSA_hom$ThresholdQALYs,PSA_hom$ThresholdL,
   xlab="Incremental QALYs saved",
   ylab="Incremental Costs (£)",
   xlim=c(-5000,40000),
   ylim=c(-25000000,80000000),
   pch=19,
   col=9,
   lwd=1,
   cex.lab=1.3,
   cex.axis=1.3)
points(PSA_hom$ThresholdQALYs,PSA_hom$ThresholdH,
     pch=19,
     col=8,
     lwd=1)
points(PSA_hom$Inc_QALYs[PSA_hom$Inc_QALYs!=0],PSA_hom$Inc_Cost[PSA_hom$Inc_QALYs!=0],
     col=5,
     lwd=1,
     pch=1)
# points(34017.90812,1267746.966,
#       lwd=10,
#       pch=7)
lines(PSA_hom$ThresholdQALYs,PSA_hom$ThresholdL,col=9,lwd=6) # ThresholdL
lines(PSA_hom$ThresholdQALYs,PSA_hom$ThresholdH,col=8,lwd=6) # Threshold H
legend("bottomright",
     legend=c("Homogeneous 42%"),
     col=c(5),
     lwd=6,
     cex=1.3,
     bg="white")
abline(h=0) # origin x
abline(v=0) # origin y
# 2 - Targeted (primary) at 100%
plot(PSA_pri$ThresholdQALYs,PSA_pri$ThresholdL,
   xlab="Incremental QALYs saved",
   ylab="Incremental Costs (£)",
   xlim=c(-5000,40000),
   ylim=c(-25000000,80000000),
   pch=19,
   col=9,
   lwd=1,
   cex.lab=1.3,
   cex.axis=1.3)
points(PSA_pri$ThresholdQALYs,PSA_pri$ThresholdH,
     pch=19,
     col=8,
     lwd=1)
points(PSA_pri$Inc_QALYs[PSA_pri$Inc_QALYs!=0],PSA_pri$Inc_Cost[PSA_pri$Inc_QALYs!=0],
     col=3,
     lwd=1,
     pch=1)
# points(33882.77435,668147.7286,
#       lwd=1,
#       pch=7)
lines(PSA_pri$ThresholdQALYs,PSA_pri$ThresholdL,col=9,lwd=6) # ThresholdL
lines(PSA_pri$ThresholdQALYs,PSA_pri$ThresholdH,col=8,lwd=6) # Threshold H
legend("bottomright",
     legend=c("Targeted (primary) 100%"),
     col=c(3),
     lwd=6,
     cex=1.3,
     bg="white")
```

```
abline(h=0) # origin x
abline(v=0) # origin y
# 3 - Targeted (secondary) at 100%
plot(PSA_sec$ThresholdQALYs,PSA_sec$ThresholdL,
    xlab="Incremental QALYs saved",
    ylab="Incremental Costs (£)",
    xlim=c(-5000,40000),
    ylim=c(-25000000,80000000),
    pch=19,
    col=9,
    lwd=1,
    cex.lab=1.3,
    cex.axis=1.3)
points(PSA_sec$ThresholdQALYs,PSA_sec$ThresholdH,
     pch=19,
     col=8,
     lwd=1)
points(PSA_sec$Inc_QALYs[PSA_sec$Inc_QALYs!=0],PSA_sec$Inc_Cost[PSA_sec$Inc_QALYs!=0],
     col=4,
     lwd=1,
     pch=1)
# points(18456.46208,670659.873905897,
#       lwd=1,
#       pch=7)
lines(PSA_sec$ThresholdQALYs,PSA_sec$ThresholdL,col=9,lwd=6) # ThresholdL
lines(PSA_sec$ThresholdQALYs,PSA_sec$ThresholdH,col=8,lwd=6) # Threshold H
legend("bottomright",
     legend=c("Targeted (secondary) 100%"),
     col=c(4),
     lwd=6,
     cex=1.3,
     bg="white")
abline(h=0) # origin x
abline(v=0) # origin y
# 4 - Heterogeneous at 48% & 34%
plot(PSA_het$ThresholdQALYs,PSA_het$ThresholdL,
    xlab="Incremental QALYs saved",
    ylab="Incremental Costs (£)",
    xlim=c(-5000,40000),
    ylim=c(-25000000,80000000),
    pch=19,
    col=9,
    lwd=1,
    cex.lab=1.3,
    cex.axis=1.3)
points(PSA_het$ThresholdQALYs,PSA_het$ThresholdH,
     pch=19,
     col=8,
     lwd=1)
points(PSA_het$Inc_QALYs[PSA_het$Inc_QALYs!=0],PSA_het$Inc_Cost[PSA_het$Inc_QALYs!=0],
     col=6,
     lwd=1,
     pch=1)
lines(PSA_het$ThresholdQALYs,PSA_het$ThresholdL,col=9,lwd=6) # ThresholdL
lines(PSA_het$ThresholdQALYs,PSA_het$ThresholdH,col=8,lwd=6) # Threshold H
legend("bottomright",
     legend=c("Heterogeneous 48% & 34%"),
     col=c(6),
     lwd=6,
     cex=1.3,
     bg="white")
abline(h=0) # origin x
abline(v=0) # origin y

#
#
# # Levelplot
# library(lattice)
# colpal <- colorRampPalette(c("white","yellow","red"))
# plot.new()
# par(mfrow=c(2,2), oma=c(2,0,2,0))
# # 1 - Finalsize
# print(levelplot(Het_results$finalsize~Het_results$privac*Het_results$secvac,
#         main=list(label="1 - Final size",cex=2.3),
#         xlab=list(label="Primary school vaccination",cex=2.0),
#         ylab=list(label="Secondary school vaccination",cex=2.0),
#         col.regions = colpal(30),
#         scales=list(x=list(cex=2.0),y=list(cex=2.0)),
#         colorkey=list(labels=list(cex=2.0))),
#         split=c(1, 1, 2, 2))
# # 3 - Efficiency
# print(levelplot(Het_results$QALYs_per_Vacc~Het_results$privac*Het_results$secvac,
#         main=list(label="2 - QALYs gained per vaccination",cex=2.3),
#         xlab=list(label="Primary school vaccination",cex=2.0),
#         ylab=list(label="Secondary school vaccination",cex=2.0),
#         col.regions = colpal(30),
#         scales=list(x=list(cex=2.0),y=list(cex=2.0)),
#         colorkey=list(labels=list(cex=2.0))),
```

```
#         split=c(1,2,2,2), newpage=FALSE)
# # 2 - Total Cost
# print(levelplot((1/1000000)*Het_results$TotalCosts~Het_results$privac*Het_results$secvac,
#         main=list(label="3 - Total cost (£ mil)",cex=2.3),
#         xlab=list(label="Primary school vaccination",cex=2.0),
#         ylab=list(label="Secondary school vaccination",cex=2.0),
#         col.regions = colpal(30),
#         scales=list(x=list(cex=2.0),y=list(cex=2.0)),
#         colorkey=list(labels=list(cex=2.0))),
#         split=c(2,1,2,2), newpage=FALSE)
# # 4 - Cost per vaccination
# print(levelplot(Het_results$Cost_per_Vacc~Het_results$privac*Het_results$secvac,
#         main=list(label="4 - Cost per vaccination (£)",cex=2.3),
#         xlab=list(label="Primary school vaccination",cex=2.0),
#         ylab=list(label="Secondary school vaccination",cex=2.0),
#         col.regions = colpal(30),
#         scales=list(x=list(cex=2.0),y=list(cex=2.0)),
#         colorkey=list(labels=list(cex=2.0))),
#         split=c(2, 2, 2, 2), newpage=FALSE)

# # Economic analysis acceptability curve for different strategies
# options(scipen=10)
# par(mfrow=c(2,2))
# # Pri
# plot(na.omit(EEAC$Pri_QALYs),na.omit(EEAC$Pri_Cost),
#     xlab="QALYs saved",
#     ylab="Total Cost (£)",
#     pch=19,
#     cex.axis=1.5,
#     cex.lab=1.5,
#     lwd=4)
# lines(na.omit(EEAC$Pri_QALYs),na.omit(EEAC$Pri_Cost),
#     lwd=2)
# # Sec
# plot(na.omit(EEAC$Sec_QALYs),na.omit(EEAC$Sec_Cost),
#     xlab="QALYs saved",
#     ylab="Total Cost (£)",
#     pch=19,
#     cex.axis=1.5,
#     cex.lab=1.5,
#     lwd=4)
# lines(na.omit(EEAC$Sec_QALYs),na.omit(EEAC$Sec_Cost),
#     lwd=2)
# # Hom
# plot(na.omit(EEAC$Hom_QALYs),na.omit(EEAC$Hom_Cost),
#     xlab="QALYs saved",
#     ylab="Total Cost (£)",
#     pch=19,
#     cex.axis=1.5,
#     cex.lab=1.5,
#     lwd=4)
# lines(na.omit(EEAC$Hom_QALYs),na.omit(EEAC$Hom_Cost),
#     lwd=2)
# # Het
# plot(na.omit(EEAC$Het_QALYs),na.omit(EEAC$Het_Cost),
#     xlab="QALYs saved",
#     ylab="Total Cost (£)",
#     pch=19,
#     cex.axis=1.5,
#     cex.lab=1.5,
#     lwd=4)
# lines(na.omit(EEAC$Het_QALYs),na.omit(EEAC$Het_Cost),
#     lwd=2)
#
# # Comparison between optimal vaccination coverage levels over the four strategies
# plot(0,0,
#     xlab="Incremental QALYs saved through vaccination",
#     ylab="Incremental Cost (£)",
#     pch=19,
#     cex.axis=1.5,
#     cex.lab=1.5,
#     lwd=9,
#     xlim=c(-18000,50),
#     ylim=c(0,30000000))
# text(0,0,
#     labels="Heterogeneous",
#     pos=2)
# points(max(na.omit(EEAC$Hom_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Hom_Cost))-max(na.omit(EEAC$Het_Cost)),
#       pch=19,lwd=9,col=("red"))
# text(max(na.omit(EEAC$Hom_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Hom_Cost))-max(na.omit(EEAC$Het_Cost)),
#     labels="Homogeneous",
#     pos=2)
# points(max(na.omit(EEAC$Pri_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Pri_Cost))-max(na.omit(EEAC$Het_Cost)),
#       pch=19,lwd=9,col=("red"))
# text(max(na.omit(EEAC$Pri_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Pri_Cost))-max(na.omit(EEAC$Het_Cost)),
#     labels="Primary",
#     pos=2)
# points(max(na.omit(EEAC$Sec_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Sec_Cost))-max(na.omit(EEAC$Het_Cost)),
```

```
#       pch=19,lwd=9,col=("red"))
# text(max(na.omit(EEAC$Sec_QALYs))-max(na.omit(EEAC$Het_QALYs)),max(na.omit(EEAC$Sec_Cost))-max(na.omit(EEAC$Het_Cost)),
#      labels="Secondary",
#      pos=3)
# arrows(x0=0,y0=0,
#        x1=(max(na.omit(EEAC$Hom_QALYs))-max(na.omit(EEAC$Het_QALYs))),
#        y1=(max(na.omit(EEAC$Hom_Cost))-max(na.omit(EEAC$Het_Cost))),
#        lwd=2,
#        lty=2)
# arrows(x0=0,y0=0,
#        x1=(max(na.omit(EEAC$Pri_QALYs))-max(na.omit(EEAC$Het_QALYs))),
#        y1=(max(na.omit(EEAC$Pri_Cost))-max(na.omit(EEAC$Het_Cost))),
#        lwd=2,
#        lty=2)
# arrows(x0=0,y0=0,
#        x1=(max(na.omit(EEAC$Sec_QALYs))-max(na.omit(EEAC$Het_QALYs))),
#        y1=(max(na.omit(EEAC$Sec_Cost))-max(na.omit(EEAC$Het_Cost))),
#        lwd=2,
#        lty=2)

# # Showing optimal vaccination coverage
# plot(CovComp$consvac[CovComp$Comment_c==1],CovComp$ICER_c[CovComp$Comment_c==1],
#      xlab="Vaccination coverage",
#      ylab="ICER (£)",
#      ylim=c(0,35000),
#      xlim=c(0,1),
#      cex.lab=1.3,
#      cex.axis=1.3)
# abline(h=30000,lty=3,lwd=4) # £30k threshold
# abline(h=20000,lty=3,lwd=4) # £20k threshold
# lines(CovComp$consvac,CovComp$ICER_c,pch=19,col=9,lwd=10)
# lines(CovComp$privac,CovComp$ICER_p,pch=19,col=3,lwd=10)
# lines(CovComp$secvac,CovComp$ICER_s,pch=19,col=4,lwd=10)
#
# # Showing optimal vaccination coverage (hetergeneous option)
# library(lattice)
# colpal <- colorRampPalette(c("blue","yellow","red"))
#
levelplot(Het_results$ICER[Het_results$ICER>0&Het_results$ICER<16926]~Het_results$privac[Het_results$ICER>0&Het_results$ICER<20000]*Het_results$secvac[Het_
results$ICER>0&Het_results$ICER<20000],
#          xlab=list(label="Primary school vaccination",cex=2.0),
#          ylab=list(label="Secondary school vaccination",cex=2.0),
#          xlim=c(0,1),
#          ylim=c(0,1),
#          col.regions = colpal(30),
#          scales=list(x=list(cex=2.0),y=list(cex=2.0)),
#          colorkey=list(labels=list(cex=2.0)))
```

ECONOMIC ANALYSIS SCRIPT

```
#################################################################################################################
# Economic Analysis script to work with output from Discrete time SEIR model
#
# Attempt 1:
#
#
# Dom Thorrington 12/05/2014
#################################################################################################################

attach(Epidemic_results)

#################################################################################################################
# Fraction of seropositives to ILI
#################################################################################################################
ILI_symp <- 0.35    # All flu

#################################################################################################################
# Final size with ILI
#################################################################################################################
ILI.FinalSize_age1 <- ILI_symp * finalsize1 * ageSize[1]
ILI.FinalSize_age2 <- ILI_symp * finalsize2 * ageSize[2]
ILI.FinalSize_age3 <- ILI_symp * finalsize3 * ageSize[3]
ILI.FinalSize_age4 <- ILI_symp * finalsize4 * ageSize[4]
ILI.FinalSize_age5 <- ILI_symp * finalsize5 * ageSize[5]

ILI.FinalSize     <- cbind(ILI.FinalSize_age1,ILI.FinalSize_age2,ILI.FinalSize_age3,ILI.FinalSize_age4,
                  ILI.FinalSize_age5)

colnames(ILI.FinalSize) <- NULL

#################################################################################################################
# Case fatality ratios
#################################################################################################################
CFR <- c((11+17+22+55)/(24743+83977+1408+12008),
      (10+51)/(42649+9874),
      (10+51)/(42649+9874),
      (112+364+674+5458)/(87985+39353+29337+99337),
      (7729+54933)/(53254+368489)) # Cromer et al. (2014)
                        # CFR for admissions

# Quality-adjusted life expectancy lost if 'flu-induced death occurs
HLE <- c(66.23,61.41,55.60,33.10,6.54)

#################################################################################################################
# Healthcare resource use
#################################################################################################################

# ILI cases and visiting the GP
VisitGP <- 0.1 # Flusurvey for 2010-11

# GP -> Hospitalisation
Hosp <- cbind(rep((330+175)/(7361+6090),overestimate),
          rep((14/3875),overestimate),
          rep((14/3875),overestimate),
          rep((12+27)/(1878+1829),overestimate),
          rep((63/582),overestimate)) # Cromer et al. (2014), both A&B, both low/high risk groups

# ILI cases and Hospitalisation - ICU
Hosp_ICU <- (41.4+70)/2000  # Baguelin et al. 2010

#################################################################################################################
# Costs
#################################################################################################################

# Societal
GPconsultation     <- 45    # /clinic consultation
HospitalAdmission  <- rep(1489,overestimate)  # /admission
ICUAdmission       <- 1937
ChildcareUsage     <- 0
ChildcareCosts     <- 0

# Vaccination
VaccineCosts <- rep(17.03,overestimate)

#################################################################################################################
# Health-related quality of life
#################################################################################################################

QALY.nothosp <- cbind(rep(0.0074,overestimate),
                rep(0.0074,overestimate),
                rep(0.0074,overestimate),
                rep(0.0082,overestimate),
                rep(0.0082,overestimate))
QALY.hosp    <- cbind(rep(0.016,overestimate),
                rep(0.016,overestimate),
```

```
                rep(0.016,overestimate),
                rep(0.018,overestimate),
                rep(0.018,overestimate))

#################################################################################################################
# Discounting of costs and benefits
#################################################################################################################
discount <- 0.035

#################################################################################################################
#################################################################################################################
## Economic Analysis
#################################################################################################################
#################################################################################################################

# Economic calculations on final sizes
ILIDeaths         <- matrix(nrow=overestimate, ncol=nage)
ILISurvivors      <- matrix(nrow=overestimate, ncol=nage)
ILI.GPconsultation <- matrix(nrow=overestimate, ncol=nage)
ILI.HospAdm       <- matrix(nrow=overestimate, ncol=nage)
ILI.ICUAdm        <- matrix(nrow=overestimate, ncol=nage)
ILI.Childcare     <- matrix(nrow=overestimate, ncol=nage)
QALYs_survivors   <- matrix(nrow=overestimate, ncol=nage)

for (i in 1:overestimate){
  for (j in 1:nage){
#     ILIDeaths[i,j]         <- ILI.FinalSize[i,j] * CFR[j]
#     ILISurvivors[i,j]      <- ILI.FinalSize[i,j] * (1-CFR[j])
    ILI.GPconsultation[i,j] <- ILI.FinalSize[i,j] * VisitGP * GPconsultation
    ILI.HospAdm[i,j]        <- ILI.FinalSize[i,j] * VisitGP * Hosp[i,j] * HospitalAdmission[i]
    ILI.ICUAdm[i,j]         <- ILI.FinalSize[i,j] * VisitGP * Hosp[i,j] * Hosp_ICU * ICUAdmission
    ILI.Childcare[i,j]      <- ILI.FinalSize[i,j] * ChildcareUsage * ChildcareCosts
    ILIDeaths[i,j]          <- ILI.FinalSize[i,j] * VisitGP * Hosp[j]  * CFR[j]
    ILISurvivors[i,j]       <- ILI.FinalSize[i,j]* VisitGP * Hosp[j]  * (1-CFR[j])
  }
}

for (i in 1:overestimate){
  for (j in 1:nage){
    QALYs_survivors[i,j]    <- ILISurvivors[i,j] * ((1-Hosp[j]) * QALY.nothosp[i,j] + Hosp[j] * QALY.hosp[i,j])
  }
}

# Vaccination programme costs
VaccCosts <- matrix(,nrow=overestimate,ncol=nage)
Vaccinated <- cbind(Vaccinated1, Vaccinated2, Vaccinated3, Vaccinated4, Vaccinated5)

for (i in 1:overestimate){
  for (j in 1:nage){
    VaccCosts[i,j] <- Vaccinated[i,j]*VaccineCosts[i] # Total vaccination costs
  }
}

# Total Costs
TotalCosts <- numeric(0)
for (i in 1:overestimate){
  TotalCosts[i] <- sum(ILI.GPconsultation[i,])+sum(ILI.HospAdm[i,])+sum(ILI.ICUAdm[i,])+sum(VaccCosts[i,])#+sum(ILI.Childcare[i,])
}

# Temporary loss of quality of life - survivors
QALYs_illness <- numeric(0)
for (i in 1:length(QALYs_survivors)/nage){
  QALYs_illness[i] <- sum(QALYs_survivors[i,])
}

# Loss of future QALYs through influenza-death
QALYs_death1 <- ILIDeaths[,1]*HLE[1]/((1+discount)^HLE[1])
QALYs_death2 <- ILIDeaths[,2]*HLE[2]/((1+discount)^HLE[2])
QALYs_death3 <- ILIDeaths[,3]*HLE[3]/((1+discount)^HLE[3])
QALYs_death4 <- ILIDeaths[,4]*HLE[4]/((1+discount)^HLE[4])
QALYs_death5 <- ILIDeaths[,5]*HLE[5]/((1+discount)^HLE[5])

QALYs_death <- QALYs_death1 + QALYs_death2 + QALYs_death3 + QALYs_death4 + QALYs_death5

TotalQALYs <- QALYs_illness + QALYs_death

# Append to dataframe
Epidemic_results[,"Deaths_1"]     <- ILIDeaths[,1]
Epidemic_results[,"Deaths_2"]     <- ILIDeaths[,2]
Epidemic_results[,"Deaths_3"]     <- ILIDeaths[,3]
Epidemic_results[,"Deaths_4"]     <- ILIDeaths[,4]
Epidemic_results[,"Deaths_5"]     <- ILIDeaths[,5]
Epidemic_results[,"TotalCosts"]   <- TotalCosts
Epidemic_results[,"QALYs_illness"] <- QALYs_illness
Epidemic_results[,"QALYs_death"]  <- QALYs_death
Epidemic_results[,"Total_QALYs"]  <- TotalQALYs

# Sort Epidemic_results by TotalCosts (column 21) ascending
```

```
Epidemic_results <- Epidemic_results[order(Epidemic_results[,21]),] # dataframe is now sorted on TotalCosts
rownames(Epidemic_results) <- NULL # Remove "row.names"

# Declare columns to add to Epidemic_results
Inc_Cost      <- numeric(0)
Inc_QALYs     <- numeric(0)
TotalVacc     <- numeric(0)
ICER          <- numeric(0)
Inc_QALYs_2   <- numeric(0)
QALYs_per_Vacc <- numeric(0)
QALDs_per_Vacc <- numeric(0)
Cost_per_Vacc  <- numeric(0)
Primary_Vacc   <- numeric(0)
Secondary_Vacc <- numeric(0)
Deaths_averted <- numeric(0)

# Calculate data to add to Epidemic_results
for (i in 1:overestimate){
 if(i==1){# First row is an exception for some columns
  Inc_Cost[i] <- 0
  Inc_QALYs[i] <- 0
  TotalVacc[i] <- Epidemic_results$Vaccinated1[i] + Epidemic_results$Vaccinated2[i] + Epidemic_results$Vaccinated3[i] + Epidemic_results$Vaccinated4[i] +
Epidemic_results$Vaccinated5[i]
  ICER[i] <- 0
  Inc_QALYs_2[i] <- 0
  QALYs_per_Vacc[i] <- 0
  QALDs_per_Vacc[i] <- 0
  Cost_per_Vacc[i] <- 0
  Primary_Vacc[i] <- Epidemic_results$privac[i]*ageSize[2]
  Secondary_Vacc[i] <- Epidemic_results$secvac[i]*ageSize[3]
  Deaths_averted[i] <- 0
 } else {
  Inc_Cost[i] <- Epidemic_results$TotalCosts[i] - Epidemic_results$TotalCosts[i-1]
  Inc_QALYs[i] <- Epidemic_results$Total_QALYs[i-1] - Epidemic_results$Total_QALYs[i]
  TotalVacc[i] <- Epidemic_results$Vaccinated1[i] + Epidemic_results$Vaccinated2[i] + Epidemic_results$Vaccinated3[i] + Epidemic_results$Vaccinated4[i] +
Epidemic_results$Vaccinated5[i]
  ICER[i] <- Inc_Cost[i]/Inc_QALYs[i]
  Inc_QALYs_2[i] <- Epidemic_results$Total_QALYs[1] - Epidemic_results$Total_QALYs[i]
  QALYs_per_Vacc[i] <- Inc_QALYs_2[i]/(TotalVacc[i] - TotalVacc[1])
  QALDs_per_Vacc[i] <- QALYs_per_Vacc[i]*365
  Cost_per_Vacc[i] <- (Epidemic_results$TotalCosts[i] - Epidemic_results$TotalCosts[1])/(TotalVacc[i] - TotalVacc[1])
  Primary_Vacc[i] <- Epidemic_results$privac[i]*ageSize[2]
  Secondary_Vacc[i] <- Epidemic_results$secvac[i]*ageSize[3]
  Deaths_averted[i] <- (Epidemic_results$Deaths_1[1] + Epidemic_results$Deaths_2[1] + Epidemic_results$Deaths_3[1] + Epidemic_results$Deaths_4[1] +
Epidemic_results$Deaths_5[1]) -
                (Epidemic_results$Deaths_1[i] + Epidemic_results$Deaths_2[i] + Epidemic_results$Deaths_3[i] + Epidemic_results$Deaths_4[i] +
Epidemic_results$Deaths_5[i])
 }
}

# Append to Epidemic_results dataframe
Epidemic_results[,"Inc_Cost"]      <- Inc_Cost
Epidemic_results[,"Inc_QALYs"]     <- Inc_QALYs
Epidemic_results[,"TotalVacc"]     <- TotalVacc
Epidemic_results[,"ICER"]          <- ICER
Epidemic_results[,"Inc_QALYs_2"]   <- Inc_QALYs_2
Epidemic_results[,"QALYs_per_Vacc"] <- QALYs_per_Vacc
Epidemic_results[,"QALDs_per_Vacc"] <- QALDs_per_Vacc
Epidemic_results[,"Cost_per_Vacc"]  <- Cost_per_Vacc
Epidemic_results[,"Primary_Vacc"]   <- Primary_Vacc
Epidemic_results[,"Secondary_Vacc"] <- Secondary_Vacc
Epidemic_results[,"Deaths_averted"] <- Deaths_averted
Epidemic_results[,"Comments"]      <- rep(1,overestimate)

# Process of finding and removing SD & WD ICERs:
#  1) Check list if negative ICERs exist
#  2) If yes, create Epidemic_results_exc (if no, move on to WD section...(6))
#  3) Move first negative ICER to Epidemic_results_exc with "SD" label attached
#  4) Recalculate all ICERs
#  5) Repeat from (1)
#  6) Create WD_testvector
#  7) Check if any element of WD_testvector > 1
#  8) If no, finish and merge lists if necessary, if yes -> (9)
#  9) Move offending ICER to _exc list with "WD" label attached
# 10) Go to (6)

#################################
# Part 1 - strongly dominated
#################################

# Check for existence of negative ICERs
Neg_ICERs <- any(Epidemic_results$ICER<0)
merge_test <- F

# Create blank Epidemic_results_exc
Epidemic_results_exc <- data.frame(Simulation=rep(NA,1),    # Record the simulation number for the conditions set
                        R0=rep(NA,1),
                        privac=rep(NA,1),
```

```
                        secvac=rep(NA,1),
                        finalsize1=rep(NA,1),
                        finalsize2=rep(NA,1),
                        finalsize3=rep(NA,1),
                        finalsize4=rep(NA,1),
                        finalsize5=rep(NA,1),
                        finalsize=rep(NA,1),
                        Vaccinated1=rep(NA,1),
                        Vaccinated2=rep(NA,1),
                        Vaccinated3=rep(NA,1),
                        Vaccinated4=rep(NA,1),
                        Vaccinated5=rep(NA,1),
                        Deaths_1=rep(NA,1),
                        Deaths_2=rep(NA,1),
                        Deaths_3=rep(NA,1),
                        Deaths_4=rep(NA,1),
                        Deaths_5=rep(NA,1),
                        TotalCosts=rep(NA,1),
                        QALYs_illness=rep(NA,1),
                        QALYs_death=rep(NA,1),
                        Total_QALYs=rep(NA,1),
                        Inc_Cost=rep(NA,1),
                        Inc_QALYs=rep(NA,1),
                        TotalVacc=rep(NA,1),
                        ICER=rep(NA,1),
                        Inc_QALYs_2=rep(NA,1),
                        QALYs_per_Vacc=rep(NA,1),
                        QALDs_per_Vacc=rep(NA,1),
                        Cost_per_Vacc=rep(NA,1),
                        Primary_Vacc=rep(NA,1),
                        Secondary_Vacc=rep(NA,1),
                        Deaths_averted=rep(NA,1),
                        Comments=rep(NA,1),
                        stringsAsFactors=F)
Epidemic_results_exc <- Epidemic_results_exc[-1,]

# Run procedure to deal with negative ICERs
if(Neg_ICERs==T){
  merge_test <- T
}

while (Neg_ICERs==T){
  Neg_index <- numeric(0)

  # Find negative ICERs
  Neg_index <- match(Epidemic_results$ICER[Epidemic_results$ICER<0],Epidemic_results$ICER)

  # Label the first negative ICER
  Epidemic_results[Neg_index[1],]$Comments <- "SD"

  # Copy first negative ICER to new dataframe
  Epidemic_results_exc <- rbind(Epidemic_results_exc,Epidemic_results[Neg_index[1],])
  rownames(Epidemic_results_exc) <- NULL # Remove "row.names"

  # Remove first negative ICER from old dataframe
  Epidemic_results <- Epidemic_results[-Neg_index[1],]
  rownames(Epidemic_results) <- NULL # Remove "row.names"

  # Update Epidemic_results
  Epidemic_results[Neg_index[1],]$Inc_Cost  <- Epidemic_results[Neg_index[1],]$TotalCosts - Epidemic_results[(Neg_index[1]-1),]$TotalCosts
  Epidemic_results[Neg_index[1],]$Inc_QALYs <- Epidemic_results[(Neg_index[1]-1),]$Total_QALYs - Epidemic_results[Neg_index[1],]$Total_QALYs
  Epidemic_results[Neg_index[1],]$ICER      <- Epidemic_results[Neg_index[1],]$Inc_Cost/Epidemic_results[Neg_index[1],]$Inc_QALYs

  # Check for existence of negative ICERs
  Neg_ICERs <- any(Epidemic_results$ICER<0)
}


################################
# Part 2 - weakly dominated
################################

# Find the weakly dominated options and move to Epidemic_results_exc, labelling as WD
WD_test <- F
WD_testvector <- numeric(0)
for (i in 2:(length(Epidemic_results[,1])-1)){
  WD_testvector <- append(WD_testvector,Epidemic_results[i,]$ICER/Epidemic_results[i+1,]$ICER)
}
if(length(WD_testvector[WD_testvector>1])>0){
  WD_test <- T
  merge_test <- T
}

while(WD_test==T){
  # Check if Epidemic_results_exc exists, if not then create it
  if (exists("Epidemic_results_exc")==F){
    Epidemic_results_exc <- data.frame(Simulation=rep(NA,1),    # Record the simulation number for the conditions set
                          R0=rep(NA,1),
```

```
                        privac=rep(NA,1),
                        secvac=rep(NA,1),
                        finalsize1=rep(NA,1),
                        finalsize2=rep(NA,1),
                        finalsize3=rep(NA,1),
                        finalsize4=rep(NA,1),
                        finalsize5=rep(NA,1),
                        finalsize=rep(NA,1),
                        Vaccinated1=rep(NA,1),
                        Vaccinated2=rep(NA,1),
                        Vaccinated3=rep(NA,1),
                        Vaccinated4=rep(NA,1),
                        Vaccinated5=rep(NA,1),
                        Deaths_1=rep(NA,1),
                        Deaths_2=rep(NA,1),
                        Deaths_3=rep(NA,1),
                        Deaths_4=rep(NA,1),
                        Deaths_5=rep(NA,1),
                        TotalCosts=rep(NA,1),
                        QALYs_illness=rep(NA,1),
                        QALYs_death=rep(NA,1),
                        Total_QALYs=rep(NA,1),
                        Inc_Cost=rep(NA,1),
                        Inc_QALYs=rep(NA,1),
                        TotalVacc=rep(NA,1),
                        ICER=rep(NA,1),
                        Inc_QALYs_2=rep(NA,1),
                        QALYs_per_Vacc=rep(NA,1),
                        QALDs_per_Vacc=rep(NA,1),
                        Cost_per_Vacc=rep(NA,1),
                        Primary_Vacc=rep(NA,1),
                        Secondary_Vacc=rep(NA,1),
                        Deaths_averted=rep(NA,1),
                        Comments=rep(NA,1),
                        stringsAsFactors=F)
  Epidemic_results_exc <- Epidemic_results_exc[-1,]
}

# Find WD coverage levels
WD_indexes <- numeric(0)
for (i in 2:(length(Epidemic_results[,1])-1)){
  if(Epidemic_results[i,]$ICER>Epidemic_results[i+1,]$ICER){
    Epidemic_results[i,]$Comments <- "WD"
    WD_indexes <- append(WD_indexes,i)
  }
}

# Move WD coverage levels
Epidemic_results_exc <- rbind(Epidemic_results_exc,Epidemic_results[WD_indexes,])
rownames(Epidemic_results_exc) <- NULL # Remove "row.names"
Epidemic_results <- Epidemic_results[-WD_indexes,]
rownames(Epidemic_results) <- NULL # Remove "row.names"

# Wipe previous columns to add to Epidemic_results
Inc_Cost       <- numeric(0)
Inc_QALYs      <- numeric(0)
ICER           <- numeric(0)

for (i in 1:length(Epidemic_results[,1])){
  if(i==1){# First row is an exception for some columns
    Inc_Cost[i] <- 0
    Inc_QALYs[i] <- 0
    ICER[i] <- 0
  } else {
    Inc_Cost[i] <- Epidemic_results$TotalCosts[i] - Epidemic_results$TotalCosts[i-1]
    Inc_QALYs[i] <- Epidemic_results$Total_QALYs[i-1] - Epidemic_results$Total_QALYs[i]
    ICER[i] <- Inc_Cost[i]/Inc_QALYs[i]
  }
}
# Append to Epidemic_results dataframe
Epidemic_results[,"Inc_Cost"]      <- Inc_Cost
Epidemic_results[,"Inc_QALYs"]     <- Inc_QALYs
Epidemic_results[,"ICER"]          <- ICER
# Re-test for WD coverage levels
WD_testvector <- numeric(0)
for (i in 2:(length(Epidemic_results[,1])-1)){
  WD_testvector <- append(WD_testvector,Epidemic_results[i,]$ICER/Epidemic_results[i+1,]$ICER)
}
if(length(WD_testvector[WD_testvector>1])>0){
  WD_test <- T
} else {
  WD_test <- F
}
}
# Add excluded ICERs to the end of the Epidemic_results dataframe
if(merge_test==T){
  Epidemic_results <- rbind(Epidemic_results,Epidemic_results_exc)
}
```

R SCRIPT FOR MATHEMATICAL MODELS USED IN CHAPTER 6

MAIN MODEL SCRIPT

```
#############################################################################################################
# Discrete time SEIR model
#
# Attempt 7: age-structured population,stochastic infection parameter, 31 patches
#          with heterogeneous vaccination coverage across school patches
#
# Dom Thorrington 28/02/2014
#############################################################################################################

datestamp  <- 20141224

# For progress bar
#install.packages("tcltk")
#install.packages("tcltk2")
#install.packages("Matrix")
require(tcltk)
#require(tcltk2)
require(Matrix)

# Set location
location <- 1  # 1 = Office
# 2 = Home

if (location==1){
  setwd("C:/Users/lsh337197/Dropbox/PhD guff/R stuff/Discrete time SEIR/31 patch/Project/5.0 New model/5.01 No vacc")
} else {
  setwd("C:/Users/Dom's Laptop/Dropbox/PhD guff/R stuff/Discrete time SEIR/31 patch/Project/5.0 New model/5.01 No vacc")
}

# General parameters - R0, beta, etc.
source('Parameters.R')

#############################################################################################################
# Population structure
#############################################################################################################
nprimary <- 25           # number of primary schools
nsecondary <- 5          # number of secondary schools
npatch <- nprimary + nsecondary + 1
SchoolPatches <- c(1:(nprimary+nsecondary))

#############################################################################################################
# Run simulations to put final size into matrix with overall progress bar
#############################################################################################################
nsims     <- 5000

masterpb <- winProgressBar(title="Running simulations", label="0% done", min=0, max=100, initial=0)

# Age-specific time series matricies - these will be used to output results to .csv
age_timeseries.1 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.2 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.3 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.4 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.5 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.6 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries.7 <- matrix(0, nrow = nsims, ncol = nsteps)

age_timeseries_exp.1 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.2 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.3 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.4 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.5 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.6 <- matrix(0, nrow = nsims, ncol = nsteps)
age_timeseries_exp.7 <- matrix(0, nrow = nsims, ncol = nsteps)

# Create dataframe in which to store main results
dataframerow <- 0
overestimate <- nsims          # upper limit of the number of rows in the dataframe
Epidemic_results <- data.frame(Simulation=rep(NA,overestimate),    # Record the simulation number for the conditions set
                               epsilon.1=rep("",overestimate),
                               R0=rep("",overestimate),
                               privac=rep("",overestimate),
                               secvac=rep("",overestimate),
                               Peak=rep("",overestimate),         # Overall epidemic peak height
                               Peak_Time=rep("",overestimate),    # Overall epidemic peak time
                               FinalSize=rep("",overestimate),    # Overall epidemic final size
```

```
                    Duration=rep("",overestimate),      # Overall epidemic duration
                    Vaccination=rep("",overestimate),    # Overall vaccination coverage achieved
                    All_infected=rep("",overestimate),   # Point at which all patches were infected
                    Mean_patch_dur=rep("",overestimate), # Mean duration of patch epidemics
                    Peak_age1=rep("",overestimate),      # Results for age groups (does not include age-specific duration)
                    Peak_age1_time=rep("",overestimate),
                    FinalSize_age1=rep("",overestimate),
                    Duration_age1=rep("",overestimate),
                    Vaccination_age1=rep("",overestimate),
                    Peak_age2=rep("",overestimate),
                    Peak_age2_time=rep("",overestimate),
                    FinalSize_age2=rep("",overestimate),
                    Duration_age2=rep("",overestimate),
                    Vaccination_age2=rep("",overestimate),
                    Peak_age3=rep("",overestimate),
                    Peak_age3_time=rep("",overestimate),
                    FinalSize_age3=rep("",overestimate),
                    Duration_age3=rep("",overestimate),
                    Vaccination_age3=rep("",overestimate),
                    Peak_age4=rep("",overestimate),
                    Peak_age4_time=rep("",overestimate),
                    FinalSize_age4=rep("",overestimate),
                    Duration_age4=rep("",overestimate),
                    Vaccination_age4=rep("",overestimate),
                    Peak_age5=rep("",overestimate),
                    Peak_age5_time=rep("",overestimate),
                    FinalSize_age5=rep("",overestimate),
                    Duration_age5=rep("",overestimate),
                    Vaccination_age5=rep("",overestimate),
                    Peak_age6=rep("",overestimate),
                    Peak_age6_time=rep("",overestimate),
                    FinalSize_age6=rep("",overestimate),
                    Duration_age6=rep("",overestimate),
                    Vaccination_age6=rep("",overestimate),
                    Peak_age7=rep("",overestimate),
                    Peak_age7_time=rep("",overestimate),
                    FinalSize_age7=rep("",overestimate),
                    Duration_age7=rep("",overestimate),
                    Vaccination_age7=rep("",overestimate),
                    stringsAsFactors=F)

# vars1 <- c(sample(c(1:3),nsims,replace=T))    # Seeding
#
# vars1 <- runif(nsims,0,0.95) # privac
#
# vars2 <- c(sample(c(1.0, 1.5, 2.0, 2.5),nsims,replace=T)) # R0
#
patch_sims       <- matrix(0,nrow=nsims,ncol=npatch)
age_sims         <- matrix(0,nrow=nsims,ncol=nage)
patch_outbreaks   <- matrix(0,nrow=nsims,ncol=npatch)
#
for (q in 1:nsims){
 # Variable of choice
 privac <- 0
 secvac <- privac

 # Uptake of vaccine according to new JCVI guidance
 uptake_gen <- c(0.00,    # uptake of 0-1
            0.00,    # uptake of 2-3   ***
            privac,    # uptake of 4-10  ***
            secvac,    # uptake of 11-16 ***
            0.00,    # uptake of 17-24
            0.00,    # uptake of 25-64
            0.00)    # uptake of 65+

 # Overall coverage
 vacc_coverage <- numeric(0)
 for (i in 1:nage){
  vacc_coverage[i] <- c(1-((uptake_risk[i]*risk_groups[i])+(uptake_gen[i]*(1-uptake_risk[i]*risk_groups[i]))))
 }


 dataframerow <- dataframerow + 1

 Sys.sleep(0.1) # slow down the progress bar code for illustration purposes
 info <- sprintf("%f%% done", round(q/nsims,2)*100)
 setWinProgressBar(masterpb, round(q/nsims,2)*100, label=info)

#############################################################################################################
# Setting population lists before model
#############################################################################################################
```

```
# Initialise population lists
S <- vector("list",npatch) # Susceptible
E <- vector("list",npatch) # Exposed
I <- vector("list",npatch) # Infectious
R <- vector("list",npatch) # Recovered
W <- vector("list",npatch) # Vaccinated in total
A <- vector("list",npatch) # Prior immunity
V <- vector("list",npatch) # Effectivelty vaccinated
N <- vector("list",npatch) # S+E+I+R+V

#########################################################################################################
# Seeding the population with infection
#########################################################################################################
seeding <-  1 # 1 - manual to assign to primary (1), secondary (2) or external (3),
# 2 - randomly assigned to primary (1), secondary (2) or external (3)

if (seeding==1){
  # 1 - primary school
  # 2 - secondary school
  # 3 - external population
  pop_index <- 1                # manual selection of primary (1), secondary (2) or external (3) for seed
} else {
  pop_index <- sample(1:3,1,replace=T) # randomly choose population to seed:
}

# Assigning seed patch
if (pop_index==1){ # randomly choose one primary school
  seed_patch <- sample(1:nprimary,1,replace=T)
} else {
  if (pop_index==2){ # randomly choose one secondary school
    seed_patch <- sample((nprimary+1):(nprimary+nsecondary),1,replace=T)
  } else { # assign to the external population
    seed_patch <- npatch
  }
}

#########################################################################################################
# Structuring the population
#########################################################################################################

for (i in 1:npatch){
  if(i < (nprimary+1)){
    N[[i]] <- c(0,0,ageSize[3]/nprimary,0,0,0,0)
  } else {
    if(i != npatch){
      N[[i]] <- c(0,0,0,ageSize[4]/nsecondary,0,0,0)
    } else {
      N[[i]] <- c(ageSize[1],ageSize[2],0,0,ageSize[5],ageSize[6],ageSize[7])
    }
  }
}

# Structure of infected population
for (i in 1:npatch){
  for (j in 1:nage){
    I[[i]][j] <- 0
  }
}

if (pop_index==1){ # seed in the appropriate primary school
  I[[seed_patch]][3] <- seed
} else {
  if (pop_index==2){ # seed in the appropriate secondary school
    I[[seed_patch]][4] <- seed
  } else { # seed in the appropriate external population age group
    ext_preindex <- sample(1:2,1,replace=T)
    if (ext_preindex==1){ # seed in age group 1 or 2
      ext_index <- sample(1:2,1,replace=T)
    } else { # seed in age group 5, 6 or 7
      ext_index <- sample(5:nage,1,replace=T)
    }
    I[[seed_patch]][ext_index] <- seed
  }
}

# Structure of incubated population
for (i in 1:npatch){
  for (j in 1:nage){
    E[[i]][j] <- 0
  }
}
```

```
# Structure of recovered population
for (i in 1:npatch){
 for (j in 1:nage){
  R[[i]][j] <- 0
 }
}

immune <- c(1-0.7837,
        1-0.7837,
        1-0.8943,
        1-0.9819,
        1-0.9496,
        1-0.9496,
        1-0.9736)

# Structure of susceptible and vaccinated populations - primary schools
if (npri_low_v!=0){
 if(npri_low_v==nprimary){                # All primary schools have low coverage
  for (i in 1:nprimary){
   W[[i]] <- c(0,0,round(ageSize[3]*(1-(vacc_coverage[3]+tau))/nprimary),0,0,0,0)
   V[[i]] <- c(0,0,round(W[[i]][3]*vac_eff[3]),0,0,0,0)
   A[[i]] <- c(0,0,round((ageSize[3]/nprimary)*immune[3]),0,0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
 } else {
  for (i in 1:(nprimary-npri_low_v)){      # Normal vacc. coverage primary schools
   W[[i]] <- c(0,0,round(ageSize[3]*(1-vacc_coverage[3])/nprimary),0,0,0,0)
   V[[i]] <- c(0,0,round(W[[i]][3]*vac_eff[3]),0,0,0,0)
   A[[i]] <- c(0,0,round((ageSize[3]/nprimary)*immune[3]),0,0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
  for (i in (nprimary-npri_low_v+1):nprimary){ # Low vacc. coverage primary schools
   W[[i]] <- c(0,0,round(ageSize[3]*(1-(vacc_coverage[3]+tau))/nprimary),0,0,0,0)
   V[[i]] <- c(0,0,round(W[[i]][3]*vac_eff[3]),0,0,0,0)
   A[[i]] <- c(0,0,round((ageSize[3]/nprimary)*immune[3]),0,0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
 }
} else {
 for (i in 1:nprimary){                   # Normal vacc. coverage primary schools
  W[[i]] <- c(0,0,round(ageSize[3]*(1-vacc_coverage[3])/nprimary),0,0,0,0)
  V[[i]] <- c(0,0,round(W[[i]][3]*vac_eff[3]),0,0,0,0)
  A[[i]] <- c(0,0,round((ageSize[3]/nprimary)*immune[3]),0,0,0,0)
  S[[i]] <- N[[i]] - V[[i]] - A[[i]]
 }
}

# Structure of susceptible and removed populations - secondary schools
if (nsec_low_v!=0){
 if (nsec_low_v==nsecondary){                # All secondary schools have low coverage
  for (i in (nprimary+1):(nprimary+nsecondary)){
   W[[i]] <- c(0,0,0,round(ageSize[4]*(1-(vacc_coverage[4]+tau))/nsecondary),0,0,0)
   V[[i]] <- c(0,0,0,round(W[[i]][4]*vac_eff[4]),0,0,0)
   A[[i]] <- c(0,0,0,round((ageSize[4]/nsecondary)*immune[4]),0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
 } else {
  for (i in (nprimary+1):(nprimary+nsec_low_v)){      # Low vacc. coverage secondary schools
   W[[i]] <- c(0,0,0,round(ageSize[4]*(1-(vacc_coverage[4]+tau))/nsecondary),0,0,0)
   V[[i]] <- c(0,0,0,round(W[[i]][4]*vac_eff[4]),0,0,0)
   A[[i]] <- c(0,0,0,round((ageSize[4]/nsecondary)*immune[4]),0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
  for(i in (nprimary+nsec_low_v+1):(nprimary+nsecondary)){ # Normal vacc. coverage secondary schools
   W[[i]] <- c(0,0,0,round(ageSize[4]*(1-vacc_coverage[4])/nsecondary),0,0,0)
   V[[i]] <- c(0,0,0,round(W[[i]][4]*vac_eff[4]),0,0,0)
   A[[i]] <- c(0,0,0,round((ageSize[4]/nsecondary)*immune[4]),0,0,0)
   S[[i]] <- N[[i]] - V[[i]] - A[[i]]
  }
 }
} else {
 for(i in (nprimary+1):(nprimary+nsecondary)){          # Normal vacc. coverage secondary schools
  W[[i]] <- c(0,0,0,round(ageSize[4]*(1-vacc_coverage[4])/nsecondary),0,0,0)
  V[[i]] <- c(0,0,0,round(W[[i]][4]*vac_eff[4]),0,0,0)
  A[[i]] <- c(0,0,0,round((ageSize[4]/nsecondary)*immune[4]),0,0,0)
  S[[i]] <- N[[i]] - V[[i]] - A[[i]]
 }
}

# Structure of susceptible and removed populations - external population
```

```
W[[npatch]] <- c(round(ageSize[1]*(1-vacc_coverage[1])),
                 round(ageSize[2]*(1-vacc_coverage[2])),
                 0,
                 0,
                 round(ageSize[5]*(1-vacc_coverage[5])),
                 round(ageSize[6]*(1-vacc_coverage[6])),
                 round(ageSize[7]*(1-vacc_coverage[7])))

for (j in 1:nage){
  V[[npatch]][j] <- round(W[[npatch]][j]*vac_eff[j])
  A[[npatch]][j] <- round(N[[npatch]][j]*immune[j])
}

S[[npatch]] <- N[[npatch]] - V[[npatch]] - A[[npatch]]

# Remove the seed from S
for (i in 1:npatch){
  for (j in 1:nage){
    S[[i]][j] <- S[[i]][j] - I[[i]][j]
  }
}

#############################################################################################################
# Patch-specific contact matricies
#############################################################################################################

# Within your patch
c_within <- c(rep(0,length(age_mix))) # initialise contact matrix
within_nonzeros <- c(1,2,5,6,7,8,9,12,13,14,17,25,29,30,33,34,35,36,37,40,41,42,43,44,47,48,49) # non-zero elements of new contact matrix
for (i in within_nonzeros){
  c_within[i] <- age_mix[i]

  if (i==17|i==25){
    c_within[i] <- epsilon.1*age_mix[i]
  }
}

# Between school patches
c_school <- c(rep(0,length(age_mix))) # initialise contact matrix
school_nonzeros <- c(17,18,24,25) # non-zero elements of new contact matrix
for (i in school_nonzeros){ # factor variable to divide number of contacts equally between different patches
  if (i==17){
    factor <- nprimary-1    # divides by number of primary schools - 1
    c_school[i] <- epsilon.2*age_mix[i]/factor
  }
  if (i==18){
    factor <- nsecondary    # divides by number of secondary schools
    c_school[i] <- age_mix[i]/factor
  }
  if (i==24){
    factor <- nprimary      # divides by number of primary schools
    c_school[i] <- age_mix[i]/factor
  }
  if (i==25){
    factor <- nsecondary-1  # divides by number of secondary schools - 1
    c_school[i] <- epsilon.2*age_mix[i]/factor
  }
}

# Between school and external
c_external <- c(rep(0,length(age_mix))) # initialise contact matrix
external_nonzeros <- c(3,4,10,11,15,16,19,20,21,22,23,26,27,28,31,32,38,39,45,46) # non-zero elements of new contact matrix
for (i in external_nonzeros){ # factor variable to divide number of contacts equally between different patches
  if (i==15|i==16|i==19|i==20|i==21|i==22|i==23|i==26|i==27|i==28){ # from pri/sec schools to external pop.
    c_external[i] <- age_mix[i]
  }
  if (i==3|i==10|i==31|i==38|i==45){ # from external pop. to primary schools
    factor <- nprimary
    c_external[i] <- age_mix[i]/factor
  }
  if (i==4|i==11|i==32|i==39|i==46){ # from external pop. to seconday schools
    factor <- nsecondary
    c_external[i] <- age_mix[i]/factor
  }
}

#############################################################################################################
# Model
#############################################################################################################
patch_timeseries     <- matrix(0, nrow = npatch, ncol = nsteps)
cumulative_patch_timeseries <- matrix(0, nrow = npatch, ncol = nsteps)
```

```
age_timeseries      <- matrix(0, nrow = nage,   ncol = nsteps) # Overall time series for one simulation for I compartment
age_timeseries_exp  <- matrix(0, nrow = nage,   ncol = nsteps) # Overall time series for one simulation for E compartment

# Initialise progress bar
progressbar <- winProgressBar(title="Simulating epidemic", label="0% done", min=0, max=100, initial=0)

for (k in 1:nsteps){
 ########################################
 # Break criteria for stochastic fadeout
 ########################################

 break_criteria <- FALSE

 for (i in 1:npatch){
  for (j in 1:nage){
   if ((do.call(sum,E)+do.call(sum,I))==0) # Criteria is that no more individuals exist
    break_criteria <- TRUE               # in model to transmit infection further
  }
 }

 if (break_criteria==TRUE){
  break
 }

 # Initialise the progress bar
 Sys.sleep(0.1) # slow down the progress bar code for illustration purposes
 info <- sprintf("%d%% done", round((k/nsteps)*100))
 setWinProgressBar(progressbar, k/(nsteps)*100, label=info)

 # initialise lists for SEIR model
 FoI  <- vector("list",npatch)
 Infe <- vector("list",npatch)
 Reco <- vector("list",npatch)

 # FoI1 - FoI within your own patch
 FoI1 <- vector("list",npatch)  # Set FoI list
 Case1 <- vector("list",npatch) # Set Case list
 for(i in 1:npatch){ # Populate list with zeros to later sum together
  FoI1[[i]] <- c(rep(0,nage))
 }

 c <- t(matrix((c_within),nrow=nage,ncol=nage))
 for (i in 1:npatch){
  if(i!=npatch){ # FoI within each school
   Im <- t(matrix((I[[i]]),nrow=1,ncol=nage))
   Nm <- sum(N[[i]])

   FoI1[[i]] <- (beta)*(c%*%(Im/Nm))
  } else { # FoI within in external pop.
   for (j in 1:nage){
    Im <- I[[i]][j]
    Nm <- N[[i]][j]

    if (N[[i]][[j]]!=0){
     FoI1[[i]][j] <- FoI1[[i]][j] + beta*c[j,j]*(Im/Nm)
    } else {
     FoI1[[i]][j] <- 0
    }
   }
  }
  for (j in 1:nage){ # calculate case numbers for internal infections
   if (S[[i]][j]!=0){
    Case1[[i]][j] <- rbinom(1,S[[i]][j],step*FoI1[[i]][j])
   } else {
    Case1[[i]][j] <- 0
   }
  }
 }

 # FoI2 - FoI between schools
 FoI2 <- vector("list",npatch)  # Set FoI list
 Case2 <- vector("list",npatch) # Set Case list
 for(i in 1:npatch){ # Populate list with zeros to later sum together
  FoI2[[i]] <- c(rep(0,nage))
  Case2[[i]] <- c(rep(0,nage))
 }

 c <- t(matrix((c_school),nrow=nage,ncol=nage))
 for (i in SchoolPatches){
  for (j in SchoolPatches[!SchoolPatches==i]){
   Im <- t(matrix((I[[j]]),nrow=1,ncol=nage))
```

```
    Nm <- sum(N[[j]])

    FoI2[[i]] <- FoI2[[i]] + t(matrix((beta)*(c%*%(Im/Nm)),nrow=1,ncol=nage))
   }
   for (j in 1:nage){ # calculate case numbers for infections between schools
    if (S[[i]][j]!=0){
     Case2[[i]][j] <- rbinom(1,S[[i]][j],step*FoI2[[i]][j])
    } else {
     Case2[[i]][j] <- 0
    }
   }
  }

  # FoI3 - FoI between schools and the external pop.
  FoI3 <- vector("list",npatch)  # Set FoI list
  Case3 <- vector("list",npatch) # Set Case list
  for(i in 1:npatch){ # Populate list with zeros to later sum together
   FoI3[[i]] <- c(rep(0,nage))
  }

  c <- t(matrix((c_external),nrow=nage,ncol=nage))
  for (i in 1:npatch){ # FoI for infections from external population into schools
   if (i!=npatch){
    for (a1 in 1:nage){
     for (a2 in 1:nage){
      if (N[[npatch]][a2]!=0){
       Im <- I[[npatch]][a2]
       Nm <- N[[npatch]][a2]

       FoI3[[i]][a1] <- FoI3[[i]][a1] + beta*c[a1,a2]*(Im/Nm)
      }
     }
    }
   } else { # so i=31, calculate FoI for infections from schools
    for (a1 in 1:nage){
     for (j in SchoolPatches){
      for (a2 in 1:nage){
       if (N[[j]][a2]!=0){
        Im <- I[[j]][a2]
        Nm <- N[[j]][a2]

        FoI3[[i]][a1] <- FoI3[[i]][a1] + beta*c[a1,a2]*(Im/Nm)
       }
      }
     }
    }
   }
   for (j in 1:nage){
    if (S[[i]][j]!=0){
     Case3[[i]][j] <- rbinom(1,S[[i]][j],step*FoI3[[i]][j])
    } else {
     Case3[[i]][j] <- 0
    }
   }
  }

#   # Sum three FoIs for main FoI list to use in the model
#   for (i in 1:npatch){
#    FoI[[i]] <- FoI1[[i]] + FoI2[[i]] + FoI3[[i]]
#   }

  # Calculate Case, Infe and Reco
  for (i in 1:npatch){
   for (j in 1:nage){
    if (E[[i]][j]!=0){
     Infe[[i]][j] <- rbinom(1,E[[i]][j],step*delta)
    } else {
     Infe[[i]][j] <- 0
    }
    if (I[[i]][j]!=0){
     Reco[[i]][j] <- rbinom(1,I[[i]][j],step*gamma)
    } else {
     Reco[[i]][j] <- 0
    }
    # Main part of the model - movement between compartments
    S[[i]][j] <- S[[i]][j] - Case1[[i]][j] - Case2[[i]][j] - Case3[[i]][j]
    E[[i]][j] <- E[[i]][j] + Case1[[i]][j] + Case2[[i]][j] + Case3[[i]][j] - Infe[[i]][j]
    I[[i]][j] <- I[[i]][j] + Infe[[i]][j] - Reco[[i]][j]
    R[[i]][j] <- R[[i]][j] + Reco[[i]][j]
   }
  }
```

```
# Time series for each patch
for (i in 1:npatch){
 patch_timeseries[i,k] <- sum(I[[i]])
 cumulative_patch_timeseries[i,k] <- sum(R[[i]])
}

 # Calculates the time series for each age group across all patches
 x_i <- numeric(0)
 y_i <- numeric(0)
 x_e <- numeric(0)
 y_e <- numeric(0)
 for (j in 1:nage){
  for (i in 1:npatch){
   z_i <- I[[i]][j]
   z_e <- E[[i]][j]
   y_i <- append(y_i,z_i)
   y_e <- append(y_e,z_e)
  }
  x_i <- append(x_i,sum(y_i))
  y_i <- numeric(0)
  x_e <- append(x_e,sum(y_e))
  y_e <- numeric(0)
 }
 # Time series for each age group
 age_timeseries[,k] <- x_i
 age_timeseries_exp[,k] <- x_e
}
close(progressbar) # Close the progress bar

# Age-specific time series
age_timeseries.1[q,] <- age_timeseries[1,]
age_timeseries.2[q,] <- age_timeseries[2,]
age_timeseries.3[q,] <- age_timeseries[3,]
age_timeseries.4[q,] <- age_timeseries[4,]
age_timeseries.5[q,] <- age_timeseries[5,]
age_timeseries.6[q,] <- age_timeseries[6,]
age_timeseries.7[q,] <- age_timeseries[7,]

age_timeseries_exp.1[q,] <- age_timeseries_exp[1,]
age_timeseries_exp.2[q,] <- age_timeseries_exp[2,]
age_timeseries_exp.3[q,] <- age_timeseries_exp[3,]
age_timeseries_exp.4[q,] <- age_timeseries_exp[4,]
age_timeseries_exp.5[q,] <- age_timeseries_exp[5,]
age_timeseries_exp.6[q,] <- age_timeseries_exp[6,]
age_timeseries_exp.7[q,] <- age_timeseries_exp[7,]

#############################################################################################################
# Final size and duration statistics
#############################################################################################################
patch_finalsize <- numeric(0)
age_finalsize   <- numeric(0)

Age_Duration.Start <- rep(0,nage)
Age_Duration.End <- rep(0,nage)
Age_Duration <- rep(0,nage)

Patch_Duration.Start <- rep(0,npatch)
Patch_Duration.End <- rep(0,npatch)
Patch_Duration <- rep(0,npatch)

# Final size matrix for calculations
finalsize <- matrix(0,nrow=npatch,ncol=nage)
for (i in 1:npatch){
 for (j in 1:nage){
  finalsize[i,j] <- R[[i]][j]
 }
}

# Final size by patch
for (i in 1:npatch){
 if (i < nprimary+1){ # Assign population size denominator and colour for plots
  pop <- ageSize[3]/nprimary
  patch_finalsize[i] <- sum(finalsize[i,])/pop
 } else {
  if (i < nprimary+nsecondary+1){
   pop <- ageSize[4]/nsecondary
   patch_finalsize[i] <- sum(finalsize[i,])/pop
  } else {
   pop <- sum(c(ageSize[1],ageSize[2],ageSize[5],ageSize[6],ageSize[7]))
   patch_finalsize[i] <- sum(finalsize[i,])/pop
```

```
   }
  }
}

# Final size by age group
for (j in 1:nage){
  age_finalsize[j] <- sum(finalsize[,j])/ageSize[j]
}

# Vaccination matrix
vaccination <- matrix(0,nrow=npatch,ncol=nage)
for (i in 1:npatch){
  for (j in 1:nage){
    vaccination[i,j] <- W[[i]][j]
  }
}

# Vaccination by patch
patch_vaccination <- numeric(0)
for (i in 1:npatch){
  if (i < nprimary+1){ # Assign population size denominator and colour for plots
    pop <- ageSize[3]/nprimary
    patch_vaccination[i] <- sum(vaccination[i,])/pop
  } else {
    if (i < nprimary+nsecondary+1){
      pop <- ageSize[4]/nsecondary
      patch_vaccination[i] <- sum(vaccination[i,])/pop
    } else {
      pop <- sum(c(ageSize[1],ageSize[2],ageSize[5],ageSize[6],ageSize[7]))
      patch_vaccination[i] <- sum(vaccination[i,])/pop
    }
  }
}

# Vaccination by age group
age_vaccination <- numeric(0)
for (j in 1:nage){
  age_vaccination[j] <- sum(vaccination[,j])/ageSize[j]
}

# Age-specific duration
for (j in 1:nage){

  # Establish start
  for (d in 1:nsteps){
    if ((age_timeseries[j,d]+age_timeseries_exp[j,d]>0)&(Age_Duration.Start[j]==0)){
      Age_Duration.Start[j] <- d
    }
  }

  # Establish end
  for (d in nsteps:1){
    if ((age_timeseries[j,d]+age_timeseries_exp[j,d]>0)&(Age_Duration.End[j]==0)){
      Age_Duration.End[j] <- d
    }
  }

  # Establish duration
  if (Age_Duration.Start[j]+Age_Duration.End[j]==0){
    Age_Duration[j] <- 0
  } else {
    Age_Duration[j] <- Age_Duration.End[j]-Age_Duration.Start[j]+1
  }
}

# patch-specific duration
for (i in 1:npatch){

  # Establish start
  for (d in 1:nsteps){
    if ((patch_timeseries[i,d]>0)&(Patch_Duration.Start[i]==0)){
      Patch_Duration.Start[i] <- d
    }
  }

  # Establish end
  for (d in nsteps:1){
    if ((patch_timeseries[i,d]>0)&(Patch_Duration.End[i]==0)){
      Patch_Duration.End[i] <- d
    }
  }
```

```
 # Establish duration
 if (Patch_Duration.Start[i]+Patch_Duration.End[i]==0){
   Patch_Duration[i] <- 0
 } else {
   Patch_Duration[i] <- Patch_Duration.End[i]-Patch_Duration.Start[i]+1
 }
}


# Enter final size data into .csv
age_sims[q,]       <- age_finalsize
patch_sims[q,]     <- patch_finalsize
patch_outbreaks[q,] <- Patch_Duration
# write.table(age_timeseries, row.names=F, col.names=T,
#           file=paste("20140425 sim number=",q,", epsilon 1=",epsilon.1,", patches=",npatch,", seeded=",pop_index," age_timeseries output.csv", sep=""))
# write.table(patch_timeseries, row.names=F, col.names=T,
#           file=paste("20140425 sim number=",q,", epsilon 1=",epsilon.1,", patches=",npatch,", seeded=",pop_index," patch_timeseries output.csv", sep=""))

#############################################################################################################
# Label stamp for standardised output document names
#############################################################################################################
labelstamp <- paste(" seed=", pop_index,
                    " epsilon.1=", round(epsilon.1,3),
                    " R0=", round(R0,2))

#############################################################################################################
# Plots
#############################################################################################################

# # Plot by age group
# png(file=paste(datestamp,", sim number=",q, labelstamp,", age output.png", sep=""))
# plot(age_timeseries[1,]/ageSize[1],
#     type="l",
#     col=2,
#     lwd=4,
#     xlab="Time, in days/10",
#     ylab="Fraction infected",
#     ylim=c(0,1.1*max(c(age_timeseries[1,]/ageSize[1],
#                    age_timeseries[2,]/ageSize[2],
#                    age_timeseries[3,]/ageSize[3],
#                    age_timeseries[4,]/ageSize[4],
#                    age_timeseries[5,]/ageSize[5],
#                    age_timeseries[6,]/ageSize[6],
#                    age_timeseries[7,]/ageSize[7]))),
#     xlim=c(0,k),
#     cex.main=0.9,
#     main=paste("31 patch stochastic model with heterogeneous vaccination \nTotal metapopulation of ",sum(ageSize),",\nnpri_low_v = ",npri_low_v,", tau =
",round(tau,4),",\nnsec_low_v = ",nsec_low_v,", k = ",k,sep=""))
# lines(age_timeseries[2,]/ageSize[2],type="l",col=3,lwd=4)
# lines(age_timeseries[3,]/ageSize[3],type="l",col=4,lwd=4)
# lines(age_timeseries[4,]/ageSize[4],type="l",col=5,lwd=4)
# lines(age_timeseries[5,]/ageSize[5],type="l",col=6,lwd=4)
# lines(age_timeseries[6,]/ageSize[6],type="l",col=7,lwd=4)
# lines(age_timeseries[7,]/ageSize[7],type="l",col=8,lwd=4)
# legend("topright",
#       legend=c("0 - 1",
#                "2 - 3",
#                "4 - 10",
#                "11 - 16",
#                "17 - 24",
#                "25 - 64",
#                "65+"),
#       col=c(2,3,4,5,6,7,8),
#       bty="n",
#       lwd=5,
#       cex=0.7)
# dev.off()
#
# #Plot by patch
# #x11()
# png(file=paste(datestamp,", sim number=",q, labelstamp,", patch output.png", sep=""))
# par(mfrow=c(7,5))
# par(mar=c(2,2,2,1))
# for (i in 1:npatch){
#   if (i < nprimary+1){ # Assign population size denominator and colour for plots
#     pop <- ageSize[3]/nprimary
#
#     if (i==seed_patch){
#       colour <- "chocolate1"
#     } else {
```

```
#      colour <- 4
#    }
#  } else {
#    if (i < nprimary+nsecondary+1){
#      pop <- ageSize[4]/nsecondary
#
#      if (i==seed_patch){
#        colour <- "chocolate1"
#      } else {
#        colour <- 5
#      }
#    } else {
#      pop <- sum(c(ageSize[1],ageSize[2],ageSize[5],ageSize[6],ageSize[7]))
#
#      if (i==seed_patch){
#        colour <- "chocolate1"
#      } else {
#        colour <- 9
#      }
#    }
#  }
#  plot(patch_timeseries[i,]/pop,
#       type="l",
#       col=colour,
#       lwd=4,
#       xlim=c(0,k),
#       ylim=c(0,max(patch_timeseries[i,]/pop)*1.1),
#       #xlab="Time, in days/10",
#       #ylab="Fraction infected",
#       cex.main=0.9,
#       main=paste("Pop:",pop,sep=""))
#  #title("Metapopulation patches", outer = TRUE )
# }
#
# dev.off()

#############################################################################################################
# Analysising the results
#############################################################################################################

# Find overall epidemic peak, time of peak
sum_I <- numeric(0)
for (i in 1:nsteps){
  sum_I[i] <- sum(age_timeseries[,i])
}
Overall_epidemic_peak <- max(sum_I)
Peak_time <- match(c(Overall_epidemic_peak),sum_I)

# Individual peaks
Peaks <- numeric(0)
Peaks_time <- numeric(0)
for (i in 1:nage){
  Peaks[i] <- max(age_timeseries[i,])

  if(max(age_timeseries[i,])==0){
    Peaks_time[i] <- 0
  } else {
    Peaks_time[i] <- match(c(Peaks[i]),age_timeseries[i,])
  }
}

# Declare time when all patches had outbreaks
All_infected <- 0
for (i in 1:nsteps){
  if(All_infected==0){
    if(is.element(0,cumulative_patch_timeseries[,i])==0){
      All_infected <- i
    }
  }
}

# Addres epidemic peaks
Peak_age1 <- Peaks[1]/ageSize[1]
Peak_age2 <- Peaks[2]/ageSize[2]
Peak_age3 <- Peaks[3]/ageSize[3]
Peak_age4 <- Peaks[4]/ageSize[4]
Peak_age5 <- Peaks[5]/ageSize[5]
Peak_age6 <- Peaks[6]/ageSize[6]
Peak_age7 <- Peaks[7]/ageSize[7]

Peak_age1_time <- Peaks_time[1]
```

```
Peak_age2_time <- Peaks_time[2]
Peak_age3_time <- Peaks_time[3]
Peak_age4_time <- Peaks_time[4]
Peak_age5_time <- Peaks_time[5]
Peak_age6_time <- Peaks_time[6]
Peak_age7_time <- Peaks_time[7]

# Append results to the data frame
Epidemic_results[dataframerow,] <- c(q,
                        epsilon.1,
                        R0,
                        privac,
                        secvac,
                        Overall_epidemic_peak/sum(ageSize),
                        Peak_time,
                        do.call(sum,R)/sum(ageSize),
                        k,
                        do.call(sum,V)/sum(ageSize),
                        All_infected,
                        sum(Patch_Duration)/nnzero(Patch_Duration),
                        Peak_age1,
                        Peak_age1_time,
                        age_finalsize[1],
                        Age_Duration[1],
                        age_vaccination[1],
                        Peak_age2,
                        Peak_age2_time,
                        age_finalsize[2],
                        Age_Duration[2],
                        age_vaccination[2],
                        Peak_age3,
                        Peak_age3_time,
                        age_finalsize[3],
                        Age_Duration[3],
                        age_vaccination[3],
                        Peak_age4,
                        Peak_age4_time,
                        age_finalsize[4],
                        Age_Duration[4],
                        age_vaccination[4],
                        Peak_age5,
                        Peak_age5_time,
                        age_finalsize[5],
                        Age_Duration[5],
                        age_vaccination[5],
                        Peak_age6,
                        Peak_age6_time,
                        age_finalsize[6],
                        Age_Duration[6],
                        age_vaccination[6],
                        Peak_age7,
                        Peak_age7_time,
                        age_finalsize[7],
                        Age_Duration[7],
                        age_vaccination[7])

 } # end of q

write.table(age_sims, row.names=F, col.names=T,
        file=paste(datestamp,", age_finalsize output.csv", sep=""))
write.table(patch_sims, row.names=F, col.names=T,
        file=paste(datestamp,", patch_finalsize output.csv", sep=""))
write.table(patch_outbreaks, row.names=F, col.names=T,
        file=paste(datestamp,", patch_duration output.csv", sep=""))

# Write age-specific time series to .csv
write.table(age_timeseries.1, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 1 output.csv", sep=""))
write.table(age_timeseries.2, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 2 output.csv", sep=""))
write.table(age_timeseries.3, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 3 output.csv", sep=""))
write.table(age_timeseries.4, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 4 output.csv", sep=""))
write.table(age_timeseries.5, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 5 output.csv", sep=""))
write.table(age_timeseries.6, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 6 output.csv", sep=""))
write.table(age_timeseries.7, row.names=F, col.names=T,
        file=paste(datestamp,", age-specific time series 7 output.csv", sep=""))
```

```
# }  # end of vars4
# }  # end of vars3
# }  # end of vars2
# }  # end of vars1
close(masterpb) # Close the master progress bar

# Export the created data frame
write.table(Epidemic_results, row.names=F, col.names=T,
        file=paste(datestamp, '', patches='',npatch, '', Epidemic results output.csv', sep=''))

# # Report final size statistics
# patch_finalsize;
# age_finalsize;
# k;

#####################################################################################################
# Create and export 2D plots
#####################################################################################################

# if (location==1){
#   source('C:/Users/lsh337197/Dropbox/PhD guff/R stuff/Discrete time SEIR/2Dcharts.R')
# } else {
#   source('C:/Users/Dom's Laptop/Dropbox/PhD guff/R stuff/Discrete time SEIR/2Dcharts.R')
# }
```

SUPPLEMENTARY FIGURES AND TABLES FOR CHAPTER 6

TARGETED VACCINATION IN PRIMARY SCHOOLS ONLY

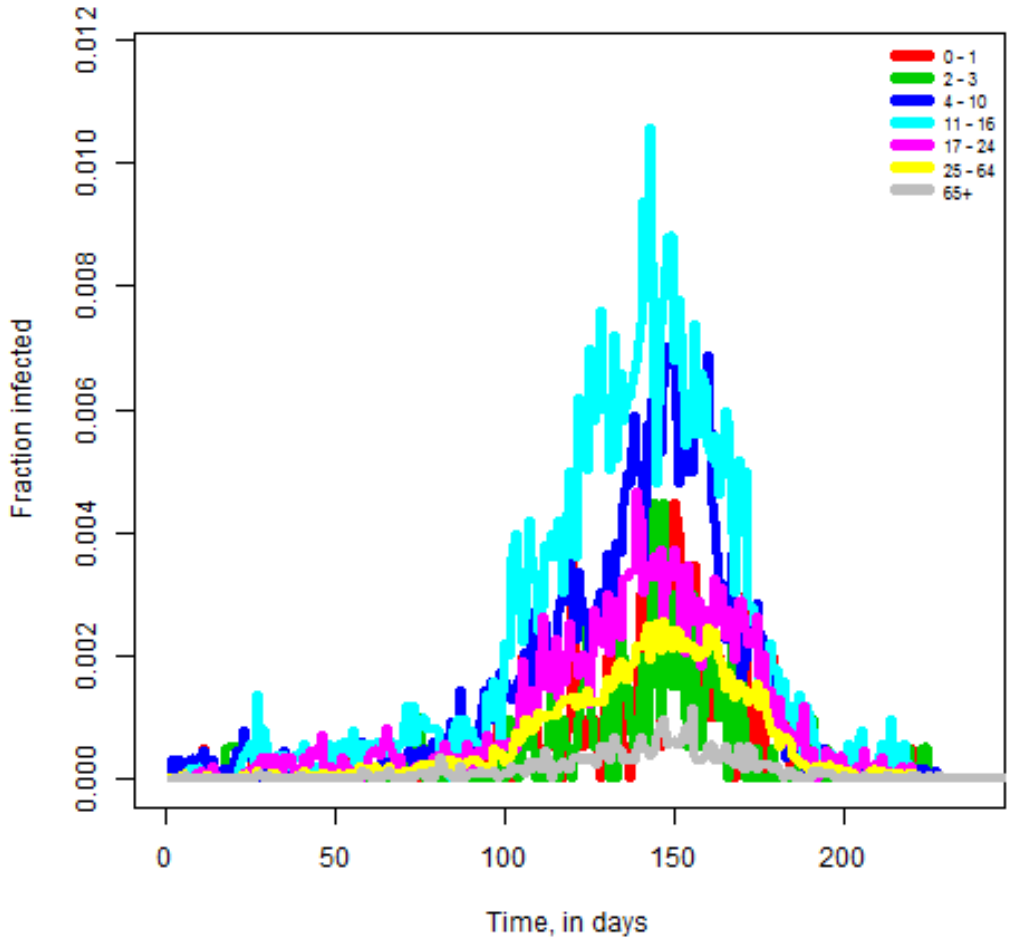


Figure 10.1 - The epidemic curve for a metapopulation configuration with homogeneous targeted vaccination in primary schools of 20% coverage

The epidemic curve for an epidemic in the metapopulation that utilised homogenous targeted vaccination in primary schools with low (20%) coverage (Figure 10.1) shows a reduced epidemic peak for the primary school group (dark blue) when compared to an epidemic without vaccination in schools shown in Figure 6.4. Figure 10.2 shows the patch-specific epidemic curves for each school and the external population. In this simulation, the epidemic started in primary school #19 and spread to several other patches very quickly, though other patches were infected only after 50 days or longer.

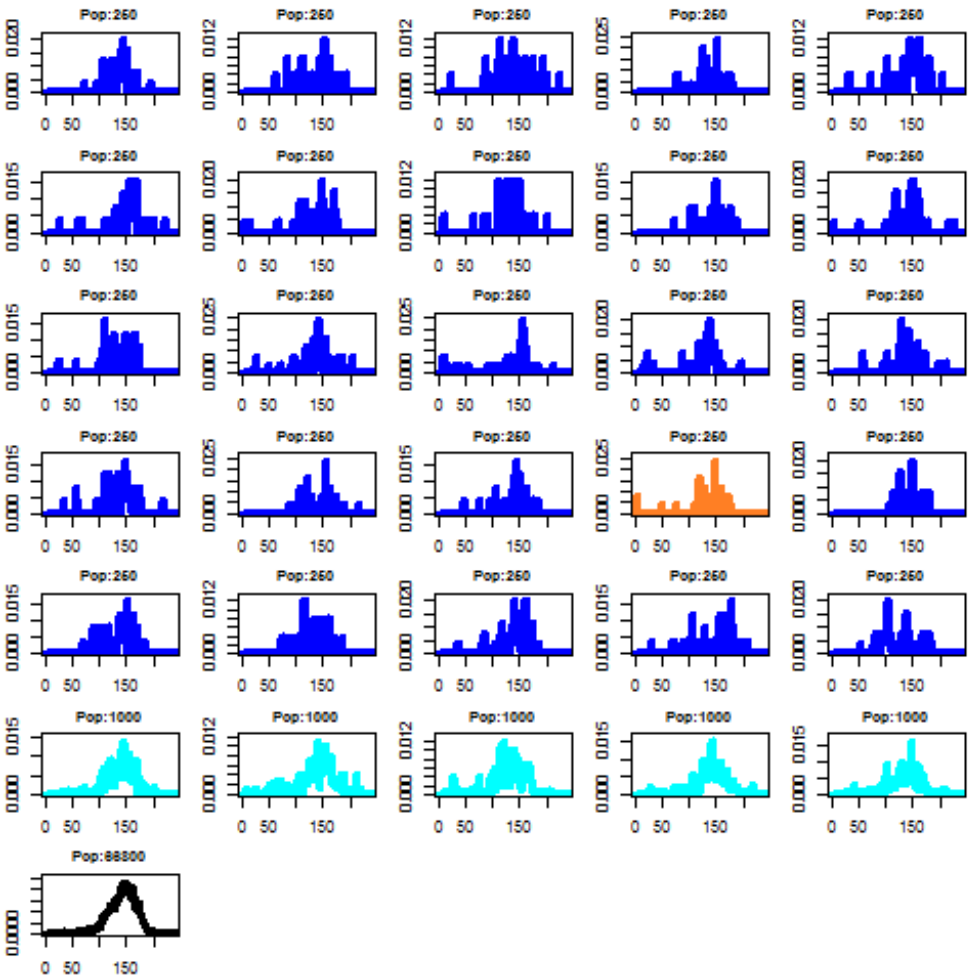


Figure 10.2 - The patch epidemic curves for a metapopulation configuration with homogeneous targeted vaccination in primary schools of 20% coverage

TARGETED HETEROGENEOUS VACCINATION IN PRIMARY SCHOOLS ONLY

The mean duration of ILI epidemics in the metapopulation is not associated with increasing heterogeneity in primary schools vaccine coverage through the number of low-coverage schools (Figure 10.3). The duration of such epidemics appears to vary no more than that expected of random variation, even at high vaccine coverage levels.

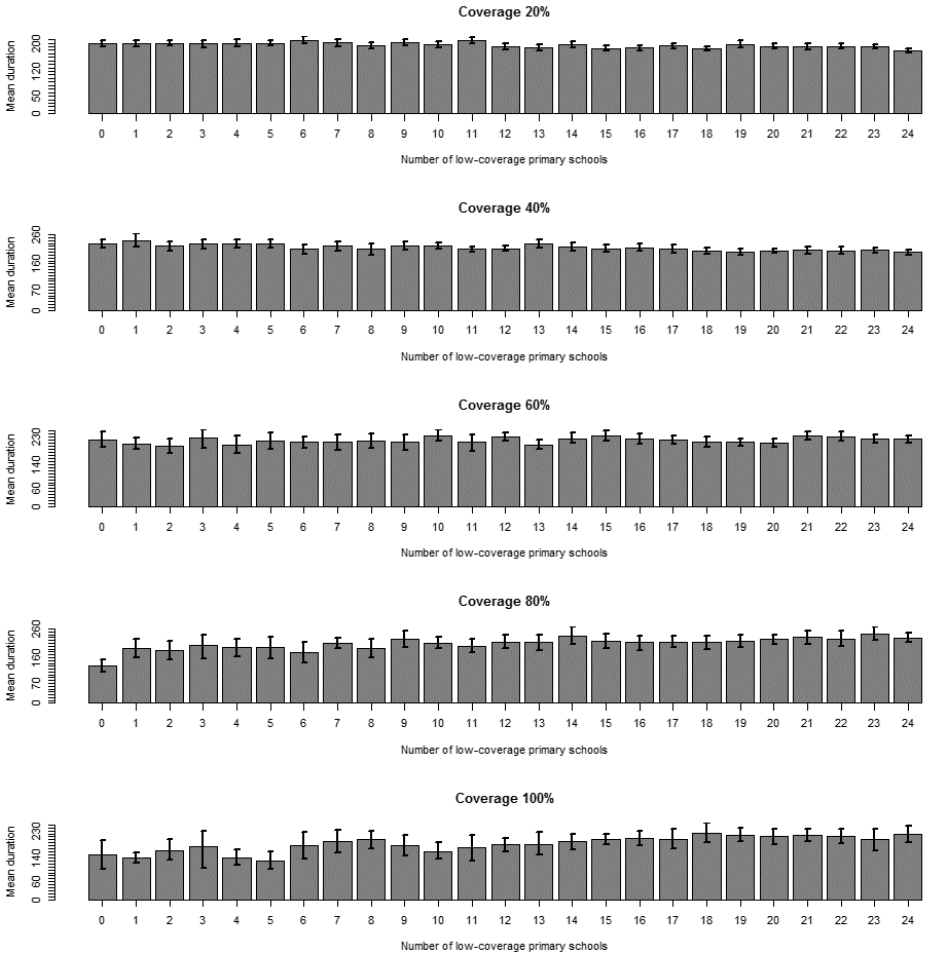


Figure 10.3 - Mean ILI duration for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in primary schools only

The results for the mean peak of ILI epidemics in the metapopulation (Figure 10.4) follow the results for the mean final size (Figure 6.8), that is the association with the number of low-coverage primary schools is weakest at low vaccination coverage of 20%, but the impact on the mean size of the epidemic peak increases as vaccination coverage increases.

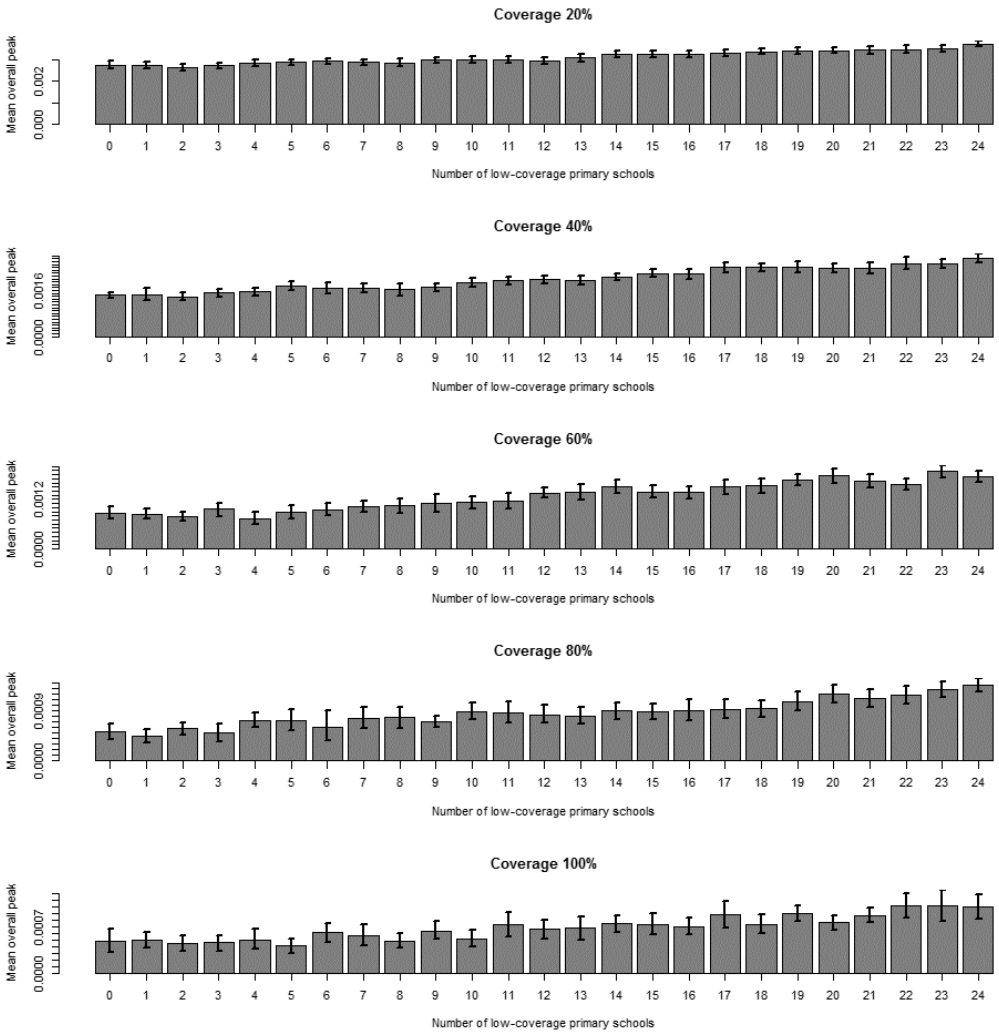


Figure 10.4 - Mean ILI peak for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in primary schools only

The mean time for all metapopulation patches to become infected has a weak association with the number of low-coverage primary schools, though it is clear that at high coverage levels a large number of low-coverage patches is associated with an increased number of epidemics that spread across all patches (Figure 10.5).

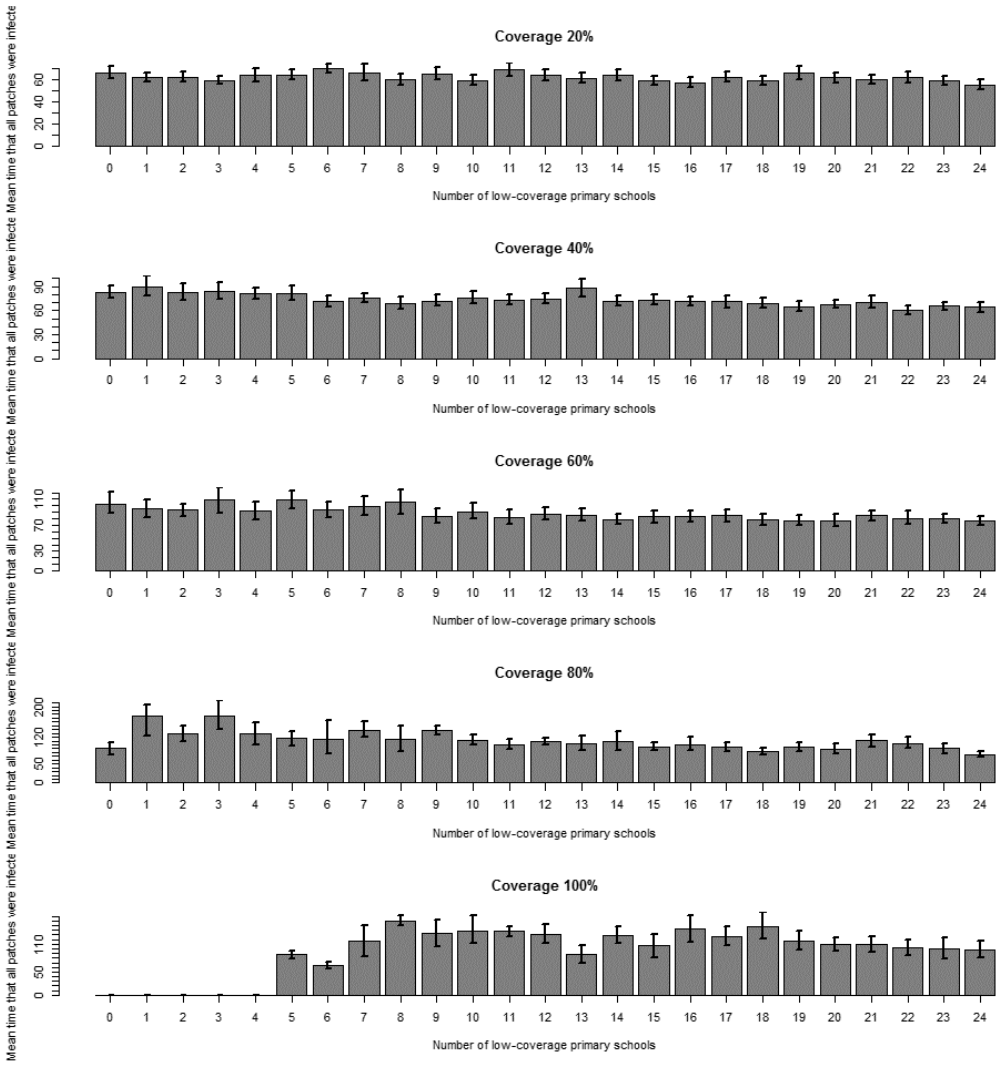


Figure 10.5 - Mean time for all patches to become infected for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in primary schools only

For coverage of 100% across primary schools, epidemics spread to all patches of the metapopulation only when 5 primary schools or more had half the coverage of the remaining 20 primary schools.

Figure 10.6 shows little association between the number of low-coverage primary schools and the mean epidemic peak time for all vaccination coverage levels.

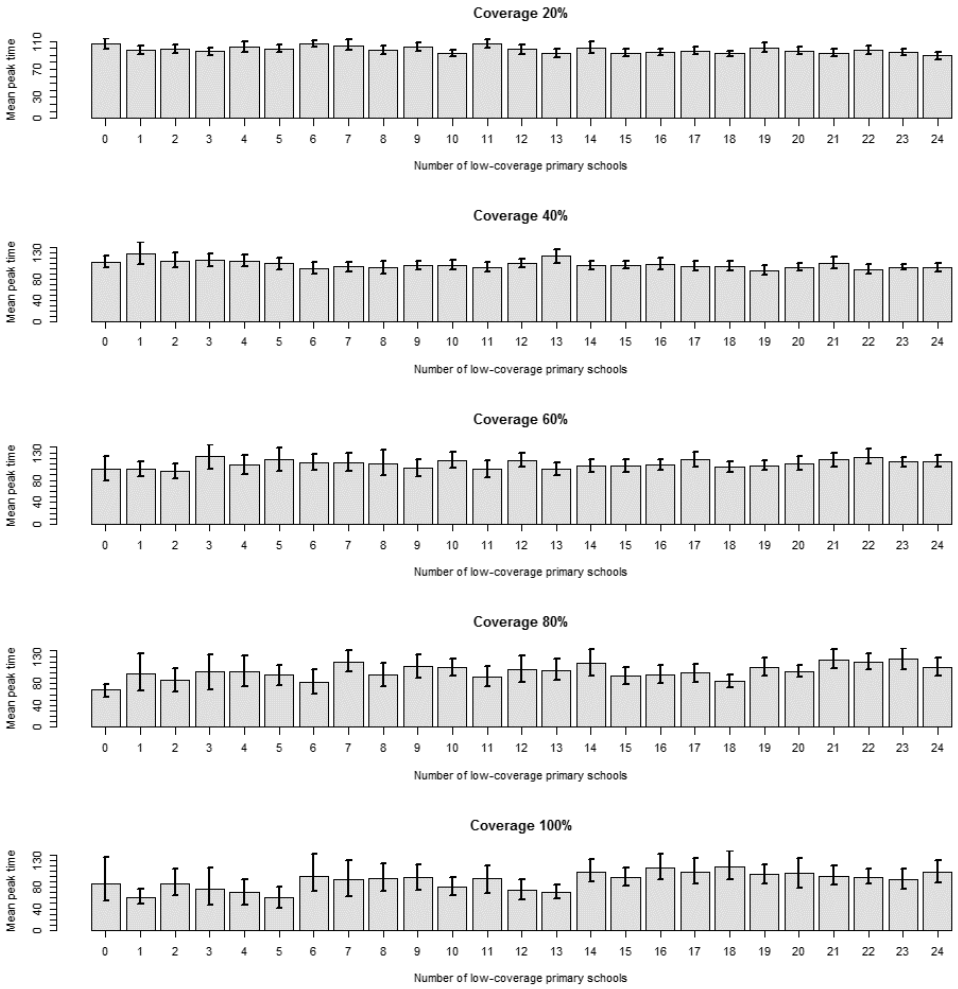


Figure 10.6 - Mean ILI peak time for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in primary schools only

VARYING THE T PARAMETER

The relationship between the level of heterogeneity in vaccination coverage between the school patches and the mean duration of epidemics is less clear than that with the mean final size of epidemics (Figure 10.7). With a greater number of low-coverage primary schools in the metapopulation, the epidemics with the biggest degree of heterogeneity in uptake saw longer epidemics with 100% targeted coverage.

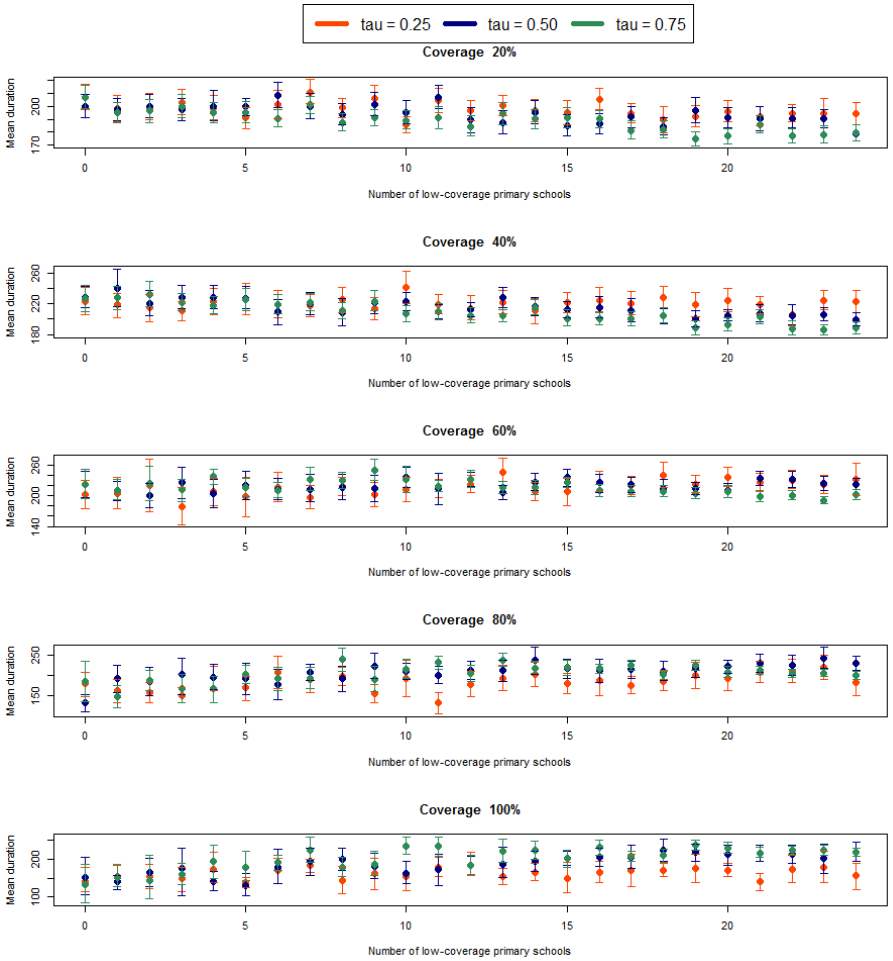


Figure 10.7 - Examining variation in the τ parameter on the mean duration

With results similar to those for the mean final size, the mean peak size of epidemics in the metapopulation is strongly associated with the level of heterogeneity between low- and high-coverage patches (Figure 10.8). High levels of heterogeneity (i.e. $\tau = 0.75$) increase the mean peak size at all vaccination coverage levels over $\tau = 0.25$ and $\tau = 0.50$.

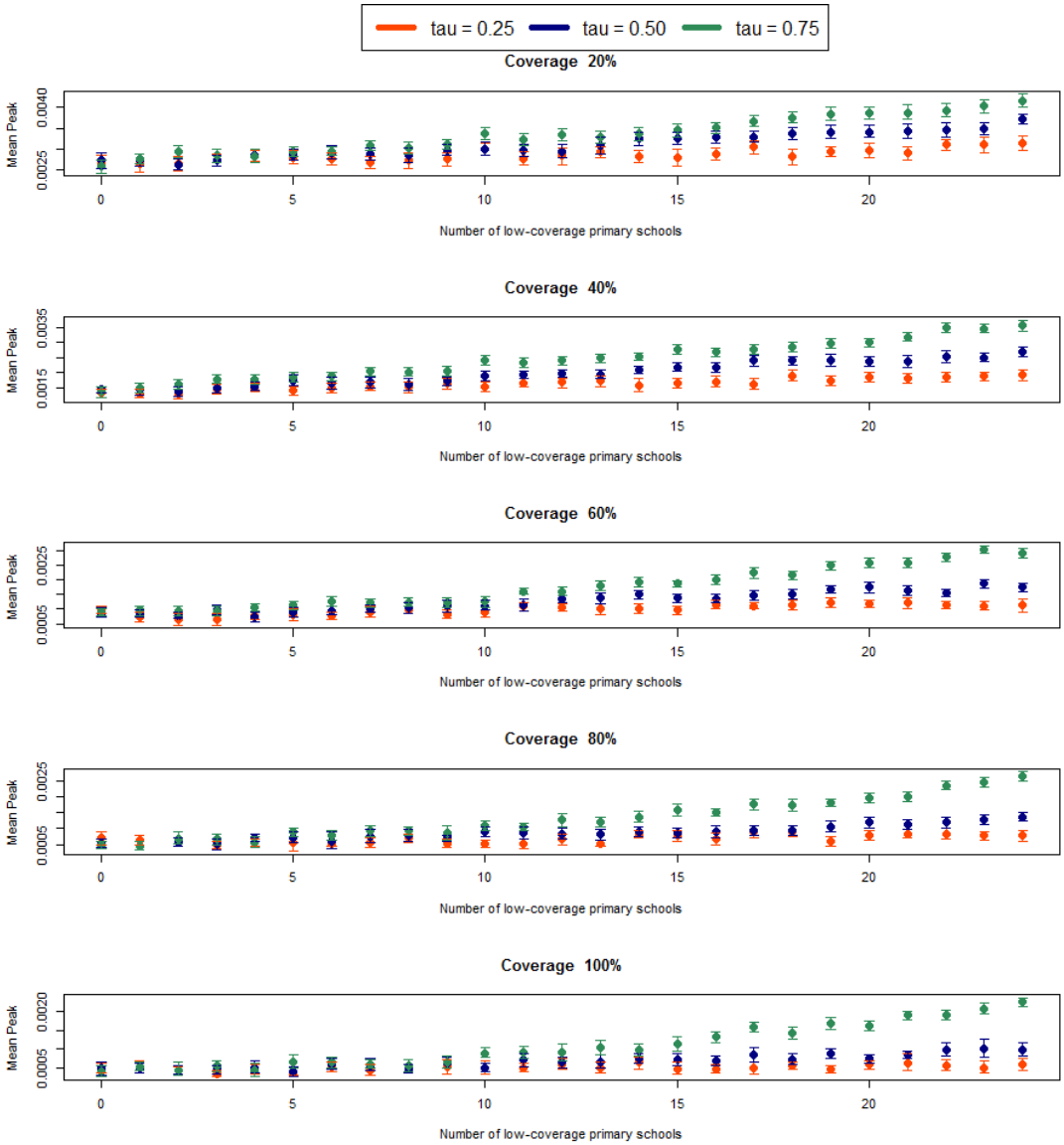


Figure 10.8 - Examining variation in the τ parameter on the mean peak size

There is little evidence that the level of heterogeneity between low- and high-coverage patches is associated with the mean time needed for all patches to become infected during the epidemics (Figure 10.9).

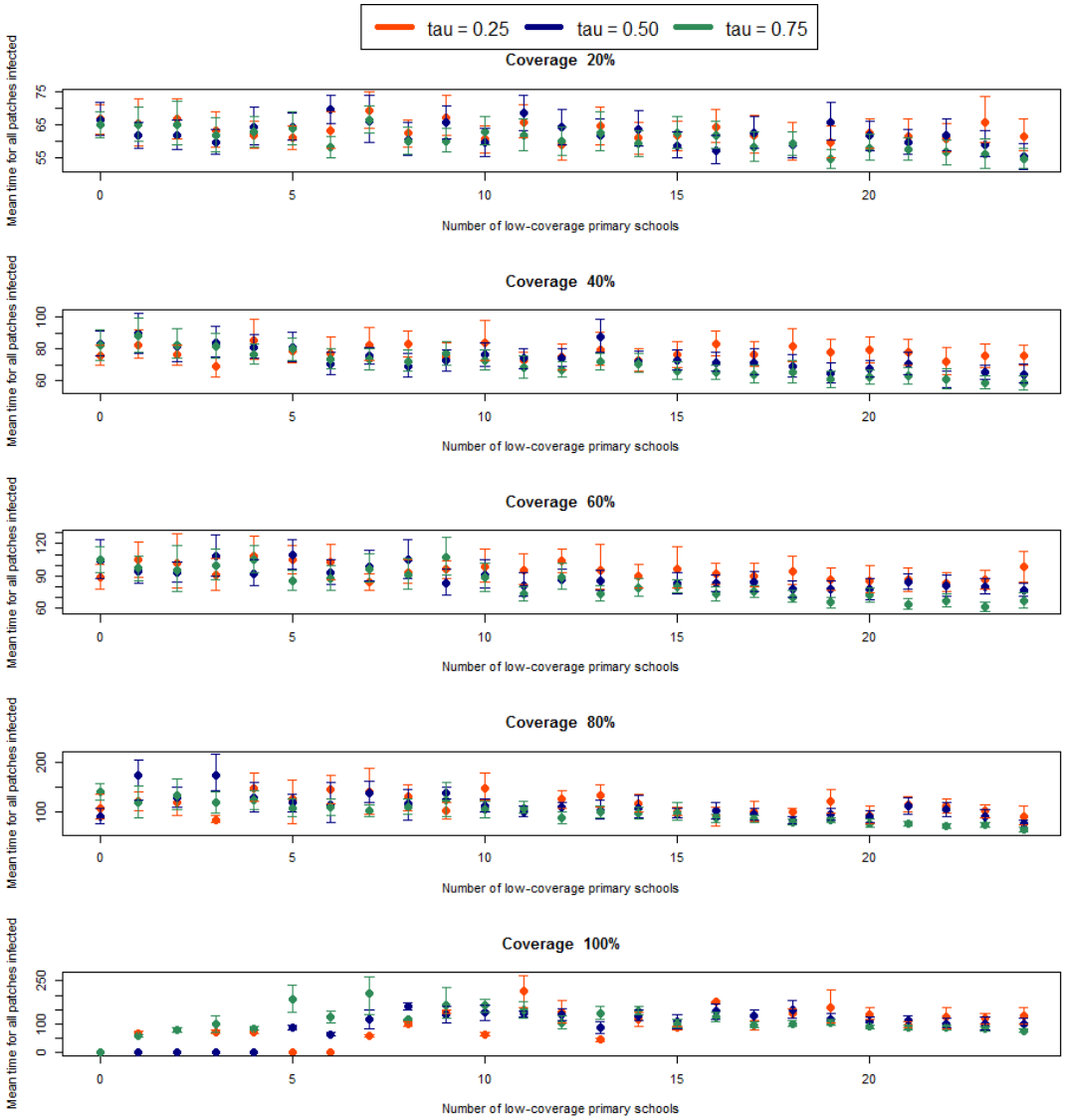


Figure 10.9 - Examining variation in the τ parameter on the mean time for all patches to be infected

There is little evidence for an association between the level of heterogeneity between the vaccination coverage of metapopulation patches and the time of the epidemic peak (Figure 10.10).

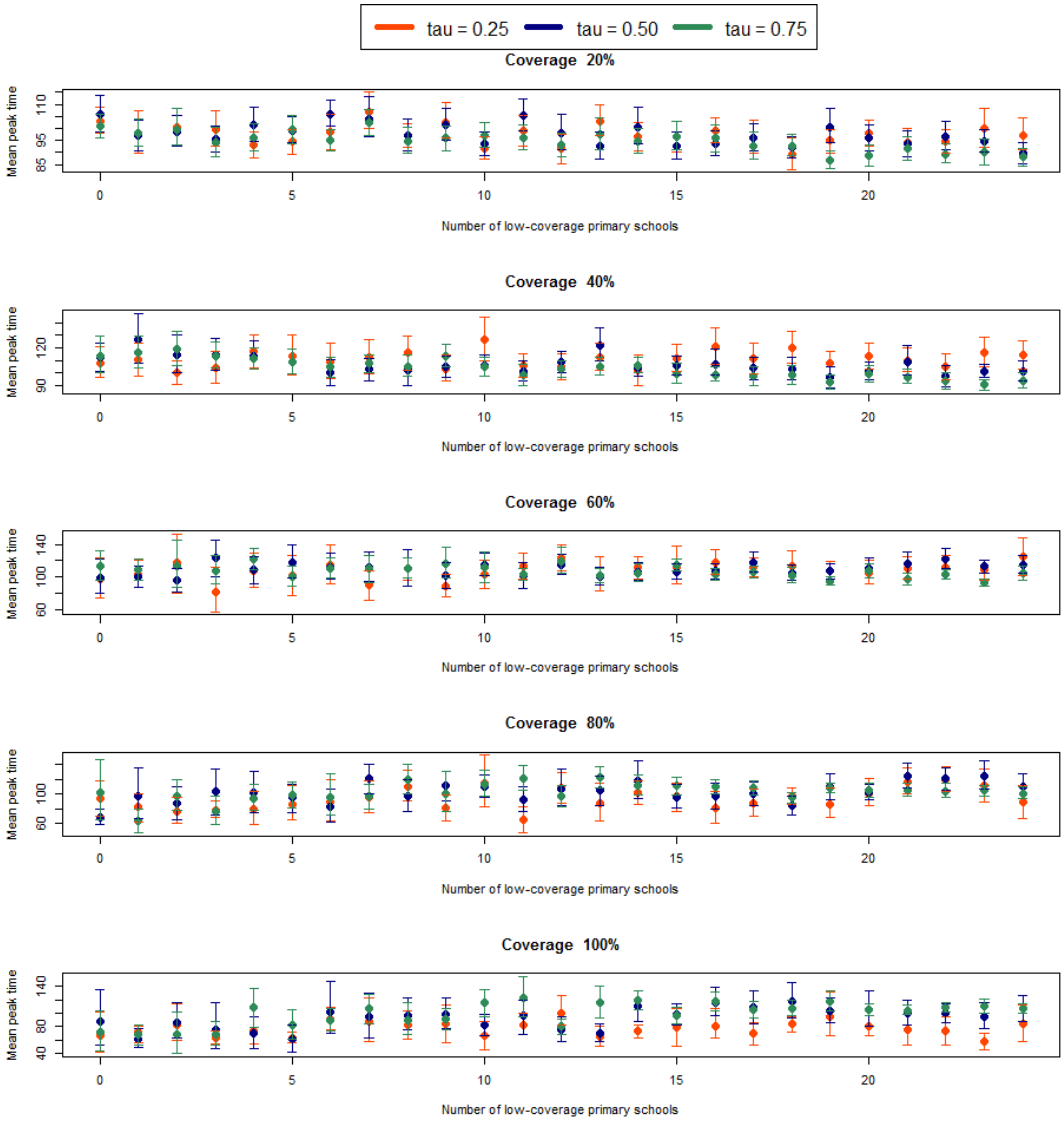


Figure 10.10 - Examining variation in the τ parameter on the mean peak time

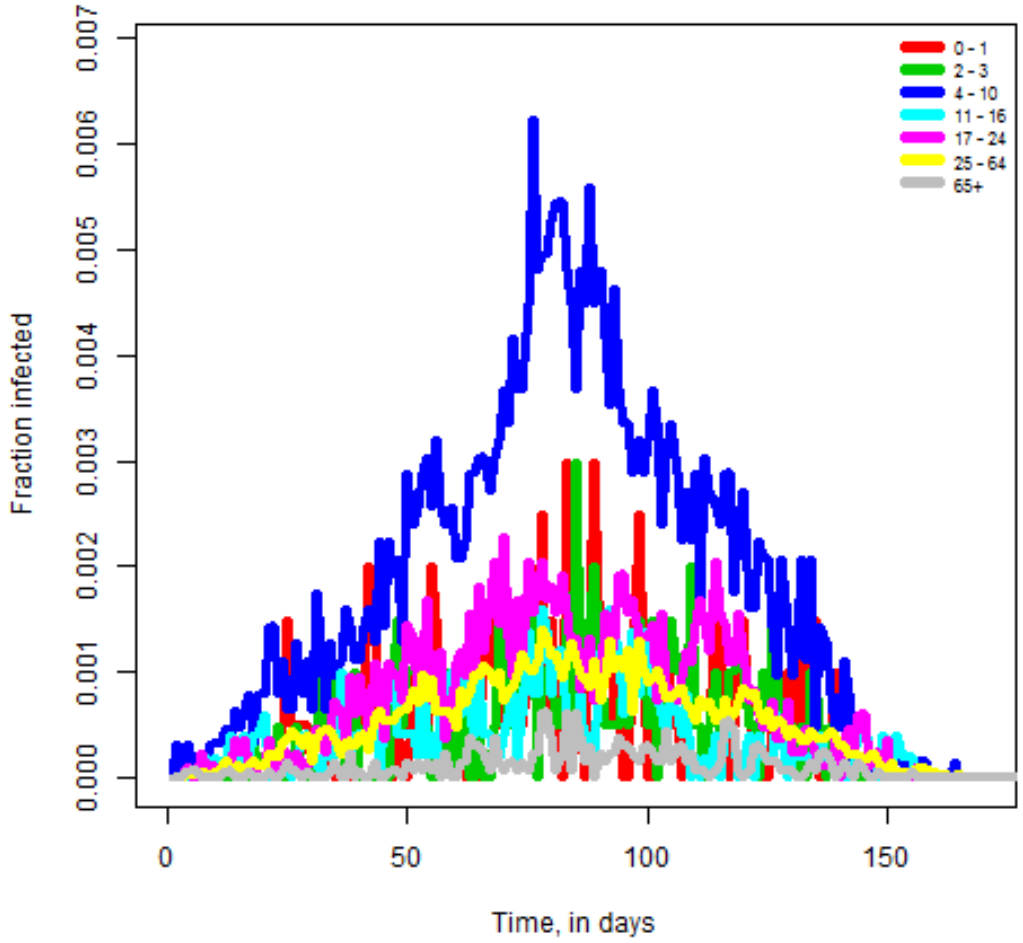


Figure 10.11 - The epidemic curve for a metapopulation configuration with homogeneous targeted vaccination in secondary schools of 80% coverage

An epidemic with 80% homogenous targeted coverage in secondary schools is shown in Figure 10.11, with patch-specific epidemic curves shown in Figure 10.12. In this metapopulation configuration, primary school #14 was seeded and subsequently infected all other patches. Secondary schools still reported infection but the epidemic peak in each secondary school was approximately 0.5%, far less than the approximate 1.2% shown in Figure 6.5 without school-based vaccination.

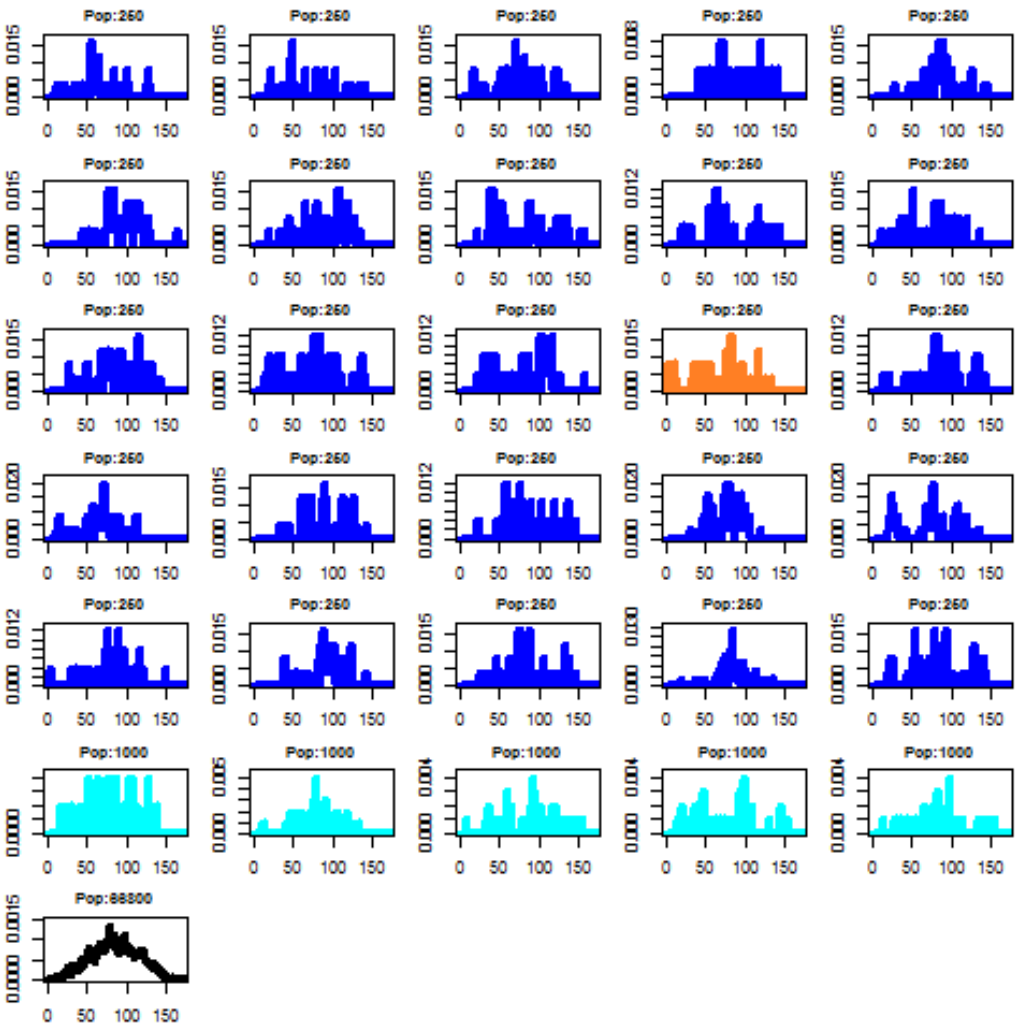


Figure 10.12 - The patch epidemic curves for a metapopulation configuration with homogeneous targeted vaccination in secondary schools of 80% coverage

The variation in the mean duration of epidemics does not follow the trend of the mean final size (Figure 10.13).

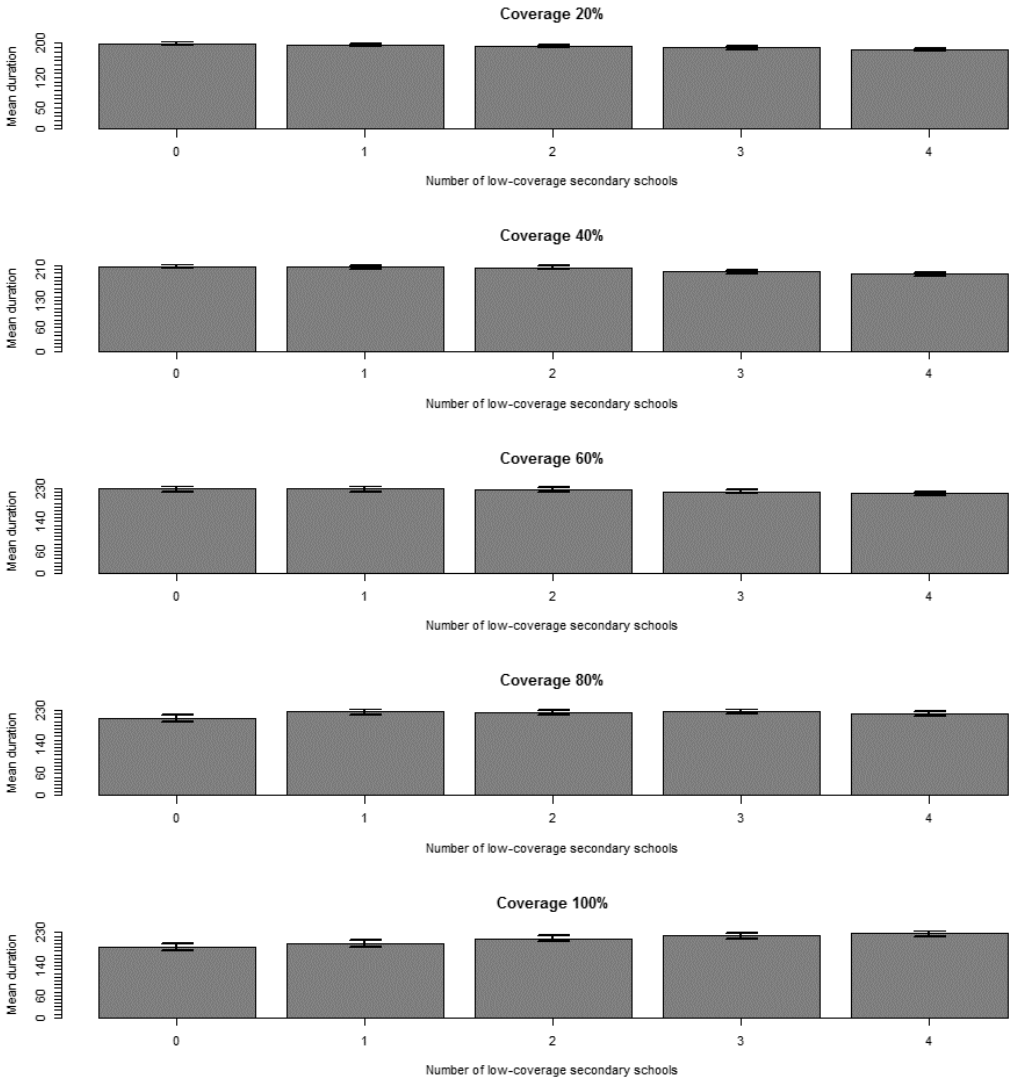


Figure 10.13 - Mean ILI duration for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in secondary schools only

For 20% coverage, increasing the number of low-coverage secondary schools decreases the mean duration of epidemics from 199.00 days (95% CI: 195.44-202.79) to 185.41 days (95% CI: 182.10-188.69), but at the 100% coverage level this trend reverses from 189.81 days (95% CI: 180.34-199.94) to 226.96 days (95% CI: 219.59-234.12).

The mean size of the epidemic peak (Figure 10.14) follows the trend of the mean final size (Figure 6.16). The difference between the mean size of the peak with 0 low-coverage schools and 4 low-coverage schools widens as targeted vaccination coverage increases from 20% to 100%.

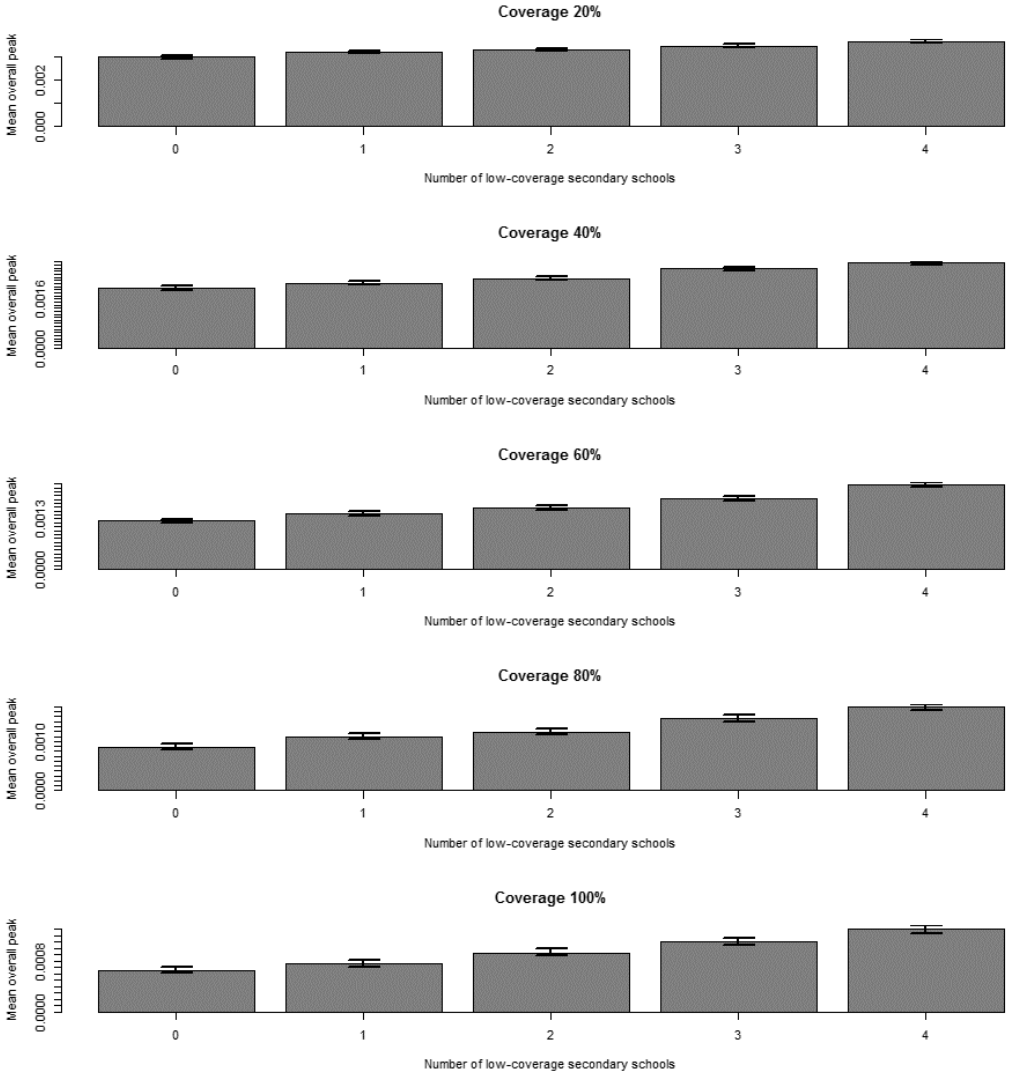


Figure 10.14 - Mean ILI peak for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in secondary schools only

The mean time for all patches to become infected is associated with the increase in low-coverage secondary school patches (Figure 10.15), in that the epidemic reaches all 31 metapopulation patches faster as unintended heterogeneity increases. At 20% coverage the mean time for all patches to become infected reduced from 60.88 days (95% CI: 58.99-62.89) to 57.11 days (95% CI: 55.28-58.96).

With 100% targeted coverage, this difference widened with the mean time of full epidemic spread taking 75.58 days (95% CI: 70.96-80.32) to 70.15 days (95% CI: 66.65-73.74).

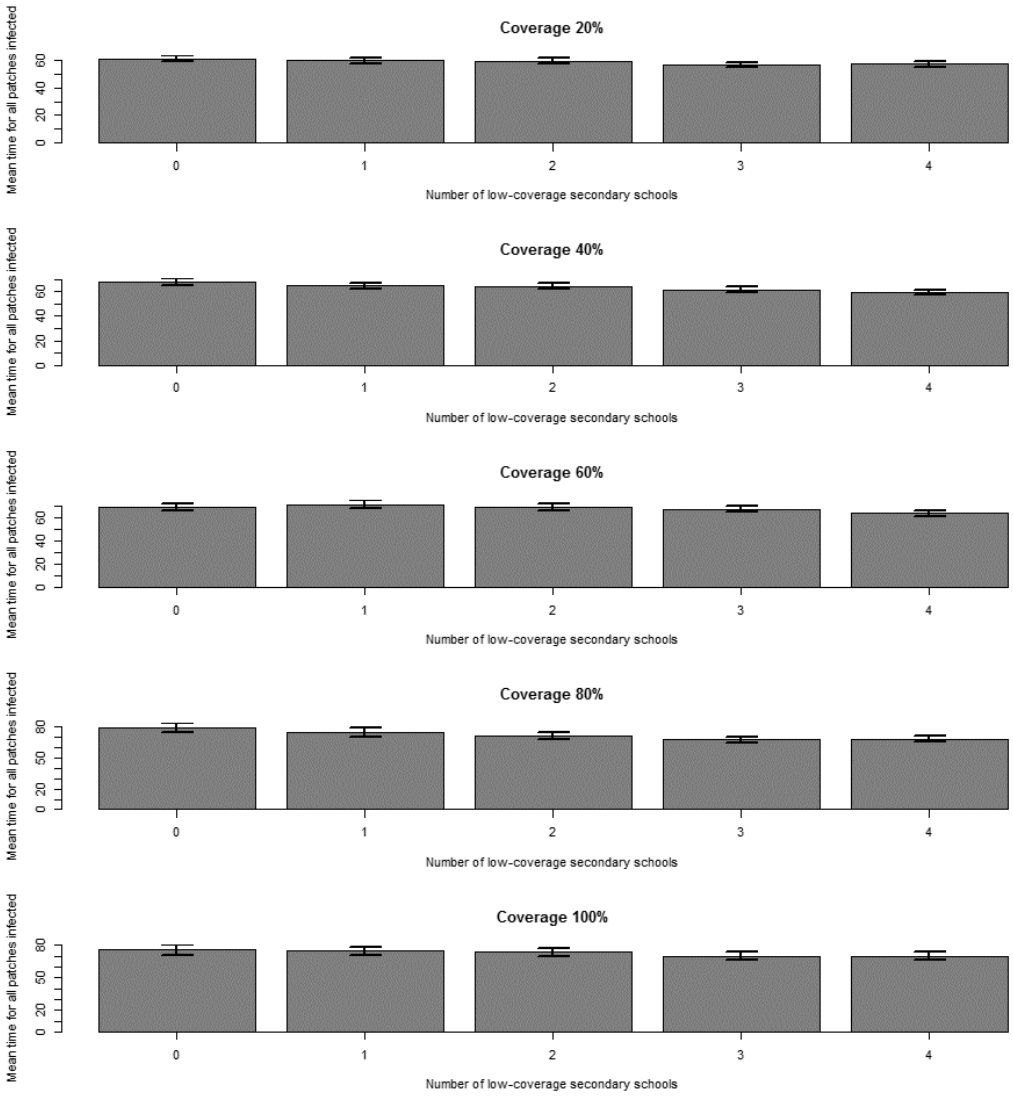


Figure 10.15 - Mean time for all patches to become infected for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in secondary schools only

Results for the mean peak time of the ILI epidemics (Figure 10.16) follow the trend seen with the mean duration of epidemics.

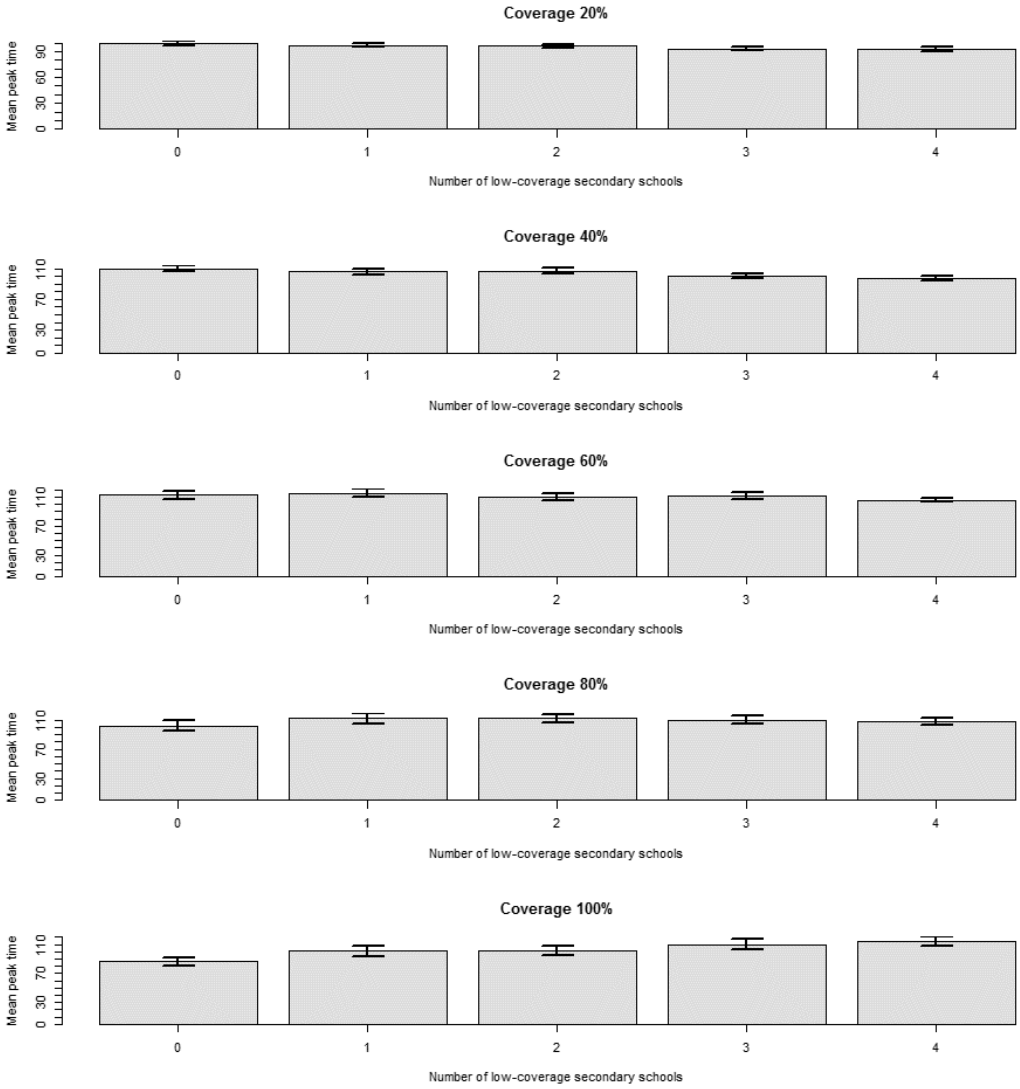


Figure 10.16 - Mean ILI peak time for epidemics in the metapopulation with targeted heterogeneous vaccination coverage in secondary schools only

VARYING THE T PARAMETER

Figure 10.17 shows that there is little evidence for a relationship between the level of heterogeneity between low- and high-coverage patches and the mean duration of epidemics in the metapopulation.

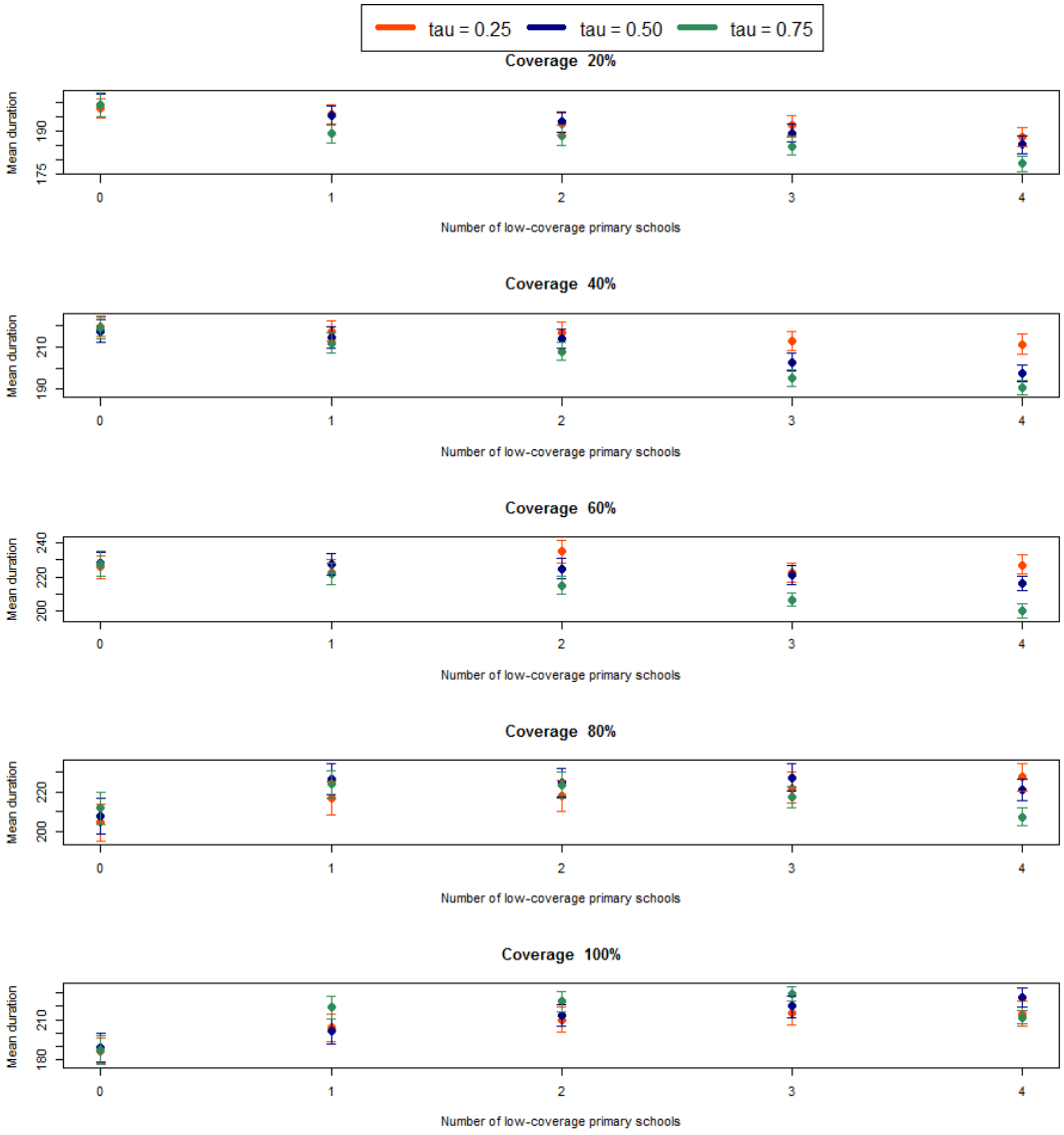


Figure 10.17 - Examining variation in the τ parameter on the mean duration

Increasing the τ parameter to increase heterogeneity in vaccination uptake also increases the mean epidemic peak (Figure 10.18). With an increasing number of low-coverage secondary schools the difference between epidemic peaks with low levels of heterogeneity and those epidemics with high levels of heterogeneity widens for all levels of vaccination coverage.

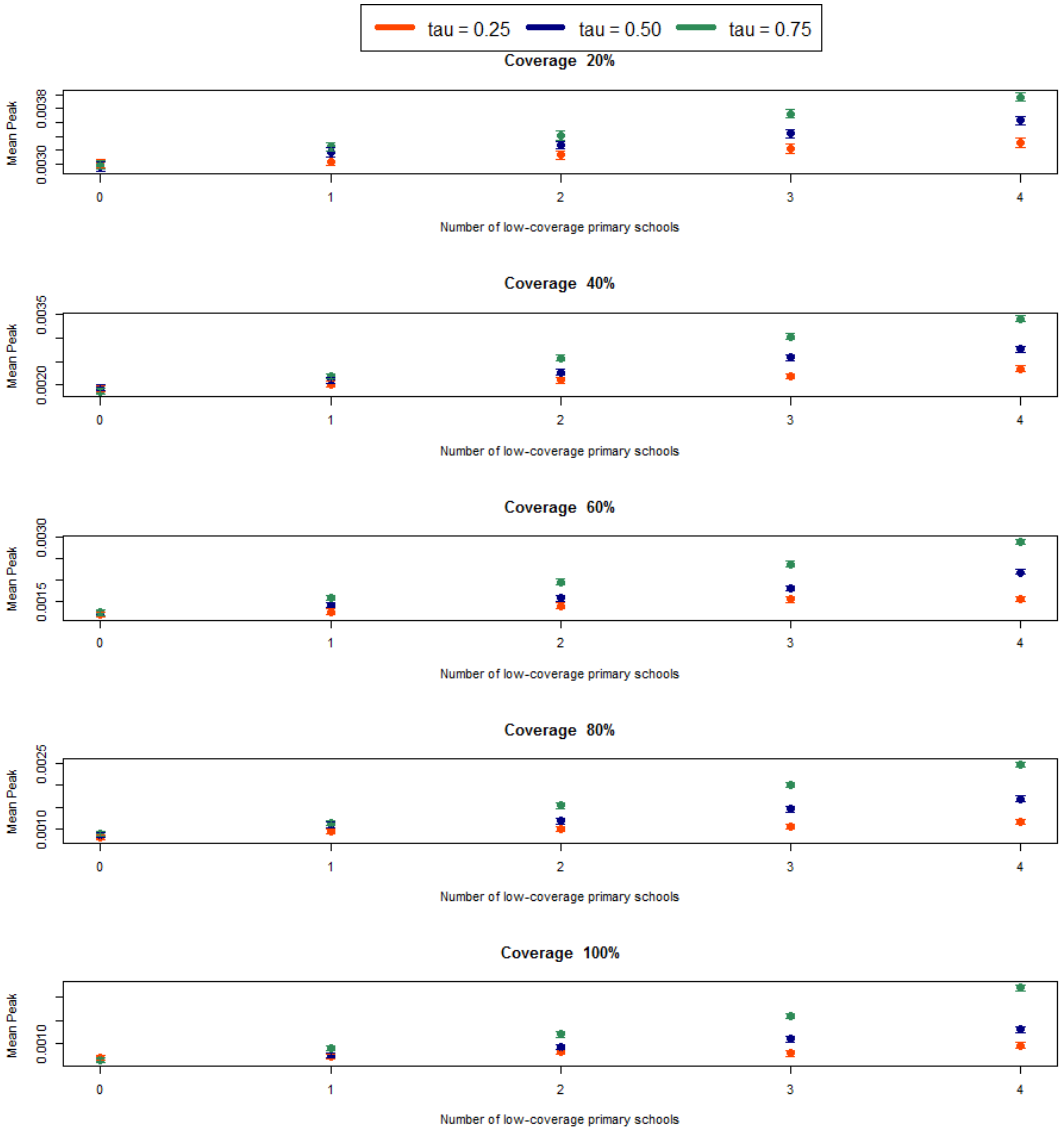


Figure 10.18 - Examining variation in the τ parameter on the mean peak size

There is little evidence for an association between the level of heterogeneity in vaccination coverage and the mean time required for all metapopulation patches to become infected, for all levels of vaccination coverage (Figure 10.19).

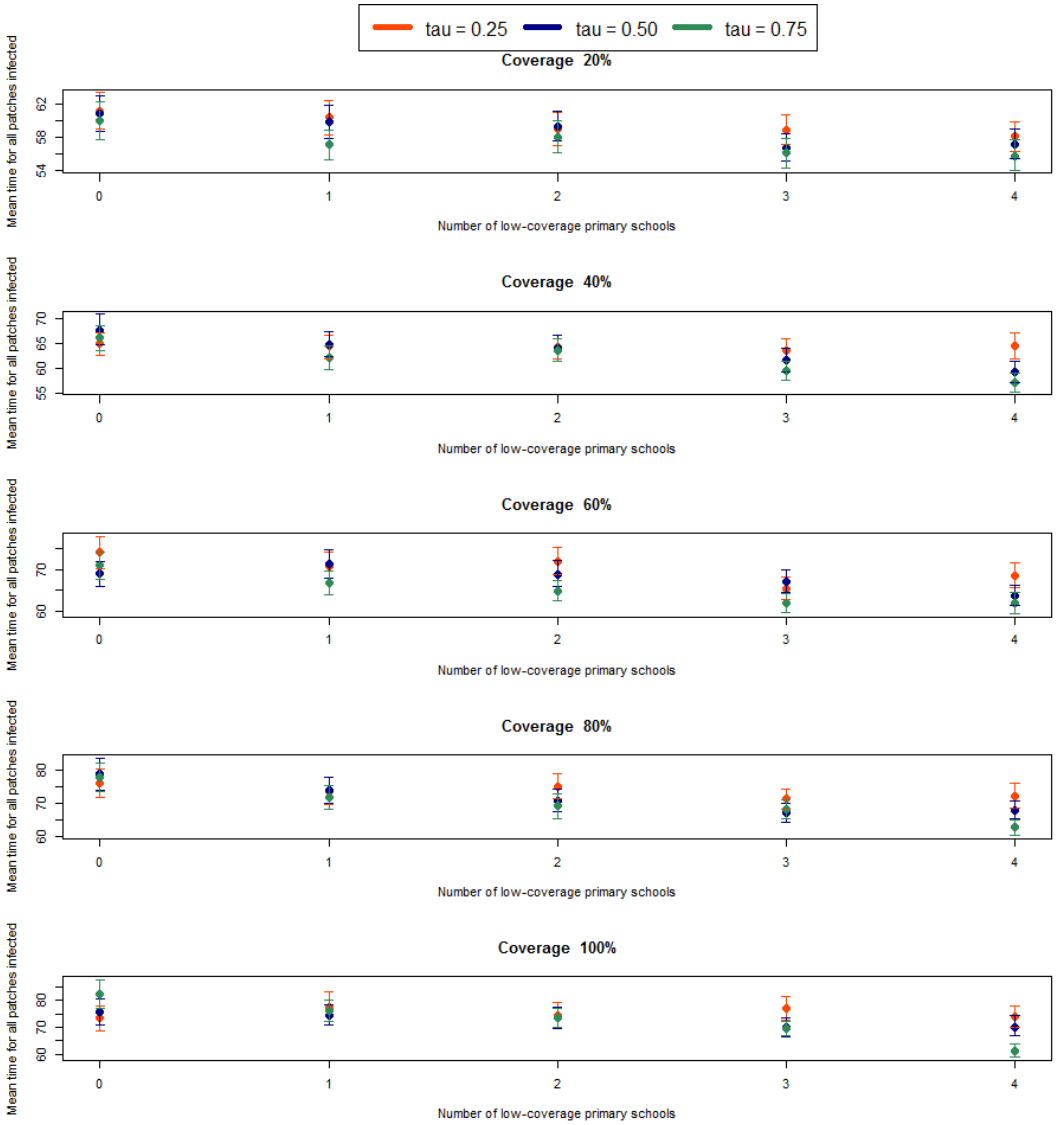


Figure 10.19 - Examining variation in the τ parameter on the mean time for all patches to be infected

There is little evidence for an association between the level of heterogeneity in vaccination coverage and the mean time of the epidemic peak (Figure 10.20).

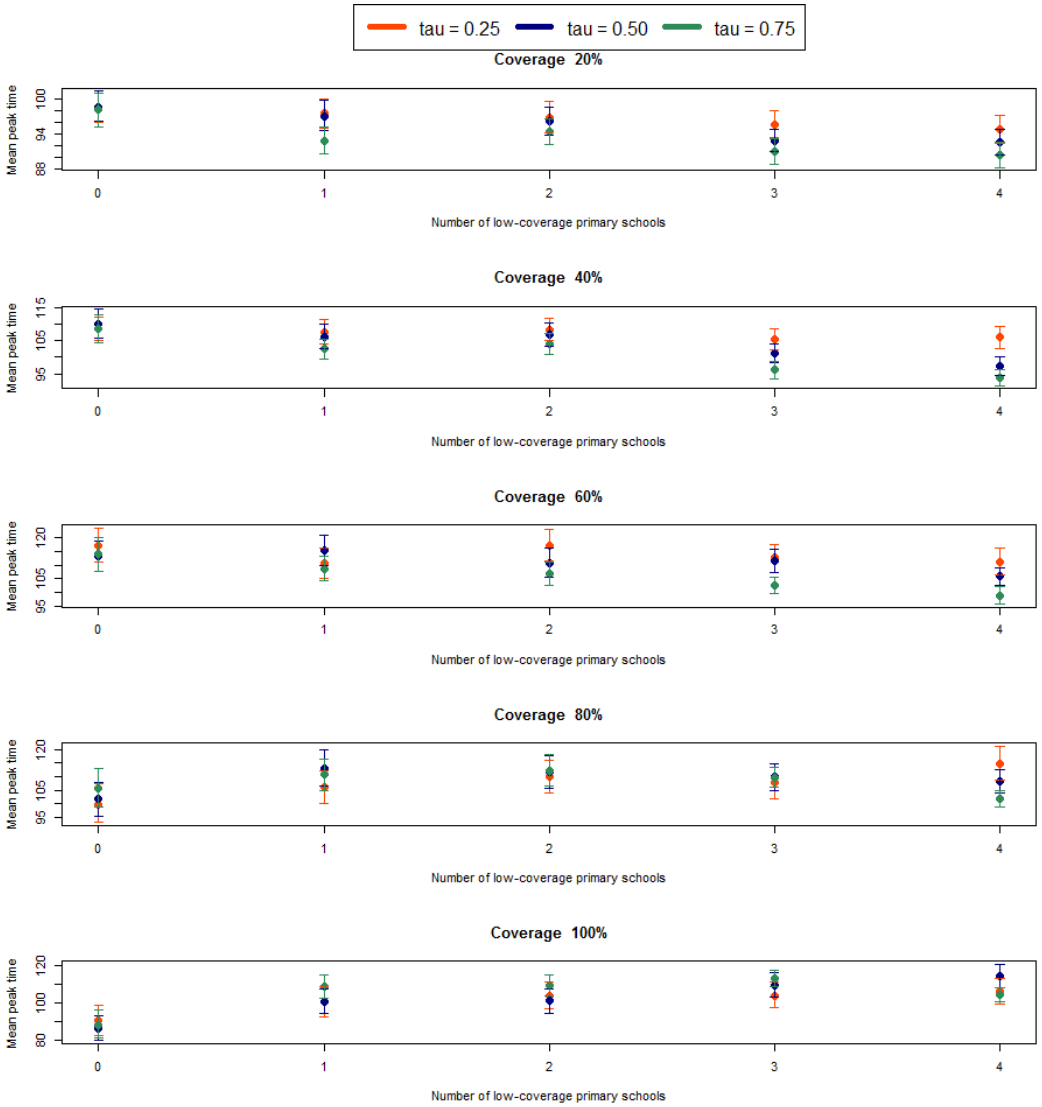


Figure 10.20 - Examining variation in the τ parameter on the mean peak time

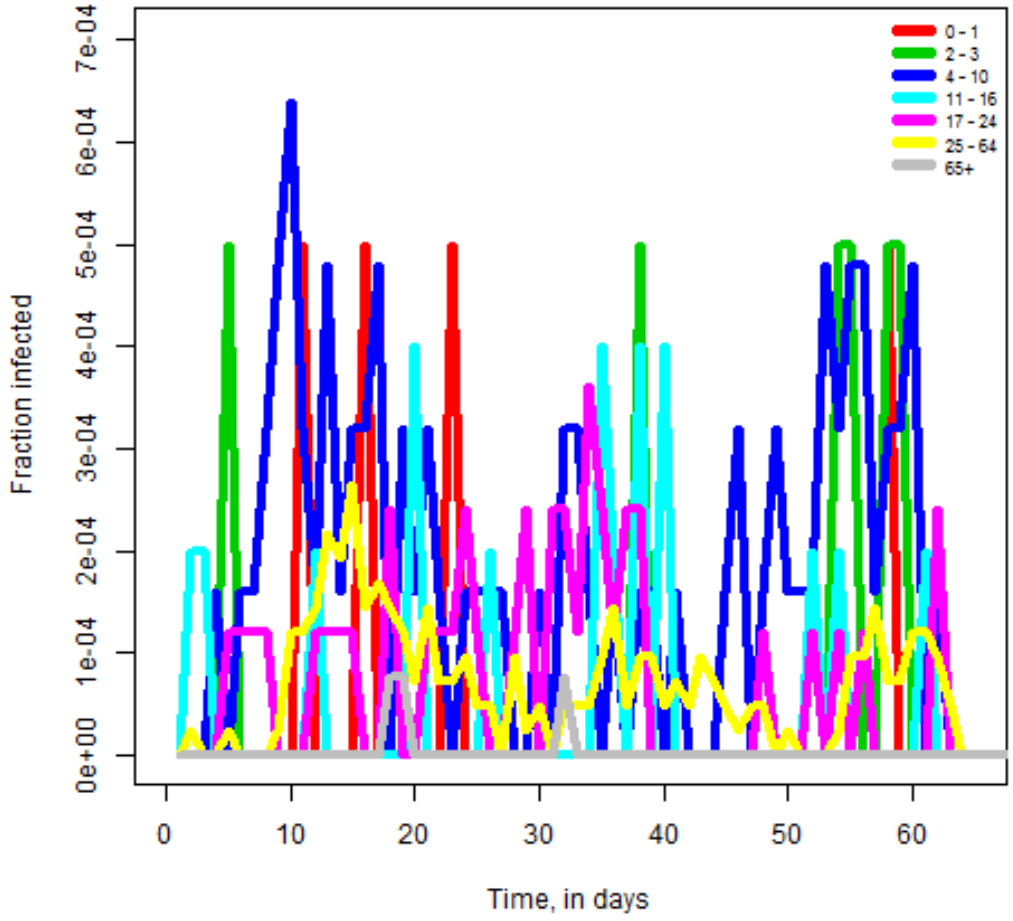


Figure 10.21 - The epidemic curve for a metapopulation configuration with homogeneous vaccination in both primary and secondary schools of 20% coverage

Administering a homogeneous vaccination policy across both school groups with just 20% coverage can reduce the mean final size of epidemics to 7.29% (95% CI: 6.99-7.57%). An epidemic in the metapopulation with this level of vaccination coverage is shown in both Figure 10.21 and Figure 10.22. Primary school #7 was seeded and several schools became infected over the course of the epidemic, though 9 primary and secondary schools reported no infections. Outbreaks in each school were sporadic in nature, but sustained community transmission was seen in the external population patch.

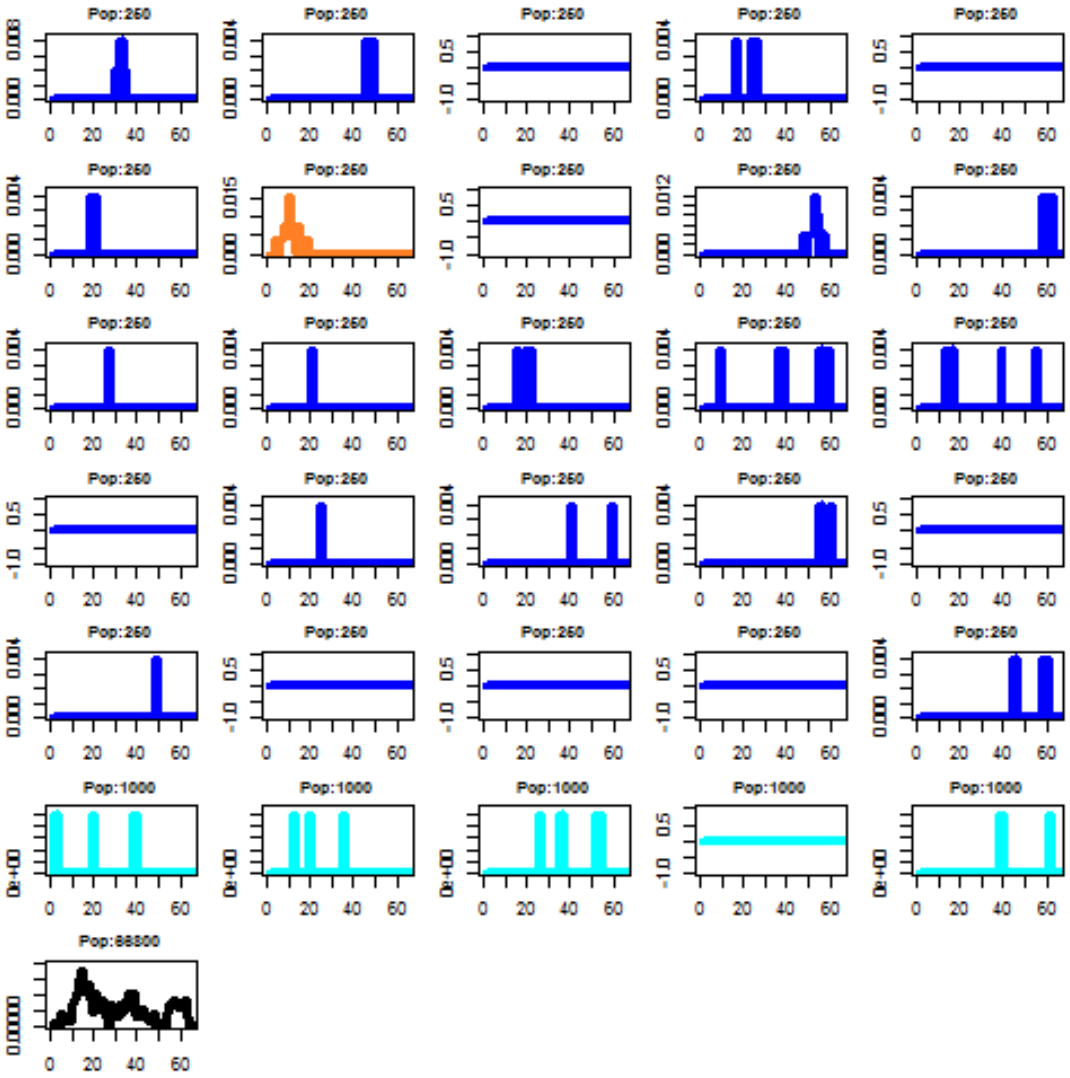


Figure 10.22 - The patch epidemic curves for a metapopulation configuration with homogeneous vaccination in both primary and secondary schools of 20% coverage

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

The duration of ILI epidemics (Figure 10.23) follows a similar trend to that of the ILI final size (Figure 6.24). There is little variation in the mean duration of ILI epidemics when vaccination coverage reaches 20%, but a more noticeable trend with 40% coverage.

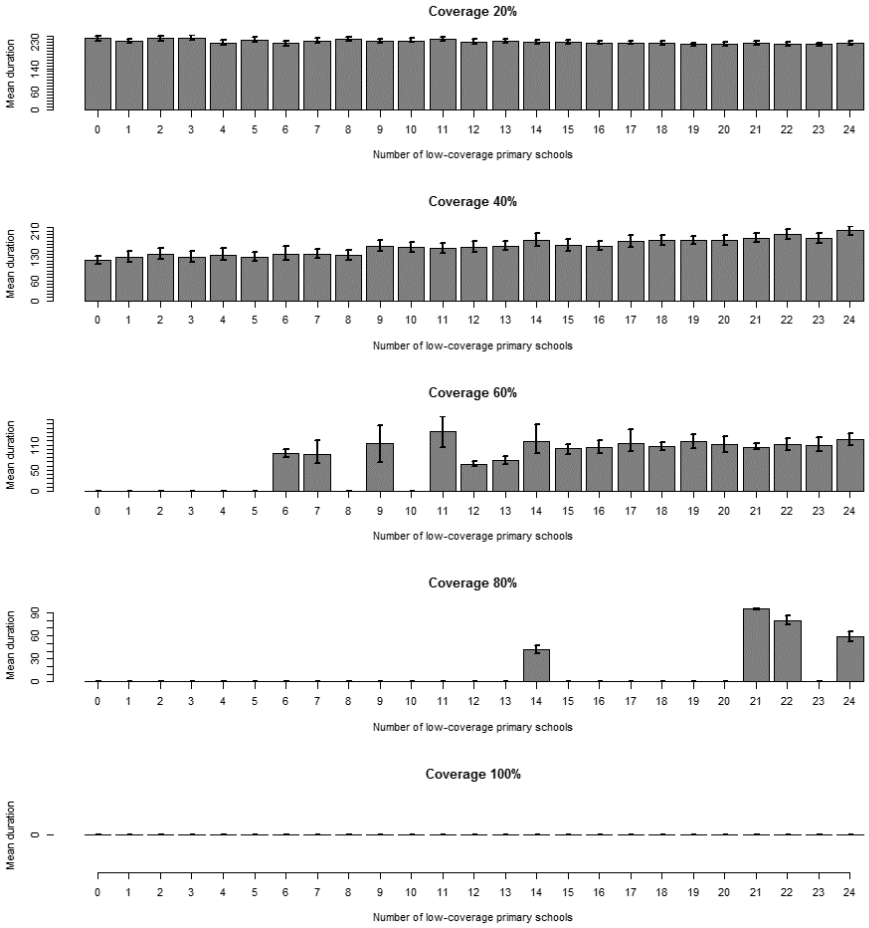


Figure 10.23 - Mean ILI duration for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage primary schools

The mean size of the epidemic peak increases as the number of low-coverage primary schools increases in the metapopulation at coverage levels of 20%, 40%, 60% and 80%, though epidemics only occur in the metapopulation with the highest coverage levels once the number of low-coverage primary schools crosses the threshold of 6 and 14 schools respectively (Figure 10.24).

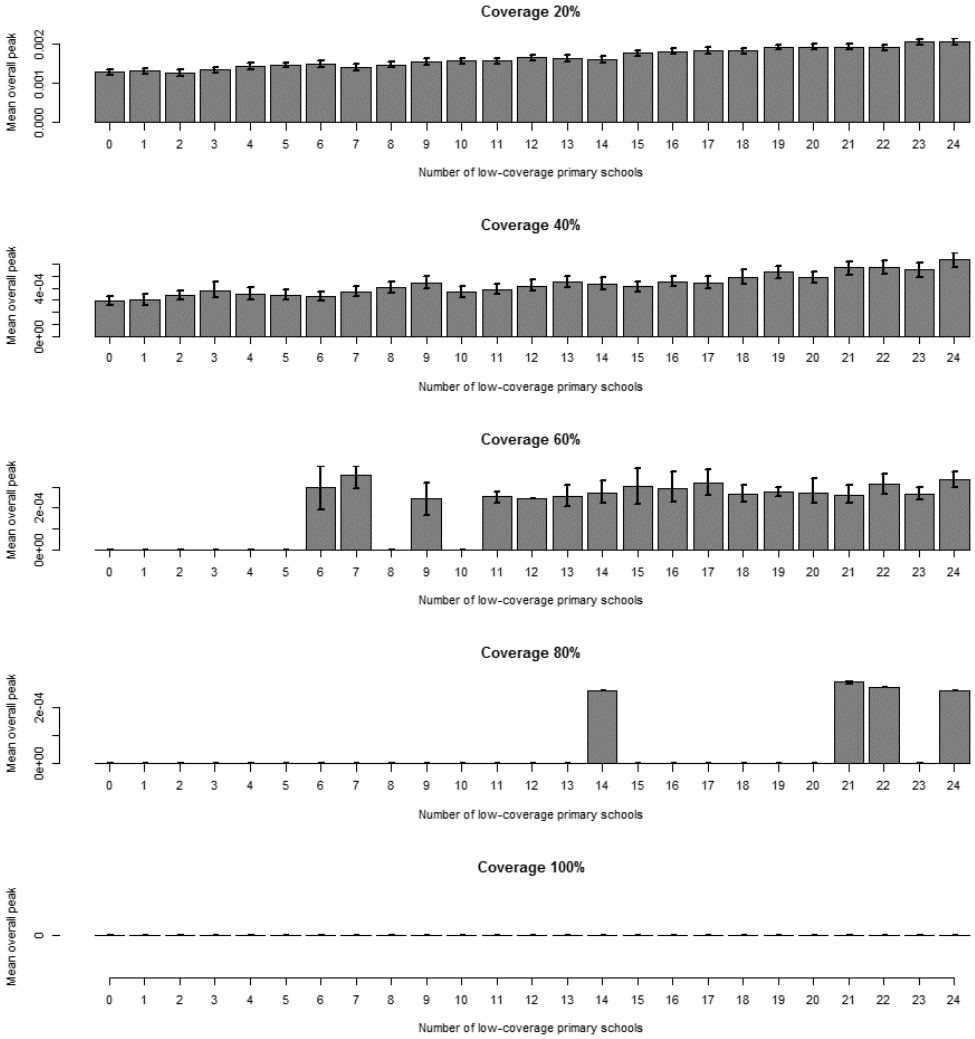


Figure 10.24 - Mean ILI peak for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage primary schools

With 60% coverage, epidemics reach all 31 metapopulation patches with 14 low-coverage primary schools or higher (Figure 10.25). With only 20% coverage, the mean time for all patches to become infected decreases slightly as the heterogeneity in uptake increases.

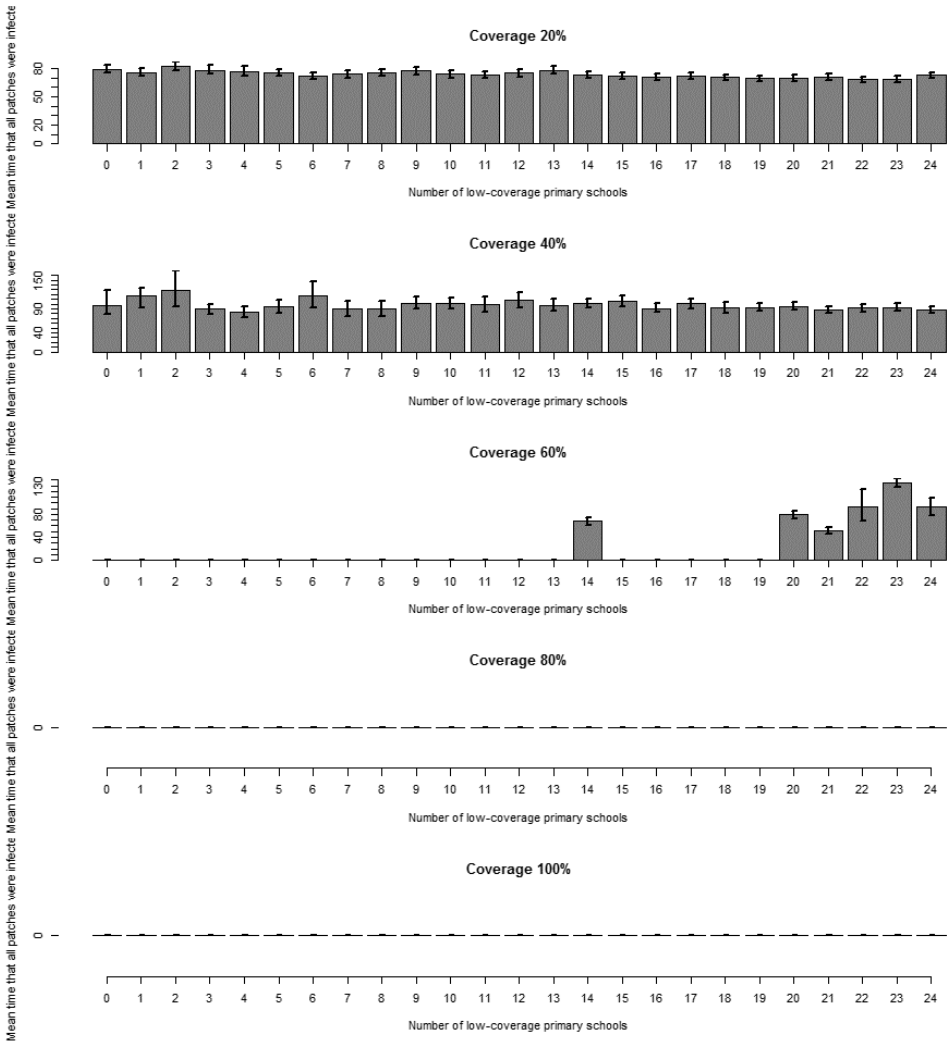


Figure 10.25 - Mean time for all patches to become infected during ILI epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage primary schools

The time of the epidemic peak increased with an increase in heterogeneity for coverage levels of 40%, 60% and 80%, though with just 20% the two variables did not appear to be linked (Figure 10.26).

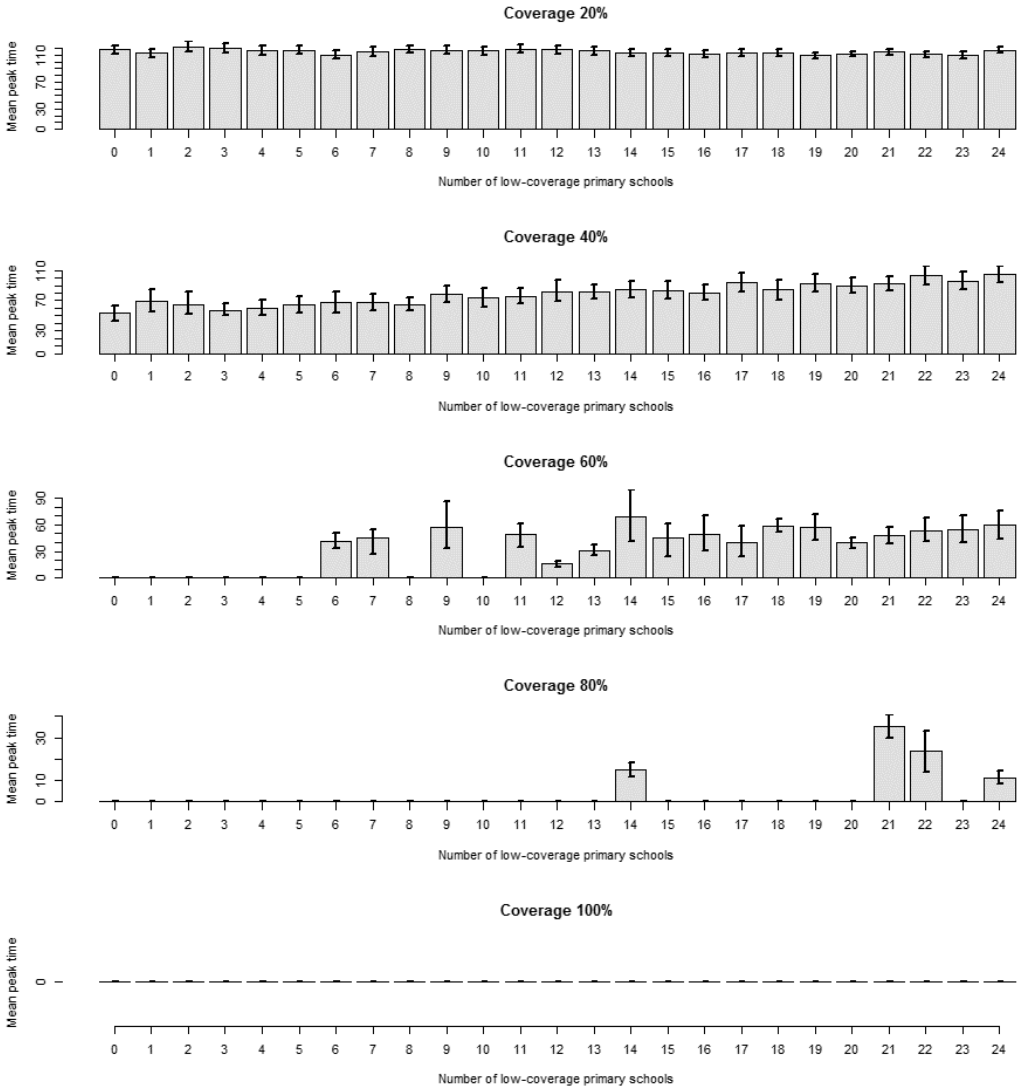


Figure 10.26 - Mean ILI peak time for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage primary schools

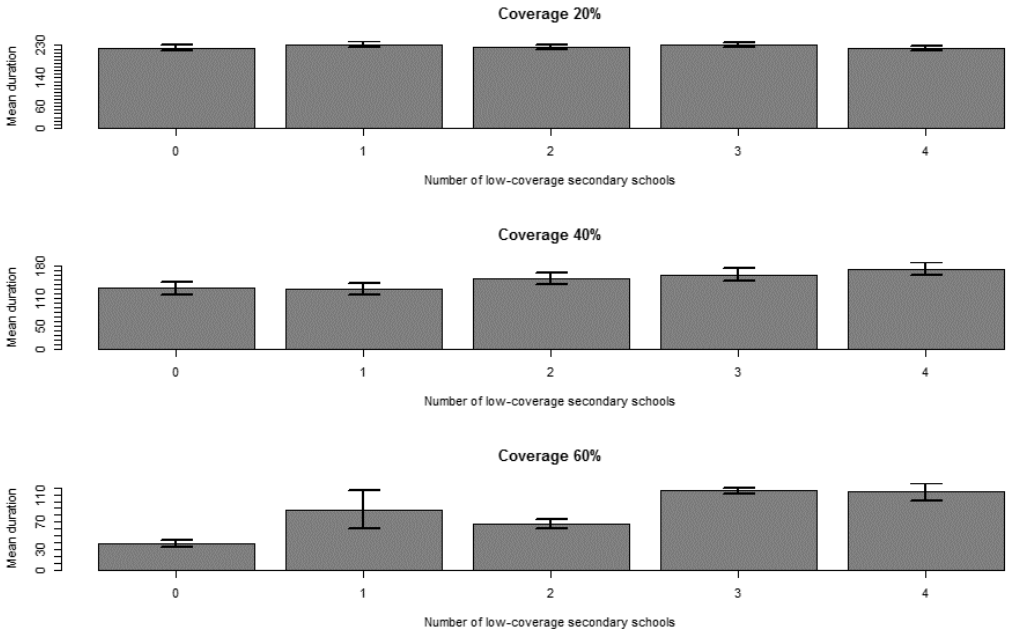


Figure 10.27 - Mean ILI duration for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage secondary schools

The mean duration of epidemics with 20% vaccination coverage did not vary with increased heterogeneity in vaccination coverage. The mean duration without low-coverage secondary schools in the metapopulation was 223.02 days (95% CI: 216.24-230.07) and 222.41 days (95% CI: 216.54-228.72) with 4 low-coverage schools. Higher coverage of both 40% and 60% saw the mean duration of epidemics increase as the number of low-coverage secondary schools increased.

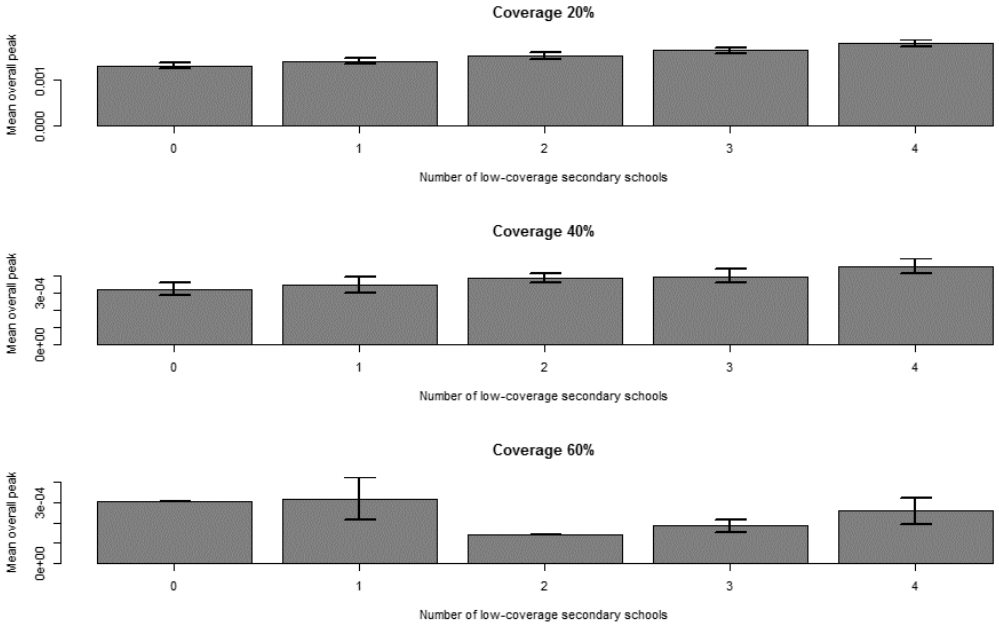


Figure 10.28 - Mean ILI peak for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage secondary schools

The mean epidemic peak increases as the number of low-coverage secondary schools increases in the population for coverage levels of both 20% and 40%. There is little evidence that this trend continues at 60% coverage but this is mostly likely due to a very small number of outbreaks that occurred with such high vaccination coverage.

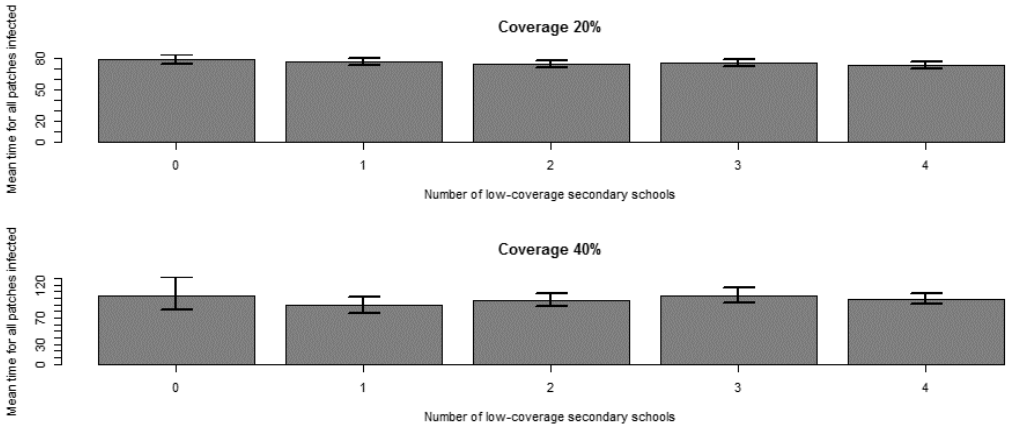


Figure 10.29 - Mean time for all patches to become infected during ILI epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage secondary schools

As previously discussed, at 60% coverage few epidemics occurred. Also, these few epidemics did not reach all 31 patches of the metapopulation (Figure 10.29). For epidemics that did infect all metapopulation patches the mean time for this to happen decreased as heterogeneity in vaccination uptake increased for the 20% coverage level – with 20% homogeneous coverage the epidemic spread to all metapopulation matches in 79.03 days (95% CI: 74.85-83.31), decreasing to 73.60 days (95% CI: 70.48-76.86) with 4 low-coverage secondary schools. There is little evidence for a similar trend at 40% coverage.

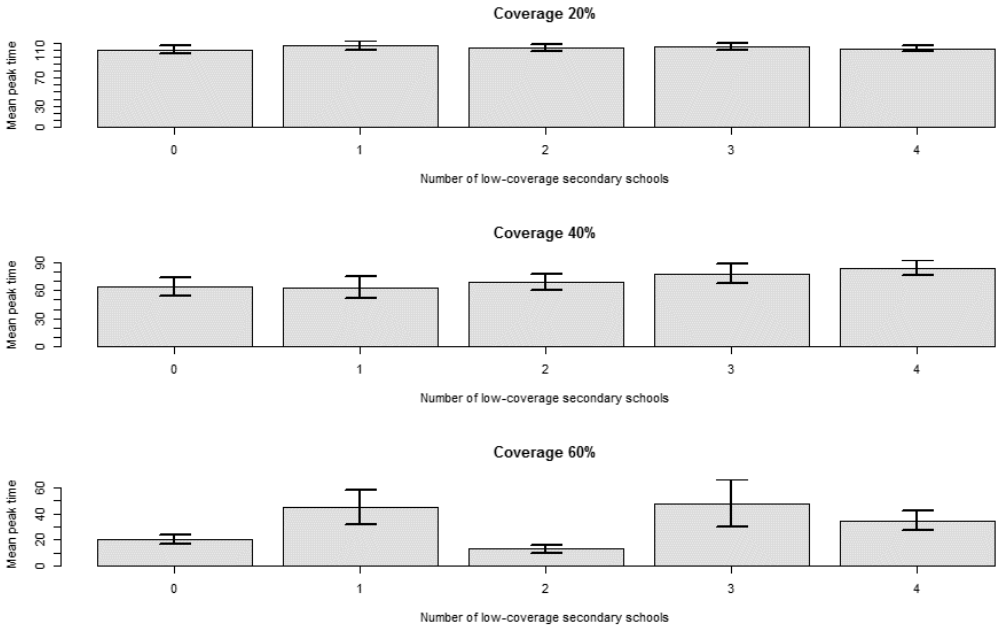


Figure 10.30 - Mean ILI peak time for epidemics with different homogeneous vaccination coverage with an increasing number of low-coverage secondary schools

The timing of the mean epidemic peak (Figure 10.30) follows the relationship between the level of heterogeneity in vaccination coverage and the mean epidemic duration. With 0 low-coverage secondary schools and 20% coverage the epidemics peaked after 110.39 days (95% CI: 105.20-115.78), and with 4 low-coverage schools they peaked at 111.97 days (95% CI: 107.70-116.49). However, increasing target coverage to 40% saw epidemics peak after 63.62 days (95% CI: 53.96-73.69) and 83.93 days (76.41-92.03) respectively.

METRICS CALCULATED IN CHAPTER 6

POPULATION EPIDEMIC DURATION

The epidemic duration is the total time for all infectious individuals in the metapopulation to recover, t_d.

$$t_d = t - t_0 \; such \; that \; \sum_p \sum_a \left(I_{pa}(t) + E_{pa}(t) \right) = 0$$

Equation 10.1 - The epidemic duration

It is also possible to record both the age-specific and patch-specific epidemic duration for all age groups and metapopulation patches.

POPULATION EPIDEMIC FINAL SIZE

The epidemic final size is the proportion of individuals in the metapopulation who pass through the compartmental model to finish in the *R* compartment after no more infectious individuals remain in the metapopulation.

$$\frac{1}{N} \sum_p \sum_a R_{pa}(t) \; such \; that \; \sum_p \sum_a \left(I_{pa}(t) + E_{pa}(t) \right) = 0$$

Equation 10.2 - The epidemic final size

It is also possible to record both the age-specific and patch-specific epidemic final size for all age groups and metapopulation patches.

POPULATION EPIDEMIC PEAK

The epidemic peak is the maximum proportion of infectious individuals in the metapopulation. The time that the epidemic peak occurs since t_0 is the epidemic peak time.

$$\text{Epidemic peak} = \max \left(\frac{1}{N} \sum_p \sum_a I_{pa}(t) \right)$$

Equation 10.3 - The epidemic peak

It is also possible to record both the age-specific and patch-specific epidemic peak for all age groups and metapopulation patches

TIME FOR ALL METAPOPULATION PATCHES TO BECOME INFECTED

At t_0 there exists one infectious individual in the metapopulation. If the epidemic is able to spread to all patches so that each patch has contained at least one infectious individual before the end of the epidemic then this time is t_a.

$$t_a = t \; such \; that \; \nexists I_{pa}(t) = 0$$

Equation 10.4 - The time for all metapopulation patches to become infected

Note: t_a is not the time that all metapopulation patches contain at least one infectious individual simultaneously.

QUESTIONNAIRES USED TO GATHER DATA FOR CHAPTER 7

The parent of guardian of «First_name»,
«Address_1»
«Address_2»
«Address_3»
«Address_4»
«Postcode»

Health Protection Agency

Immunisation, Hepatitis and Blood Safety Department
61 Colindale Avenue
London NW9 5EQ

Tel +44 (0)20 8200 4400
Fax +44 (0)20 8327 7404
www.hpa.org.uk

Friday 1st June 2012

Dear the parent or guardian of «First_name»,

Your child has recently been notified to the HPA by your doctor as having suspected measles. Our local office in Cheshire and Merseyside may already have contacted you with a kit to test their saliva. This test will confirm whether the illness is true measles or a similar illness due to another infection. We would also like to know how severe your child's illness was, which will help us make clinical and public health decisions about how best to control measles and related illnesses.

Should you wish to help us with this, we would be grateful if you or your child would please fill out a short survey (in three parts: on white paper, yellow paper and pink paper), and mail it back to us in the enclosed stamped addressed envelope – no need to provide a stamp. If your child is unable to fill it out on their own then please assist them with any questions that they cannot answer.

We would like you to fill out the questionnaire for you or your child twice:

1. once for today (yellow paper)
2. once for the worst day that your child experienced during their recent illness (pink paper).

We will also contact you in three weeks time to see how your child is feeling, and we would then ask you to fill out a very similar questionnaire.

This questionnaire will be returned without your name/s. Neither you nor your child have to fill in this questionnaire – it will not affect any care you are given. This information will only be used for informing clinical and public health decisions. Your information will not be shared with any third parties. If you have any questions about this survey, then please contact either Albert Jan van Hoek (0208 327 6065) or myself (Mary Ramsay 0208 327 7084) at the address given above.

Yours sincerely,

Mary Ramsay

Dr Mary Ramsay

This questionnaire has been designed to be completed by the parent, legal guardian or care-giver of the child who is suffering from, or has recently had, suspected measles.

Background information

1. What is the date today? …….....-……..-2012

About the child:

2. How old is the child? ……..years and…….month(s)

3. What is the child's sex? MALE / FEMALE

About the child's recent suspected measles:

4. What date did the child first experience symptoms? ……..-……..-2012
(If you cannot remember the exact date please include your best estimate of the full date)

5. Because of the suspected measles how many times did you contact any of the following? (Please indicate the number of times for **ALL** that apply, writing the date you first contacted them in the next column)

None	❑ (please tick if you did not contact any of the services listed below)	
	Number of times contacted	**Date first contacted**
Phone or email NHS Direct / NHS 24 / NHS Choices		
Phone or email GP – response from the receptionist		
Phone or email GP – response from the doctor / nurse		
Visit (face-to-face) a GP or nurse		
Hospital A&E department (inc. out of hours service)		
Other medical services		

6a. Did the child spend any nights in hospital due to symptoms related to their suspected measles?

YES / NO

6b. If YES how many nights did they spend in hospital?

……..nights

---- TURN THE PAGE ----

7. Did the child also have any of the following conditions during the recent suspected measles? (Please tick **ALL** that apply)

Fever	❑
Diarrhoea	❑
Vomiting	❑
Eye infection (conjunctivitis)	❑
Inflammation of the voice box (laryngitis)	❑
Inner ear infection and inflammation (otitis media)	❑
Difficulty in breathing / coughing	❑
Confusion / drowsiness / headache	❑

Other (please specify) .....

8a. Does the child have any ongoing medical condition requiring treatment?

YES / NO

8b. If YES, please state what it is:

.....

9a. Has the child had to take any time off school/nursery due to symptoms related to the suspected measles?

YES / NO

9b. If YES how many days? .....days

10a. Has anyone had to take time off from work to provide care for the child due to their symptoms related to the suspected measles?

YES / NO

10b. If YES how many days? .....days

About the duration of symptoms

To measure the severity of your suspected measles we need to know how long the child's symptoms last. To do this we will contact you again in around three weeks time to ask if you are still experiencing symptoms

(Information provided will not be used for any purpose other than this study)

About the child's health status TODAY:

1. Is the child experiencing any of the following due to suspected measles today (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

2. If they are no longer experiencing symptoms on which date did their symptoms end?

……-……-2012

---- TURN THE PAGE ----

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

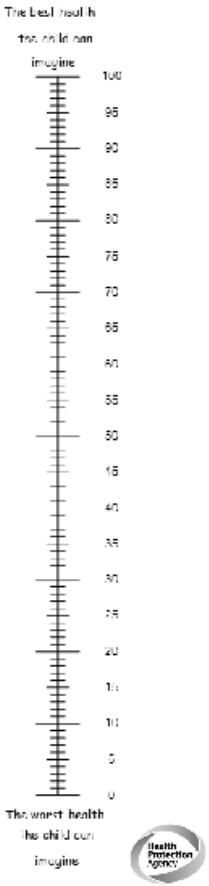
He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is the health of the child TODAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health TODAY
- This line is numbered from 0 to 100
- 100 means the best health the child can imagine

  0 means the worst health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health TODAY



About the child's health status on the <u>WORST DAY</u> of the suspected measles

What was the date of the **worst day**? ……..-……-2012

Did the child experience any of the following due to their suspected measles on the **worst day** (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

---- TURN THE PAGE ----

Describing the child's health ON THE WORST DAY

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, mark the ONE box that you think **the child** would mark to describe his/her own health **ON THE WORST DAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she had no problems walking about ❑
He/she had some problems walking about ❑
He/she had a lot of problems walking about ❑

Looking after myself

He/she had no problems washing or dressing him/herself ❑
He/she had some problems washing or dressing him/herself ❑
He/she had a lot of problems washing or dressing him/herself ❑

Doing usual activities (for example. *going to school, hobbies, sports, playing, doing things with family or friends)*

He/she had no problems doing his/her usual activities ❑
He/she had some problems doing his/her usual activities ❑
He/she had a lot of problems doing his/her usual activities ❑

Having pain or discomfort

He/she had no pain or discomfort ❑
He/she had some pain or discomfort ❑
He/she had a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

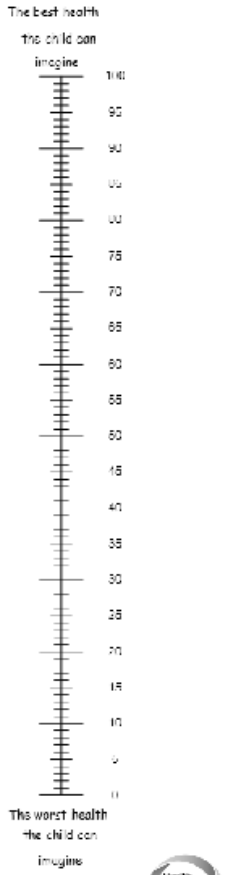
He/she was not worried, sad or unhappy ❑
He/she was a bit worried, sad or unhappy ❑
He/she was very worried, sad or unhappy ❑

How good was the health of the child ON THE WORST DAY

- We would like to know how good or bad you think **the child** would rate **his/her** own health on the WORST day
- This line is numbered from 0 to 100
- 100 means the **best** health the child can imagine

  0 means the **worst** health the child can imagine

Please, mark an X on the line that shows how good or bad you think **the child** would rate **his/her** health on the WORST day



The parent or guardian of «First_name»
«Address_1»
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«Postcode»

Health Protection Agency

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Dear the parent or guardian of «First_name»,

Your child has recently been notified to the HPA by your doctor as having suspected measles. Our local office in Cheshire and Merseyside may already have contacted you with a kit to test their saliva. This test will confirm whether the illness is true measles or a similar illness due to another infection. We would also like to know how severe your child's illness was, which will help us make clinical and public health decisions about how best to control measles and related illnesses.

Should you wish to help us with this, we would be grateful if you or your child would please fill out a short survey (in three parts: on white paper, yellow paper and pink paper), and mail it back to us in the enclosed stamped addressed envelope – no need to provide a stamp. If your child is unable to fill it out on their own then please assist them with any questions that they cannot answer.

We would like you to fill out the questionnaire for you or your child twice:

1. once for **today** (yellow paper)
2. once for the **worst day** that your child experienced during their recent illness (pink paper).

We will also contact you in three weeks time to see how you or your child is feeling, and we would then ask you to fill out a very similar questionnaire.

This questionnaire will be returned without your name/s. Neither you nor your child have to fill in this questionnaire – it will not affect any care you are given. This information will only be used for informing clinical and public health decisions. Your information will not be shared with any third parties. If you have any questions about this survey, then please contact either Albert Jan van Hoek (0208 327 6065) or myself (Mary Ramsay 0208 327 7084) at the address given above.

Yours sincerely,

Mary Ramsay

Dr Mary Ramsay

This questionnaire has been designed to be completed by the person who is suffering from, or has recently had, suspected measles.

You may wish to complete this with your parents (or legal guardians) **OR** your parents (or legal guardians) may complete the questionnaire on your behalf.

Background information

1. What is the date today? ……..-……..-2012

About You:

2. How old are you? ……..years and…….month(s)

3. What is your sex? MALE / FEMALE

About your recent suspected measles:

4. What date did you first experience symptoms? ……..-……-2012
(If you cannot remember the exact date please include your best estimate of the full date)

5. Because of the suspected measles how many times did you contact any of the following? (Please indicate the number of times for **ALL** that apply, writing the date you first contacted them in the next column)

None	❑ (please tick if you did not contact any of the services listed below)	
	Number of times contacted	**Date first contacted**
Phone or email NHS Direct / NHS 24 / NHS Choices		
Phone or email GP – response from the receptionist		
Phone or email GP – response from the doctor / nurse		
Visit (face-to-face) a GP or nurse		
Hospital A&E department (inc. out of hours service)		
Other medical services		

6a. Did you spend any nights in hospital due to symptoms related to your suspected measles?

YES / NO

6b. If YES how many nights did you spend in hospital?

…….nights

---- TURN THE PAGE ----

7. Did you also have any of the following conditions at any point during the recent suspected measles? (Please tick **ALL** that apply)

Fever	❑
Diarrhoea	❑
Vomiting	❑
Eye infection (conjunctivitis)	❑
Inflammation of the voice box (laryngitis)	❑
Inner ear infection and inflammation (otitis media)	❑
Difficulty in breathing / coughing	❑
Confusion / drowsiness / headache	❑

Other (please specify) .....

8a. Do you have any ongoing medical condition requiring treatment?

YES / NO

8b. If YES, please specify what it is:

.....

9a. Have you had to take any time off school due to symptoms related to the suspected measles?

YES / NO

9b. If YES how many days? .....days

10a. Has anyone had to take time off from work to provide care for you due to your symptoms related to the suspected measles?

YES / NO

10b. If YES how many days? .....days

About the duration of symptoms

To measure the severity of your suspected measles we need to know how long your symptoms last. To do this we will contact you again in around three weeks time to ask if you are still experiencing symptoms

(Information provided will not be used for any purpose other than this study)

About your health status TODAY:

1. Are you experiencing any of the following due to your case of suspected measles **today** (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

2. If you are no longer experiencing symptoms on which date did your symptoms end?

……..-……..-2012

---- TURN THE PAGE ----

Describing your health today

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility *(walking about)*

I have no problems walking about ❑
I have some problems walking about ❑
I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑
I have some problems washing or dressing myself ❑
I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑
I have some problems doing my usual activities ❑
I have a lot of problems doing my usual activities ❑

Having pain or discomfort

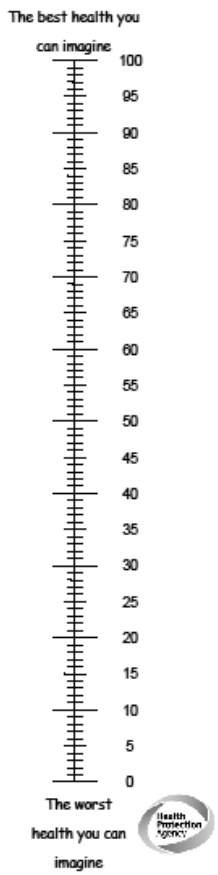
I have no pain or discomfort ❑
I have some pain or discomfort ❑
I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

I am not worried, sad or unhappy ❑
I am a bit worried, sad or unhappy ❑
I am very worried, sad or unhappy ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
  0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health is TODAY



About your health status on the <u>WORST DAY</u> of the suspected measles

What was the date of the worst day? ……..-……..-2012

Did you experience any of the following due to your suspected measles on the worst day (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

---- TURN THE PAGE ----

Describing your health for the WORST DAY

Under each heading, mark the ONE box that best describes your health for the WORST day.

Mobility *(walking about)*

I have no problems walking about ❑
I have some problems walking about ❑
I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑
I have some problems washing or dressing myself ❑
I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑
I have some problems doing my usual activities ❑
I have a lot of problems doing my usual activities ❑

Having pain or discomfort

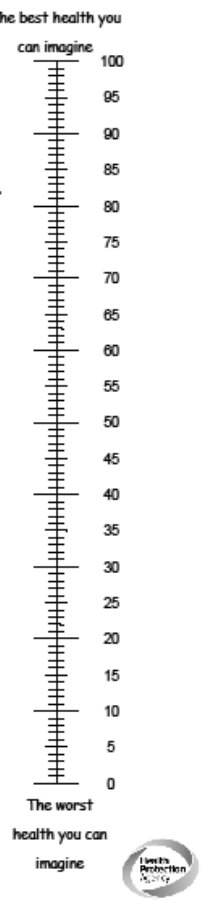
I have no pain or discomfort ❑
I have some pain or discomfort ❑
I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

I am not worried, sad or unhappy ❑
I am a bit worried, sad or unhappy ❑
I am very worried, sad or unhappy ❑

How good was your health on the WORST DAY

- We would like to know how good or bad your health was on the WORST day
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
  0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health was on the WORST day



«First_name» «Surname»
«Address_1»
«Address_2»
«Address_3»
«Address_4»
«Postcode»

Health Protection Agency

Immunisation, Hepatitis and Blood Safety Department
61 Colindale Avenue
London NW9 5EQ

Tel +44 (0)20 8200 4400
Fax +44 (0)20 8327 7404
www.hpa.org.uk

Friday 1st June 2012

Dear «First_name»,

You have recently been notified to the HPA by your doctor as having suspected measles. Our local office in Cheshire and Merseyside may already have contacted you with a kit to test your saliva. This test will confirm whether the illness is true measles or a similar illness due to another infection. We would also like to know how severe your illness was, which will help us make clinical and public health decisions about how best to control measles and related illnesses.

Should you wish to help us with this, we would be grateful if you would please fill out a short survey (in three parts: on white paper, yellow paper and pink paper) and mail it back to us in the enclosed stamped addressed envelope – no need to provide a stamp.

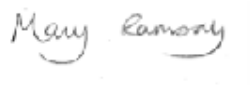
We would like you to fill out the questionnaire twice:

1. once for **today** (yellow paper)
2. once for the **worst day** that you experienced during your recent illness (pink paper).

We will also contact you in three weeks time to see how you are feeling, and we would then ask you to fill out a very similar questionnaire.

This questionnaire will be returned without your name. You do not have to fill in this questionnaire – it will not affect any care you are given. This information will only be used for informing clinical and public health decisions. Your information will not be shared with any third parties. If you have any questions about this survey, then please contact either Albert Jan van Hoek (0208 327 6065) or myself (Mary Ramsay 0208 327 7084) at the address given above.

Yours sincerely,



Dr Mary Ramsay

This questionnaire has been designed to be completed by the person who is suffering from, or has recently had, suspected measles.

If you are under 16 years old:

- you may wish to complete this with your parents (or legal guardians) **OR**
- your parents (or legal guardians) may complete the questionnaire on your behalf.

Background information

1. What is the date today? ……..-……..-2012

About You:

2. How old are you? ……..years and……month(s)

3. What is your sex? MALE / FEMALE

About your recent suspected measles:

4. What date did you first experience symptoms? ……..-……-2012
(If you cannot remember the exact date please include your best estimate of the full date)

5. Because of the suspected measles how many times did you contact any of the following? (Please indicate the number of times for **ALL** that apply, writing the date you first contacted them in the next column)

None	❑ (please tick if you did not contact any of the services listed below)	
	Number of times contacted	**Date first contacted**
Phone or email NHS Direct / NHS 24 / NHS Choices		
Phone or email GP – response from the receptionist		
Phone or email GP – response from the doctor / nurse		
Visit (face-to-face) a GP or nurse		
Hospital A&E department (inc. out of hours service)		
Other medical services		

6a. Did you spend any nights in hospital due to symptoms related to your suspected measles?

YES / NO

6b. If YES how many nights did you spend in hospital?

……nights

---- TURN THE PAGE ----

7. Did you also have any of the following conditions during the recent suspected measles? (Please tick **ALL** that apply)

Fever	❑
Diarrhoea	❑
Vomiting	❑
Eye infection (conjunctivitis)	❑
Inflammation of the voice box (laryngitis)	❑
Inner ear infection and inflammation (otitis media)	❑
Difficulty in breathing / coughing	❑
Confusion / drowsiness / headache	❑

Other (please specify) .....

8a. Do you have any ongoing medical condition requiring treatment?

YES / NO

8b. If YES, please specify what it is:

.....

9a. Have you had to take any time off school or work due to symptoms related to your suspected measles?

YES / NO

9b. If YES how many days? .....days

10a. Has anyone taken time off from work to provide care for you due to your symptoms related to your suspected measles?

YES / NO

10b. If YES how many days? .....days

About the duration of symptoms

To measure the severity of your suspected measles we need to know how long your symptoms last. To do this we will contact you again in around three weeks time to ask if you are still experiencing symptoms

(Information provided will not be used for any purpose other than this study)

About your health status TODAY:

1. Are you experiencing any of the following due to your suspected measles **today** (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

2. If you are no longer experiencing symptoms on which date did your symptoms end?

……-……-2012

---- TURN THE PAGE ----

Describing your health today

Under each heading, please tick the ONE box that best describes your health

TODAY

Mobility *(walking about)*

I have no problems walking about ❑
I have some problems walking about ❑
I am confined to bed ❑

Self-care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

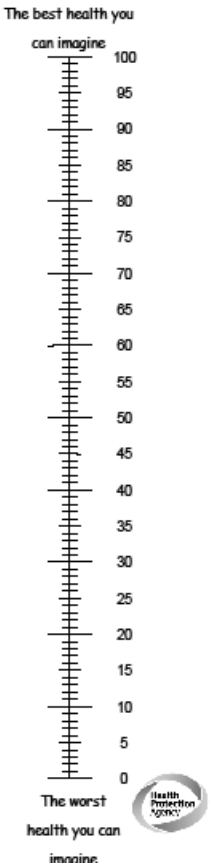
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
  0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health is TODAY



About your health status on the <u>WORST DAY</u> of the suspected measles

What was the date of the **worst day**? .....-.....-2012

Did you experience any of the following due to your suspected measles on the **worst day** (tick **ALL** that apply)

None of the symptoms below	❑
Rash	❑
Runny nose	❑
Watery eyes	❑
Swollen eyelids	❑
Sneezing	❑
Cough	❑
Blood shot eyes (red eyes)	❑
Severe temperature or fever	❑
Sore mouth and/or throat	❑
Tiredness, lack of energy	❑
Aches and pains	❑
Poor appetite	❑

---- TURN THE PAGE ----

Describing your health for the WORST DAY

Under each heading, mark the ONE box that best describes your health for the WORST day.

Mobility *(walking about)*

I had no problems walking about ❑
I had some problems walking about ❑
I was confined to bed ❑

Self-care

I had no problems with self-care ❑
I had some problems washing or dressing myself ❑
I was unable to wash or dress myself ❑

Usual activities *(e.g. work, study, housework, family or leisure activities)*

I had no problems with performing my usual activities ❑
I had some problems with performing my usual activities ❑
I was unable to perform my usual activities ❑

Pain/Discomfort

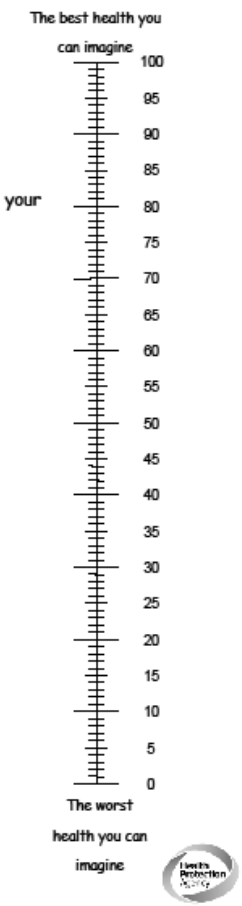
I had no pain or discomfort ❑
I had moderate pain or discomfort ❑
I had extreme pain or discomfort ❑

Anxiety/Depression

I was not anxious or depressed ❑
I was moderately anxious or depressed ❑
I was extremely anxious or depressed ❑

How good was your health on the WORST DAY

- We would like to know how good or bad your health was on the WORST day
- This line is numbered from 0 to 100
- 100 means the best health you can imagine
  0 means the worst health you can imagine
- Please, mark an X on the line that shows how good or bad your health was on the WORST day



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Chapter 11 - Publications arising from this thesis

THORRINGTON, D., EAMES, K., RAMSAY, M., EDMUNDS, J., VAN HOEK, A. J., & VIVANCOS, R. (2013). THE EFFECT OF MEASLES ON HEALTH-RELATED QUALITY OF LIFE: A POPULATION-BASED PROSPECTIVE STUDY, IN PUBLIC HEALTH SCIENCE CONFERENCE. THE LANCET: 382, S12.

The effect of measles on health-related quality of life: a population-based prospective study

Dominic Thorrington, Ken Eames, Mary Ramsay, John Edmunds, Albert Jan van Hoek, Roberto Vivancos

Published Online November 29, 2013

London School of Hygiene and Tropical Medicine, London, UK (D Thorrington MSc, K Eames PhD, Prof J Edmunds PhD); Public Health England, London, UK (M Ramsay FFPH, A J van Hoek PhD); and Public Health England, Cheshire and Merseyside, Liverpool, UK (R Vivancos MD)

Correspondence to: Mr Dominic Thorrington, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
dominic.thorrington@lshtm.ac.uk

Abstract

Background To enable decisions about investment across different areas of health care, health needs to be measured in a standardised way. In the UK, the quality-adjusted life-year (QALY) is the preferred metric. However, no measure of the QALY loss associated with measles is available, either for the UK or elsewhere. This study aimed to estimate the quality of life effect of measles by surveying patients with measles in England.

Methods We did a population-based prospective study using postal questionnaires to request information about people's illness along with an age-specific EQ-5D—a validated questionnaire commonly used to quantify QALYs. Public Health England reported 3207 laboratory-confirmed cases of measles in England between Jan 1, 2012, and June 30, 2013. Beginning in June, 2012, cases confirmed by IgM detection or PCR, or both, were sent postal questionnaires. Individuals with laboratory-confirmed measles reported in travellers communities were not invited to participate in the study. Public Health England engages with this community through different protocols and procedures. Public Health England has ethics approval to conduct enhanced outbreak surveillance. This approval includes the collection of health-related quality of life (HRQoL) data. Consent was implied through the return of a completed questionnaire to Public Health England.

Findings 507 questionnaires have been sent to individuals with confirmed measles; 203 have been returned (40·0%). The mean HRQoL loss per measles case was the equivalent of 6·9 days (95% CI 6·0–7·8), or 0·019 QALYs, after undertaking a missing value regression analysis. 37 (18·2%) of 203 responses were from parents or guardians of patients less than 1 year old. There was no evidence that patients who were hospitalised were more likely to respond to the questionnaire. 196 (96·6%) of 203 patients reported at least one complication, including fever (187 [92·1%]), conjunctivitis (114 [56·2%]), and difficulty breathing or coughing (162 [79·8%]). The mean duration of illness was 13·8 days (95% CI 12·5–15·1). 128 (63·1%) of 203 patients recorded absence from work or school, with a mean duration of 9·6 days (95% CI 8·3–11·0). 75 (39·6%) of 203 patients recorded that their primary caregivers were absent from work, with a mean duration of 7·3 days (95% CI 5·8–8·7). 74 patients (36·5%) reported spending at least one night in hospital, with a mean stay of 4·2 nights (95% CI 3·3–5·2). 193 patients (95·1%) reported contact with health-care services, with a mean of 4·0 contacts (95% CI 3·7–4·4). 71 (78·0%) of 91 patients reported severe problems due to measles infection on the EQ-5D dimension of health concerning their ability to undertake their usual activities. 24 (26·4%) of 91 patients reported severe problems in the depression or anxiety dimension.

Interpretation The HRQoL loss due to measles was greater than we had expected. With a mean duration of infection of 13·8 days, this finding can be interpreted as living with 50% health utility for almost 2 weeks. For context, the mean HRQoL loss for influenza is 0·008 QALYs or 2·92 days. The mean HRQoL loss due to varicella is 0·0027 QALYs or 0·99 days (<15 years old) and 0·0038 QALYs or 1·39 days (≥15 years old). The HRQoL results will inform cost-effectiveness analyses that test new or existing interventions for measles outbreaks.

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 of Health Research, or the Department of Health.

Contributors
DT, MR, KE, JE, AJvH, and RV designed the study and questionnaires. DT sent the questionnaires. DT analysed the results with input from KE.

Conflicts of interest
We declare that we have no conflicts of interest.

THORRINGTON, D., RAMSAY, M., VAN HOEK, A. J., EDMUNDS, W. J., VIVANCOS, R., BUKASA, A., & EAMES, K. (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

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PLOS ONE

The Effect of Measles on Health-Related Quality of Life: A Patient-Based Survey

Dominic Thorrington[1]*, Mary Ramsay[2], Albert Jan van Hoek[2], W. John Edmunds[1], Roberto Vivancos[3], Antoaneta Bukasa[2], Ken Eames[1]

1 Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom, 2 Public Health England (Colindale), London, United Kingdom, 3 Public Health England (Cheshire and Merseyside), Liverpool, United Kingdom

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.

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.

Citation: 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

Editor: Fausto Baldanti, Fondazione IRCCS Policlinico San Matteo, Italy

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Competing Interests: The authors have declared that no competing interests exist.

* Email: dominic.thorrington@lshtm.ac.uk

Introduction

Measles is a highly infectious notifiable disease that can be severe in infants, pregnant women and immunocompromised individuals [1,2]. Measles is preventable through the measles-mumps-rubella vaccination programme (MMR), with measles vaccination introduced in the UK in 1968 [1]. The reported coverage is 92.9% [3] although uptake fell in the late 1990s from 92% in 1996 to 80% in 2003 [4] after the suggestion of a potential link between the vaccine and autism [5] that subsequently proved to be unfounded [6–8].

Previous measles outbreak reports focus on the epidemiology of the disease [9–11], 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 [12,13].

A standard method to measure the disease burden is the use of quality-adjusted life years (QALYs). A QALY is a generic measure incorporating both the length of time that patients experience health reduction and the magnitude of the health reduction [14]. 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. Health utilities commonly take values between 0 and 1, corresponding to utilities for death and perfect health respectively (although some systems of measurement allow utilities of less than 0 to be reported). These utilities are used in conjunction with the duration of the health reduction to calculate the QALY-loss (and thus the potential QALY-gain for any proposed intervention or new health technology).

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.

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 1st June 2012 and the study was extended throughout England from 2nd October 2012 to 5th 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 [11]:

- 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 [15]. 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.

Unless stated, the analysis that follows is based on individuals with confirmed measles.

EuroQol EQ-5D-3L

The EuroQol EQ-5D-3L is a generic multi-attribute health-state classification system [16,17]. 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. The National Institute for Health and Clinical Excellence recommends the EuroQol EQ-5D-3L for use in cost-effectiveness analyses in the United Kingdom [13].

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 [18] 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.

One year is equivalent to 365 days; therefore 1 QALY would be equivalent to 365 quality-adjusted life days (QALDs). The QALD has previously been used to report the impact of influenza on HRQoL [19], and for ease of interpretation we express loss of HRQoL in terms of QALDs below.

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 [20], 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.

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 1. A more precise picture would be possible if patients completed the EQ-5D-3L more frequently during their infection. In absence of these data we assume that we can represent the QALY loss as a linear deterioration in HRQoL from a recovery reading to its level on the worst day of infection. 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 [21], Public Health England may process confidential patient information with a view to monitoring and managing

i. outbreaks of communicable disease;
ii. incidents of exposure to communicable disease;

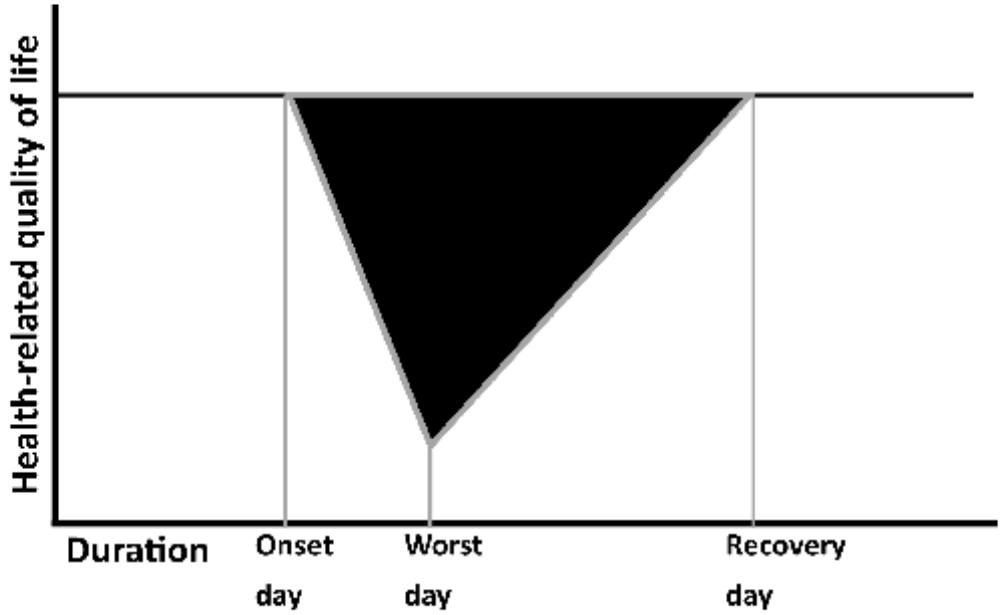

Figure 1. Illustration of the calculation of short-term loss of health-related quality of life (HRQoL). HRQoL is plotted against time; the area of the black triangle represents the loss of HRQoL due to illness.
doi:10.1371/journal.pone.0105153.g001

iii. the delivery, efficacy and safety of immunisation programmes.

Data analysis

Data were analysed using Microsoft Excel 2007 and R (version 3.0.2) [22]. 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. We calculated the QALY-loss due to measles using the EQ-5D-3L and the VAS and compared the two systems. We examined the three age-specific EQ-5D-3L questionnaires and looked for differences in the QALYs lost due to measles infection. 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. [23] 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.

Demographic and vaccination data

101 (49.8%) of the 203 responses were from female patients. 68 (33.5%) of the respondents were under five years old (Figure 2). 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 2).

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

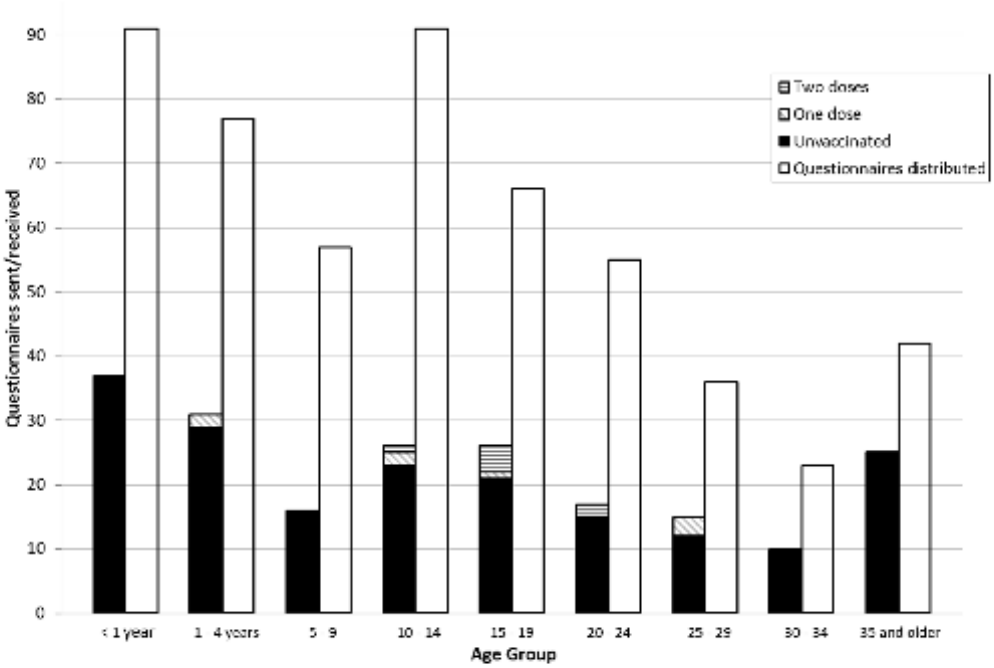

Figure 2. Age-specific distribution of questionnaires sent, questionnaire response, and vaccination status for confirmed cases of measles. The right columns of each age group show the age-distribution of questionnaires sent to confirmed measles cases (left axis); the left columns show the age-distribution of responses (left axis), split into those who are have received no MMR vaccinations (black), one MMR vaccination (diagonal stripe) and two MMR vaccinations (horizontal stripe).
doi:10.1371/journal.pone.0105153.g002

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. Figure 3 shows the number of questionnaires sent and eventually used in the analysis.

Impact at home

128 (63.1%) individuals with confirmed measles reported spending time off work or school due to measles infection (Table 1), 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.

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 2.

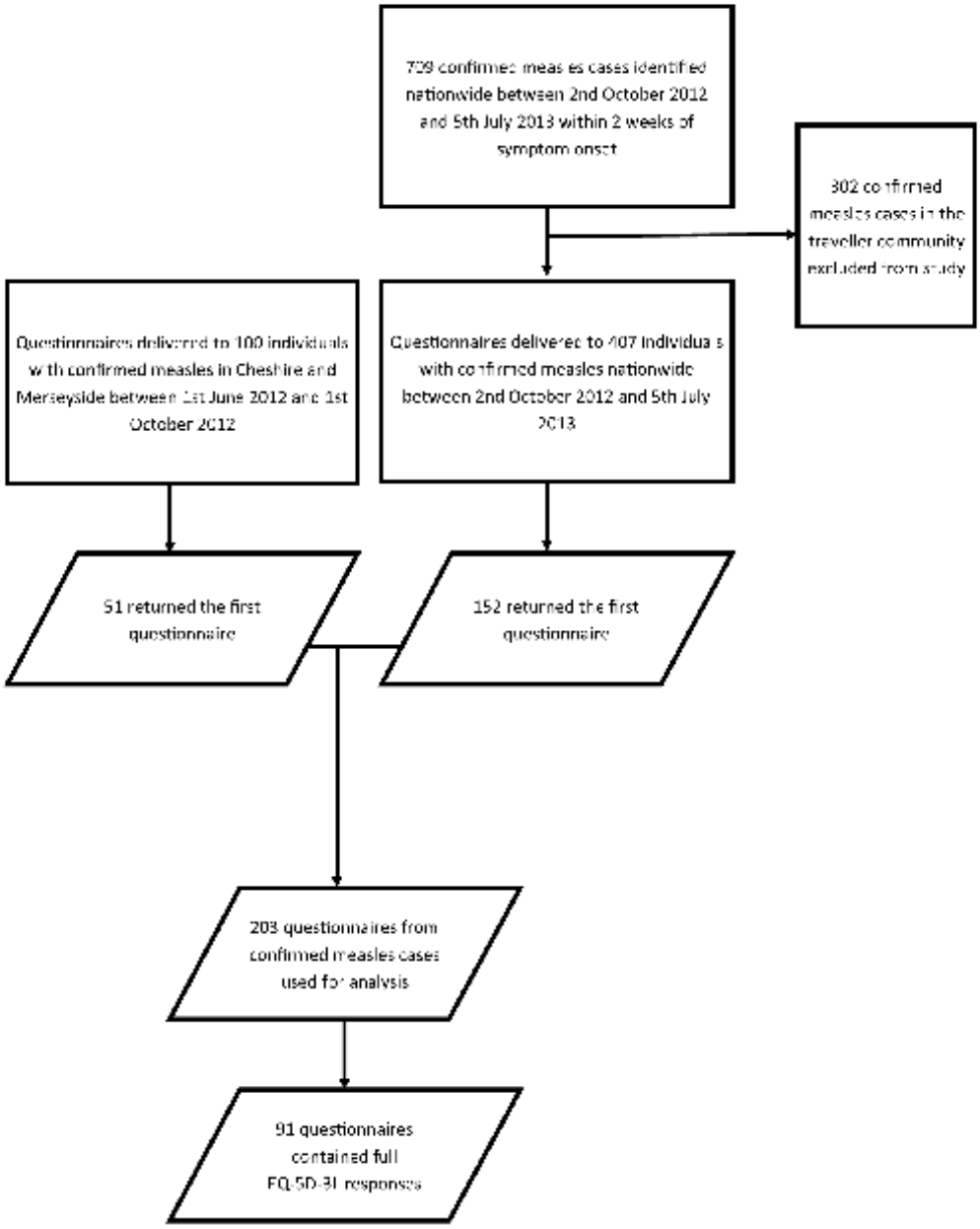

Figure 3. Flow chart for the study showing the number of questionnaires that were distributed to confirmed measles cases; the number of questionnaires returned for analysis; and the number of questionnaires returned for analysis that included the necessary information for EQ-5D-3L health utilities to be calculated.
doi:10.1371/journal.pone.0105153.g003

Table 1. Impact of measles infection.

	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

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.

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194 of the 203 individuals with confirmed measles (95.6%) who returned a questionnaire also returned a completed VAS.

HRQoL results

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 3).

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 1st June 2012, the beginning of the study period [24,25]. 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 [26] 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 3.

Table 2. 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.

	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%)

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Table 3. Impact on HRQoL of measles for the 91 individuals with confirmed measles for whom QALY loss could be calculated using the EQ-5D-3L.

	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)

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.

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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 4). This suggests that parents or guardians have difficultly 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.

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 [19]. The impact on HRQoL of natural varicella was 0.0027 QALYs, or 0.99 QALDs (<15 years old) [27] and 0.0038 QALYs, or 1.39 QALDs (≥15 years old) per patient [28].

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 [29].

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 4). 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 completed 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 [30–32] and EuroQol are currently developing a child-specific tariff for the EQ-5D-Y.

Table 4. Number of missing responses to each EQ-5D dimension of health on the worst day of infection.

	Responses	Complete responses	Missing: Mobility	Missing: Self-care	Missing: Usual activities	Missing: Pain	Missing: Depression
EQ-5D proxy	70	20 (28.6%)	28 (40.0%)	49 (70.0%)	16 (22.9%)	8 (11.4%)	12 (17.1%)
EQ-5D-Y	25	25 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EQ-5D	108	102 (94.4%)	5 (4.6%)	3 (2.8%)	3 (2.8%)	2 (1.9%)	2 (1.9%)
	203 (100%)	147 (72.4%)					

doi:10.1371/journal.pone.0105153.t004

We note that in the regional epidemics in Cheshire and Merseyside only 18% of confirmed cases were hospitalised [11], 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

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.

We assumed that the deterioration in HRQoL is linearly related to the duration of infection (Figure 1) 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) [33] 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.

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 $p = 0.19$).

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.

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.

Acknowledgments

An abstract of this study was presented at the Public Health England conference in Warwick in September 2013 [34].

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.

Questionnaires and the dataset are available on request.

Author Contributions

Conceived and designed the experiments: DT MR AJvH WJE RV AB KE. Performed the experiments: DT. Analyzed the data: DT KE. Wrote the paper: DT KE WJE AJvH.

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RESEARCH ARTICLE

Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature

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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.

Conclusions

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

Rationale

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 [1]. 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 [1].

A CUA is also the recommended economic evaluation for submissions to the Canadian Agency for Drugs and Technologies in Health (CADTH) [2]; in Australia with submissions to The Pharmaceutical Benefits Advisory Committee (PBAC) [3]; in Sweden with submission to The Swedish Council on Health Technology Assessment (SBU) [4]; in New Zealand with submissions to The Pharmaceutical Management Agency (PHARMAC) [5] and other countries [6].

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 [7]). 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 [1], 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 [1].

There is evidence that children and adolescents are able to report on the state of their own health [8]. Children aged 3 years can report on feelings of nausea and pain that are reliable and clinically meaningful [9–11]. 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 [12, 13], in the same way that adult-specific methods may not be appropriate for recording health utilities of adolescents [14]. 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 [12, 15].

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 [16]. 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 [17].

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) [18] and the Pediatric Asthma Health Outcome Measure (PAHOM) [19].

The advantage of using generic calculation methods in CUAs is that results can be compared across populations, conditions, and for different treatments or interventions [20]. 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 [21], 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 [17]. 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 [22, 23], though it

has been suggested that parents may misjudge the health of their child owing to their own anxiety during the illness [24, 25] and further studies have shown differences between parent and child ratings for the child's health [26–28]. 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 [22, 29] so results are of questionable validity [30]. Teachers will not be able to provide HRQoL assessments for the child at home or in clinics [22] but will be able to evaluate a child's emotional and physical functioning.

In a systematic review published in 2005, Griebsch et al. [31] 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 [32].

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.

Objective

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 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? 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?

Previous reviews

Kromm et al. (2012) [14] 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 [33] and also that 10% of economic evaluations for children and adolescents published between 1980 and 1999 were CUAs [34], they assessed the quality of such CUAs using the 57-item Pediatric Quality Appraisal Questionnaire (PQAQ) [35]. Only 16 (8%) of the studies included in the review gathered health utilities as part of the analysis (Table 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 [36]. Study authors may assume that adult health

Table 1. Results from Kromm et al. (2012) [14] for studies that measured health utilities as part of the CUA.

Were health utilities measured in the study?	From whom?	Direct measurement methods used	Indirect measurement methods used
Yes (n = 16)	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

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utilities apply to children and adolescents and assume a uniform utility throughout childhood and adolescence, ignoring the child's development [12, 13]. 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) [37] 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) [31] 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) [38] discussed how the practice of paediatric CUAs has evolved over time, with reference to methods described in the NICE reference case [1]. 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

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 were not 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 Griebsch et al. [31], 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 30th September 2014.

Data items

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

- Reference
- Year of publication
- Country
- Direct or indirect calculation method(s) used
- Health condition (if applicable)
- Sample size
- Age range of participants
- Mode of assessment:
  - Self-completion of questions
  - Completion of questions via proxy (parents, clinicians, primary caregivers, etc.)
  - Patient interviews
  - Interviews with proxies (parents, clinicians, primary caregivers, etc.)
  - Other methods
  - Methods not stated
- Study type:
  - Validation of calculation method
  - CUA
  - Health utility assessment
  - Comparison of calculation methods

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: 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

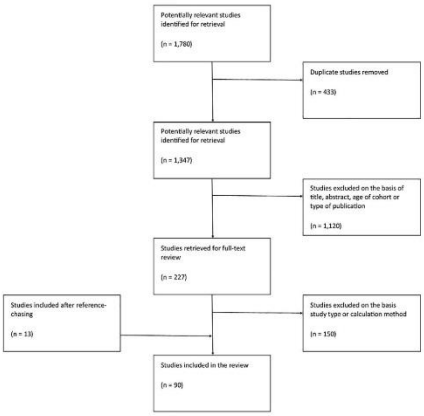

Fig 1. Identification of studies of measuring HRQoL in children and adolescents.

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additional 13 studies were found in the list of references. In total, 90 studies were included in the review (Fig 1).

The earliest publication date for a study included in the review was 1994 (Fig 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.

25 different countries were featured in the studies included in the review (Fig 3). The UK was featured the most. Three studies included multiple countries [39–41].

Study characteristics

47 studies (52.2% of 90) were CUAs of which 21 [42–62] (44.7% of 47) were incorporated into randomised controlled trials for interventions. 23 [39, 40, 63–83] studies (25.6% of 90) were health-state utility assessments. Eight [19, 84–90] studies (8.9% of 90) were validations of calculation methods. The remaining 12 [62, 91–101] 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 [62, 69, 71, 75, 77, 84, 88]) or providing health-state utility assessments (four studies [19, 41, 93, 102]).

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 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).

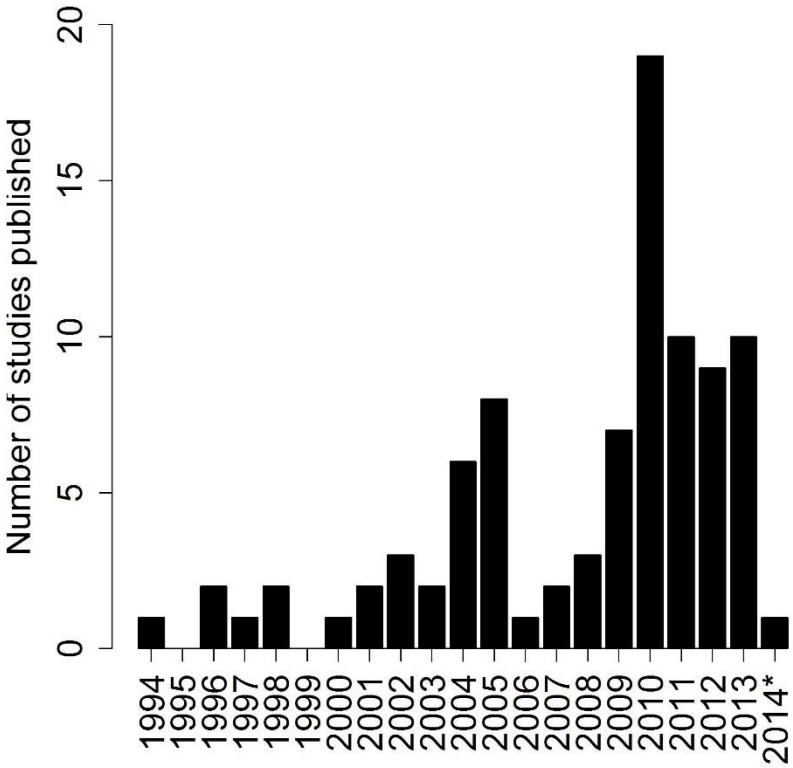

Fig 2. Year of publication for studies included in the review.

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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 [103] to studies sampling from large national databases of patients that included 84,443 patients of all ages [65] 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.

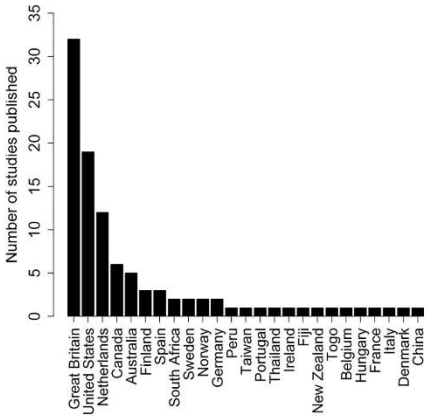

Fig 3. Countries featured in studies using direct or indirect calculation methods for obtaining health utilities from paediatric patients.

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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 [8–11], 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) [123] acknowledged that proxy reporting may overestimate health utility gains for cochlear implants; Chiou et al. (2005) [19] 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) [97] recommended the use of self-reporting rather than proxy-reporting, acknowledging the potential issues with proxy-reporting; Oostenbrink et al. (2002) [100] stated that health utilities for CUAs should be measured from patients rather than proxies, as

Table 2. Frequency of use for calculation methods found during the review.

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
	22	**137**

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Table 3. Direct and indirect calculation methods to obtain health utilities from the paediatric population.

Abbreviation	Methods of obtaining utilities	Generic or disease-specific	Frequency of use
15D	15D Instrument [104]	Generic	1
ACQ	Asthma Control Questionnaire [105]	Disease specific	3
AQoL-6D	Assessment of Quality of Life 6D [106]	Generic	1
CAVE	Escala de calidad de vida del niño con epilepsia [107]	Disease specific	1
CHU-9D	Child Health Utility 9D [108]	Generic	3
EQ-5D	EuroQol 5D [109]	Generic	41
EQ-5D+	Expanded EuroQol 5D	Disease specific	1
EQ-5D-Y	EuroQol 5D Youth Version [110]	Generic	10
HALex	Health and Activities Limitation Index [111]	Generic	1
HUI-2	Health Utilities Index 2 [112]	Generic	10
HUI-3	Health Utilities Index 3 [112]	Generic	16
Mini AQLQ	Mini Asthma Quality of Life Questionnaire [113]	Disease specific	2
PAHOM	Pediatric Asthma Health Outcome Measure [19]	Disease specific	2
PAQLQ	Paediatric Asthma Quality of Life Questionnaire [114]	Disease specific	1
QLQ-C30	EORTC Quality of Life Questionnaire-Core 30 [115]	Disease specific	1
QWB	Quality of Well Being [116]	Generic	3
SF-12	Short Form 12 [117]	Generic	2
SF-36	Short Form 36 [118]	Generic	4
SF-6D	Short Form 6D [119]	Generic	2
SG	Standard Gamble [120]	Generic	9
TTO	Time Trade Off [121]	Generic	9
VAS	Visual Analogue Scale [122]	Generic	14

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proxies may have difficulty evaluating the impact of conditions on dimensions of health such as pain and emotion; Tilford et al. (2005) [79] 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) [102] cite the use of proxies as a limitation in their study; Wasserman et al. (2005) [82] 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) [124] said that clinician-proxy was suitable due to the clinicians' familiarity with each case; Bodden et al. (2008) [42] referred to previous studies that used EQ-5D through proxies; Chadha et al. (2010) [93] stated that their results showed no difference between self- and proxy-reported utilities; Friedman et al. (2004) [64] claimed that parental-proxy is consistent in evaluating HRQoL for children with atopic dermatitis; Gerald et al. (2012) [88] claimed that clinician-proxy reporting of health utilities is the gold standard; Hollman et al. (2013) [67] refered to previous studies to justify their use of proxy-reporting; Matza et al. (2005) [71] claimed that SG methods through parental-proxies are a suitable method for obtaining health utilities from children; Petrou & Kupek (2009) [73] 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) [125] 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 [81].

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 4). The number of health dimensions included ranges from three to nine. Three

Table 4. List of child- and/or adolescent-specific calculation methods used.

Abbreviation	Name of calculation method	Age range and mode of completion	Dimensions of health	Studies found using this method
AQoL-6D	Assessment of quality of life (adolescent version)	15–17 years, Self-completion	Independent living, Relationship, Mental health, Coping, Pain, Senses	[68]
CAVE	Escala de calidad de vida del niño con epilepsia	< 17 years, Self-completion, but proxy-completion for younger children	Behaviour, School compliance, Learning, Autonomy, Social relations, Frequency of seizures, Intensity of seizures, Parents opinions	[126]
CHU-9D	Child health utility, 9 dimensions	7–17 years, Self-completion, but proxy-completion for younger children	Worried, Sad, Pain, Tired, Annoyed, School work, Sleep, Daily routine, Joining with activities	[89, 90, 92]
EQ-5D-Y	EuroQol 5 dimensions, youth version	8–15 years, Self-completion	Mobility, Self-care, Usual activities, Pain or discomfort, Worried, sad or unhappy	[63, 78, 80, 83, 86, 92, 94, 96, 97, 99]
PAQLQ	Paediatric asthma quality of life questionnaire	7–17 years, Self-completion	Symptoms, Activity limitations, Emotional function	[66]
PAHOM	Pediatric asthma health outcome measure	7–12 years, Self-completion	Symptoms, Emotion, Activity	[19, 88]

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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 [83, 92, 99], 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 [78]. It has previously been noted by Kromm et al. (2012) [14] that slow progress is being made in developing age-specific utility weights.

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) [67], Jelsma (2010) [96], Radford et al. (2013) [53], Thorrington et al. (2014) [78] Tilford et al. (2012) [102] and Wyatt et al. (2012) [62] all present data for missing or incomplete responses for their respective calculation methods, but only Jelsma (2010) [96] and Thorrington et al. (2014) [78] discuss these data with respect to the age of the respondents.

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 Griebsch 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 [110].

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 [17]. Nevertheless responses should be elicited directly from those children being evaluated when verbal capacity is not a barrier [32].

Using multiple calculation methods and respondents. Only four studies compared self- and proxy- reported health utilities. Chadha et al. 2010 [93] found no difference between utilities. Gerald et al. (2012) [88] reported that PAHOM scores for parental proxies were significantly lower than self-reported scores from children. Jelsma & Ramma (2010) [97] found agreement with the EQ-5D-Y scores. Lock et al. (2010) [47] 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 [94], 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 [41, 45, 48, 51–56, 60, 61, 67, 70, 73, 84, 91, 127, 128].

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, Griebsch et al. (2005) [31] 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 [35] and the checklist for economic analysis outlined by Drummond et al. (2005) [129]. 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.

Supporting Information

S1 PRISMA Checklist.
(DOCX)

S1 PRISMA Flowchart.
(DOCX)

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Author Contributions

Conceived and designed the experiments: DT KE. Performed the experiments: DT KE. Analyzed the data: DT. Contributed reagents/materials/analysis tools: DT. Wrote the paper: DT KE.

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Targeted vaccination in healthy school children – Can primary school vaccination alone control influenza?

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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. We explore whether targeting vaccination at either primary or secondary schools would be more effective and/or cost-effective than the current strategy.
Methods: 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.
Findings and conclusion: 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. 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 2–16 years.

1. Introduction

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 [1].

The UK has had a long-standing 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 [2,3]. 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 [2]. In 2013 Baguelin et al. reported that it would be cost-effective to offer vaccination to children in addition to the other groups currently offered the vaccine [4].

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 [5]. 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 [6,7].

Children and adolescents attending schools play a large role in the spread of influenza in the community [8–10]. Transmission within schools is maintained because of the high number of close

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Table 1
Total population of England, clinically at-risk population and the number of seasonal influenza vaccinations administered to those clinically at-risk before new JCVI vaccination policy is implemented.

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

contacts between school children [11], as well as less acquired immunity in children [12] and a longer period of virus-shedding once infected [13,14]. 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 [15,16].

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 and January 2014. Six of the seven geographical areas used a school-based vaccination programme for which the overall average coverage level was 56.27% (91,782/163,115) [17]. In addition, children aged 2–3 years were offered vaccination via primary care, with the intention to extend this to school-age children throughout England.

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. 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 that 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 [4,21], but adopted a simpler model to highlight key results related to optimally targeting age groups for paediatric vaccination.

2. Methods

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.

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 1). Individuals have close contacts with others in the model according to the POLYMOD survey of contact frequency in Europe [11]. 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, $\beta_{i,j}$.

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].

2.1. 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. 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 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 (see Appendix for further details about the model and its calibration).

2.2. 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 over 65 years only). The outputs from this

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Table 2
Transmission model parameters. The † symbol indicates that the parameter was used in the multivariate parametric sensitivity analysis.

Parameter	Value	Source
R_0, 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 46% (95% CI: −17 to 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

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 to 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 to 100% then at each level examined the effect of supplementary vaccination in secondary schools from 0 to 100%, including the homogenous case.

2.3. 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. [21] with sources updated where possible (Table 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. [1]. 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. QALY loss due to clinical influenza were taken from EuroQol EQ-5D-3L

Table 3
Economic evaluation model parameters. The † symbol indicates that the parameter was used in the multivariate parametric sensitivity analysis.

Parameter	Value	Source
Proportion of infected cases with ILI symptoms	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+	[1]
Quality-adjusted life expectancy	67.34 quality-adjusted life years at birth	2009 data
Proportion of ILI cases visiting their GP	0.1	[34]
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+	[1]
Proportion of hospitalised cases requiring intensive care	0.0557	RMN, FluZone
Cost of GP consultation†	Log normal from $N(\mu = £45, \sigma = £8.4)$	[35]
Cost of hospital admission (non-elective)†	Log normal from $N(\mu = £1489, \sigma = £192.1)$	[36]
Cost of admission to intensive care†	Triangular with min = £1449, max = £2300, mode = £2034	[36]
Cost of vaccine per dose†	£14	[37]
Cost of vaccine delivery and administration per dose†	£3.03	[38]
QALY loss (not hospitalised)†	$N(\mu = 0.0074, \sigma = 0.00085)$ for 0–16 $N(\mu = 0.0082, \sigma = 0.00180)$ for 17+ years	[18,39]
QALY loss (hospitalised)†	$N(\mu = 0.0160, \sigma = 0.00180)$ for 0–16 $N(\mu = 0.0180, \sigma = 0.00180)$ for 17+ years	[18,40]
Discount rate	3.5% per annum	[2]

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surveys conducted in the United Kingdom during the 2009 H1N1v pandemic [18,39]. Life expectancy data were taken from quality-adjusted life expectancy tables.

We used the same cost items as Baguelin et al. [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 [37] plus 10 min of a Band 7 nurse's time [38].

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 [2].

2.4. Sensitivity analyses

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 ±5% of the parameter value used in the model, or according to the distributions from previous studies as shown in Tables 2 and 3 (marked with †). We sampled the proportion of each age group with prior immunity to influenza from the best-fitting 5% of realisations from the calibration exercise. We ran 5000 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.

3. Results

3.1. Burden of disease without childhood vaccination programme extension

The proportion of the total population infected over a season prior to the extension of vaccination to low-risk children is 25.0% (13.3 m), of which 4.7 m are clinical influenza cases (Fig. 1). 4309 deaths occur due to influenza and 35.8% of those are deaths in the 65+ years age group. Baguelin et al. [18] estimated 370–4700 seasonal influenza-attributable deaths per year in a low-severity scenario, a range that includes the estimates from our model. The outbreak costs £188 m from the perspective of the health care provider with 38,600 QALYs lost due to infection.

3.2. Burden of disease with homogeneous vaccination programme extension

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. The most cost-effective level of vaccine coverage is 42% (ICER of £14,394 per QALY saved). At this level the policy costs £210.7 m 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 (Fig. 2). 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.

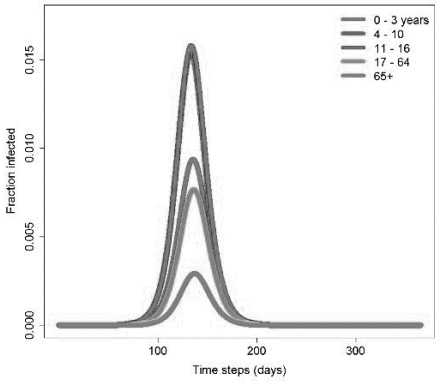

Fig. 1. Epidemic curve plotting the fraction of each age group infected for the baseline scenario, in which there are no vaccination programme extensions beyond those in at-risk groups and adults of age 65+ years.

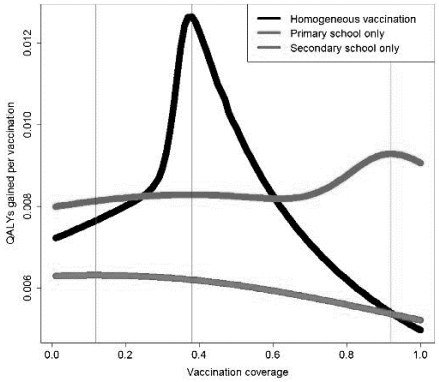

Fig. 2. QALYs gained per vaccination administered for each vaccination policy. Homogeneous vaccination efficiency across both primary and secondary schools (black) peaks when coverage reaches 38%. QALYs gained per vaccination in primary schools (green) peaks when coverage reaches 92%. QALYs gained per vaccination in secondary schools (blue) peaks when coverage reaches 12%).

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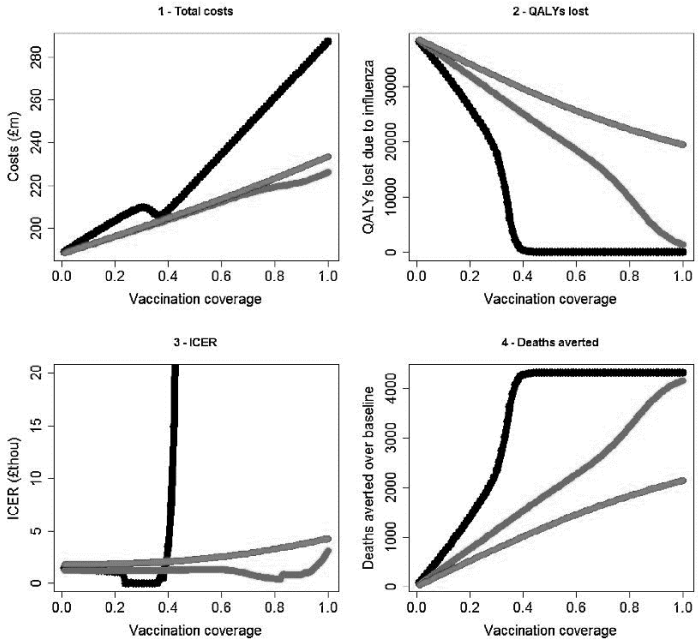

Fig. 3. (1) The total costs of the vaccination policies plus healthcare and treatment costs, (2) the QALYs lost due to influenza, (3) the incremental cost-effectiveness ratio and (4) the number of deaths averted over baseline. Homogeneous vaccination (black), targeted vaccination in primary schools (green)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

3.3. Comparison of vaccination scenarios

3.3.1. Targeted vaccination in primary schools

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

The optimal cost-effectiveness occurs when coverage reaches 100% (ICER of £3117 per QALY, Fig. 3, Chart 3). At this level of coverage the targeted policy costs £226.1 m and saves 37,244 QALYs over baseline (Table 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 (Fig. 2). The mean number of pupils in a state-funded primary school in England is 263 [41] 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.

3.3.2. Targeted vaccination in secondary schools

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% (6.31 m total infections of which 2.21 m would be clinical influenza). The optimal cost-effectiveness occurs threshold when coverage reaches 100% (£4280 per QALY saved, Fig. 3). The number of QALYs saved per vaccination administered in secondary schools peaks at 0.0063 QALYs or 2.30 QALDs at 12% coverage.

Table 4
Comparing three new vaccination policies.

	Most cost-effective scenario	Maximum QALYs gained per vaccination	Minimum total costs per vaccination
Targeted policy in primary schools	100% (ICER = £3117)	0.0093 (92% coverage)	£9.13 (92% coverage)
Targeted policy in secondary schools	100% (ICER = £4280)	0.0063 (12% coverage)	£11.26 (1% coverage)
Heterogeneous policy	48% and 34% (ICER = £16,152)	0.0128 (45% and 28%)	£6.14 (44% and 29%)

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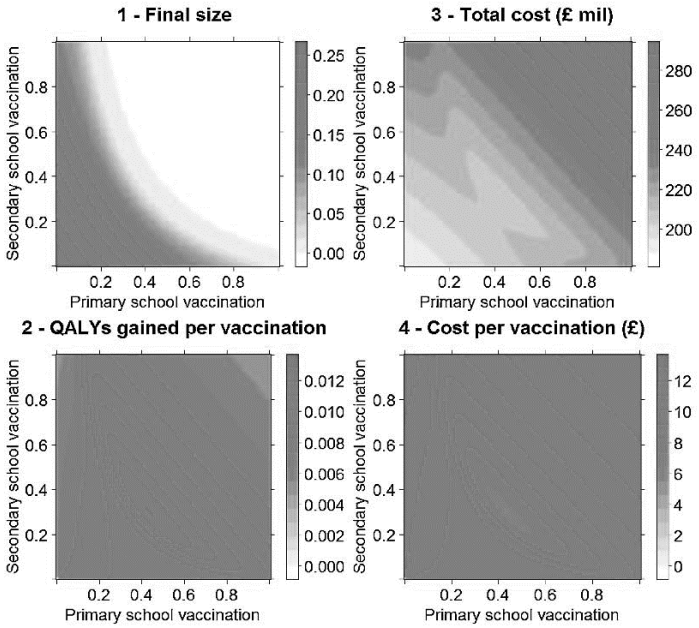

Fig. 4. Examining the impact of heterogeneous vaccination coverage: (1) final size of outbreak, (2) the QALYs gained per vaccination administered, (3) the total cost of the vaccination policy (£ millions) and (4) the costs per vaccination administered (£). Horizontal axis shows the proportion of vaccination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

3.3.3. Heterogeneous coverage across primary and secondary schools

The optimal cost-effectiveness occurs at a coverage level of 48% in primary schools and 34% in secondary schools (£16,152 per QALY saved, Fig. 4). At this level of coverage the total cost of the policy is £210.0 m 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 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.

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 [41]), implementing a policy of heterogeneous coverage to these coverage levels for one primary school and one secondary school saves 4.94 QALYs or 1804 QALDs.

Herd immunity effects can be seen when the number of QALYs saved per vaccination administered reaches this maximum value. Indeed, coverage between 30 and 62% in primary schools with 15–50% in secondary schools maximises this value (Fig. 4). The non-linear relationship between vaccinations administered and health benefits gained is due to indirect benefits of vaccination in a population.

3.4. Sensitivity analyses

Fig. 5 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.

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.

4. 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 and 100% and calculated the ICERs for each coverage level for four different vaccination strategies.

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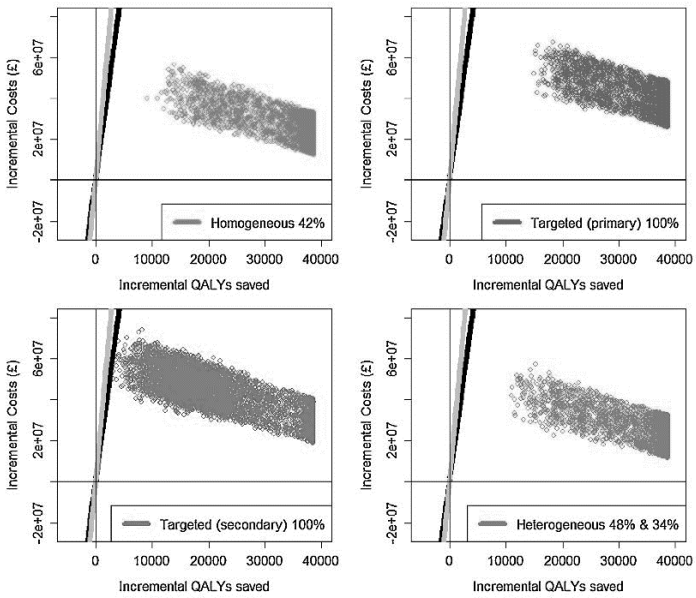

Fig. 5. Sensitivity analysis of the most cost-effective strategies of each of the four different vaccination policies when compared with no implementation of the new JCVI-recommended programme. Grey and black lines denote the £30,000 per QALY and £20,000 per QALY ratios respectively.

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.

4.1. Study limitations

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.

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 [42–44]. 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. 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.

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 [17]. 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.

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

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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.

Finally, the model was calibrated to 2006–07 data which was a year of low incidence (as have been recent years [45,46]), 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.

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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.

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Appendix.

Contact matrix

Mossong et al. [11] surveyed 1012 individuals in Great Britain on the number of both physical and conversational contacts. Diaries recorded sociodemographic details of both the study participants and their daily contacts in order to inform mathematical models with data on typical mixing patterns of the population. We used their results in our model to include the measured assortative mixing patterns (Fig. A.1).

Model and assumptions

The transmission model was an age-structured deterministic discrete time SEIR-type model with addition age-structured compartments for individuals not susceptible to influenza before transmission starts (i.e. those vaccinated under the vaccination policy or those with pre-existing immunity to influenza).

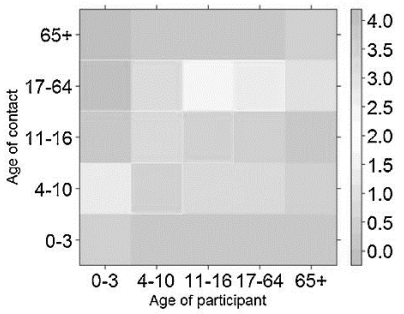

Fig. A.1. Weighted social contact matrix from POLYMOD contact survey, showing the mean number of long-duration physical contacts per day for participants in Great Britain. The age group of participants and their contacts are shown on the axes.

Appendix equation 1: The SEIR-type age-structured transmission model

$$\begin{aligned}\frac{dS_i}{dt} &= -\lambda_i S_i \\ \frac{dE_i}{dt} &= \lambda_i S_i - \gamma E_i \\ \frac{dI_i}{dt} &= \gamma E_i - \delta I_i \\ \frac{dR_i}{dt} &= \delta I_i\end{aligned} \tag{A.1}$$

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). γ^{-1} is the time that an individual is exposed but not yet infectious and δ^{-1} is the time that an individual is infectious. λ_i is the force of infection for age group i.

Appendix equation 2: The age-dependent force of infection

$$\lambda_i = \sigma_i \sum_j \frac{\beta_{ij} I_j}{N_j} \tag{A.2}$$

$\beta_{i,j}$ is the matrix of the mean daily number of contacts between an individual of age group i with age group j. σ_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.

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 on the interval [0,1] 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.

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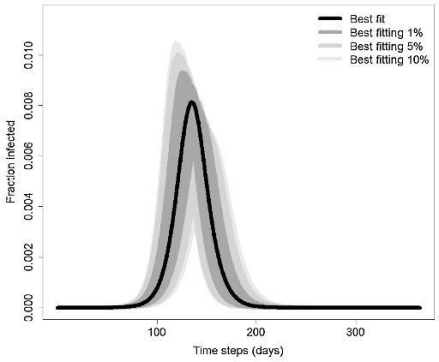

Fig. A.2. The epidemic curves of the best fitting models from 25,000 parameter sets sampled using uniform Latin Hypercube sampling.

Appendix equation 3: The binomial log-likelihood minimised to estimate the age-specific proportion of individuals with previously acquired immunity

$$\ln \mathcal{L} = \sum_{i=1}^{5} y_i \ln p_i + (n_i - y_i) \ln (1 - p_i) \quad \text{(A.3)}$$

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 (Fig. A.2).

We used the set of parameters that minimised the binomial log-likelihood but we kept the best-fitting 5% of realisations (Appendix Fig. A.2) for sensitivity analyses.

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The economic cost of measles: Healthcare, public health and societal costs of the 2012–13 outbreak in Merseyside, UK

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ABSTRACT

Background: Measles is a highly contagious vaccine-preventable infection that caused large outbreaks in England in 2012 and 2013 in areas which failed to achieve herd protection levels (95%) consistently. We sought to quantify the economic costs associated with the 2012–13 Merseyside measles outbreak, relative to the cost of extending preventative vaccination to secure herd protection.
Methods: A costing model based on a critical literature review was developed. A workshop and interviews were held with key stakeholders in the Merseyside outbreak to understand the pathway of a measles case and then quantify healthcare activity and costs for the main NHS providers and public health team incurred during the initial four month period to May 2012. These data were used to model the total costs of the full outbreak to August 2013, comprising those to healthcare providers for patient treatment, public health and societal productivity losses. The modelled total cost of the full outbreak was compared to the cost of extending the preventative vaccination programme to achieve herd protection.
Findings: The Merseyside outbreak included 2458 reported cases. The estimated cost of the outbreak was £4.4 m (sensitivity analysis £3.9 m to £5.2 m) comprising 15% (£0.7 m) NHS patient treatment costs, 40% (£1.8 m) public health costs and 44% (£2.0 m) for societal productivity losses. In comparison, over the previous five years in Cheshire and Merseyside a further 11,793 MMR vaccinations would have been needed to achieve herd protection at an estimated cost of £182,909 (4% of the total cost of the measles outbreak).
Interpretation: Failure to consistently reach MMR uptake levels of 95% across all localities and sectors (achieve herd protection) risks comparatively higher economic costs associated with the containment (including healthcare costs) and implementation of effective public health management of outbreaks.
Funding: Commissioned by the Cheshire and Merseyside Public Health England Centre.

1. Introduction

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) [1] and over 65% of the population live in the most socioeconomically deprived national quintile [2].

Measles is a highly contagious infection. Between 1998 and 2012, 6081 cases of laboratory confirmed measles were recorded in England and Wales, increasing from 28 in 2001 and reaching 1001 in 2008 [3]. Around 1 in 5000 cases in England result in death [3].

Immunisation is highly effective in controlling the spread of measles. In England around 90% of susceptible individuals receiving the Measles, Mumps and Rubella (MMR) vaccine through the national childhood immunisation programme will develop immunity after one dose at 13 months of age, and 99% develop immunity after a second dose at three years and four months. Between 2001 and 2012, vaccination coverage declined across many European countries, including the UK [4]. Failing to maintain high levels of vaccination was linked to inaccurate reports of adverse events and vaccine hesitancy among particular groups [5–7].

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In 2012 outbreaks of measles were reported in England concentrated in areas with lower MMR immunisation coverage including Wales [6], Liverpool [8], Manchester [9] and the North East [10]. Despite good vaccination uptake rates in recent years, the largest measles outbreak in the Merseyside area since MMR vaccination was introduced began in February 2012 and continued until August 2013, with 2458 reported cases (651 confirmed cases and 1808 probable and possible cases). The largest number of confirmed cases was in children aged under the age of 5 years, accounting for 42% (276/651) of all confirmed cases [11].

The costs of controlling an outbreak of measles could be substantial. To date, most studies have measured either the costs of treatment [12–14] or the cost of containment [15–18], but have not considered the total societal costs of outbreaks. We sought to quantify the costs associated with the response to the 2012–13 Merseyside measles outbreak including treatment, public health and societal costs. We compared the total cost of the outbreak response to the counterfactual costs that would have been incurred through preventative vaccination.

2. Methods

The costing study commenced in March 2012 to identify all NHS treatment, public health and productivity loss activity and cost items to establish the economic impact of the first 4 months of the outbreak. These results were then used to model the total cost of the whole outbreak after it was declared over.

Following a comprehensive critical literature review to inform the study methodology, a workshop was held with multi-agency partners and stakeholders to inform the cost assessment process, including mapping the pathway of a measles case and developing a costing model (Box 1 – scope of the model; Box 2 – process map of costs by organisation; and Box 3 – process map of cost by groups affected and activity).

Costs were classified in two categories: direct cost of the outbreak subdivided into direct costs to healthcare providers (treatment and other costs) and public health (control and management costs); and productivity loss costs. We linked these subcategories to each organisation to illustrate the distribution of costs. Although most costs were directly calculated from available data specifically linked to the first 4 months of the outbreak, some were extrapolated and therefore we used the term estimated costs for the first 4 months. The modelled cost for the entire outbreak was calculated based on the first 4 months estimated costs.

We included all cases in Merseyside in the study and one case that was confirmed in Manchester as the infection was likely acquired in Merseyside due to an epidemiological link. Cases were defined using guidance adapted from the HPA National Measles Guidelines [19]:

- 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.

2.1. Direct costs to healthcare providers

Direct costs to healthcare providers included: General Practitioner (GP) consultation time; Accident & Emergency Unit time; additional staff hours; hospitalisation and associated costs.

Secondary care treatment costs were calculated using information obtained from both Royal Liverpool Broadgreen University Hospitals Trust (RLBUHT) and Alder Hey Hospital Trust, the trusts most affected by the outbreak where detailed cost calculations were undertaken. Records of the number of patients treated, length of stay and treatment code enabled us to identify the treatment costs for confirmed and suspected cases of measles by hospital. Treatment costs were calculated using the Healthcare Resource Group (HRG) tariffs recorded for patients.

Community healthcare providers were also affected. Costs for GPs were extrapolated from the number of cases per GP surgery, multiplied by 1.5× the cost of a standard GP consultation [12,20] as this was the estimated additional time taken to see a suspected measles case.

2.2. Direct costs to public health

Direct public health costs included: contact tracing of household and other contacts; vaccinations; maintenance to improve infection control and isolation facilities; immunity status screening; healthcare staff exclusions for unknown or negative immunity status; and public engagement activities. Additional hours of staff time were calculated from timesheets. Other organisations for which costs were calculated included the local Ambulance Trust and the Manchester Public Health Laboratory.

Data from Primary Care Trusts (PCTs) were limited to public health functions to avoid double counting of resources deployed to support the local health protection team. 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.

2.3. Productivity costs

Productivity costs included: costs to employers for sickness absence due to measles related issues; and healthcare workers diverted to deal with cases.

We assigned an economic value to: costs incurred by cases and their carers; employers of affected individuals; vulnerable people at risk of contracting the virus who may be excluded from work, school or social events or received prophylaxis; and members of the general public who were unsure of their immunisation status or needed advice.

Measles-related absenteeism was calculated as [(Total no. of confirmed cases − confirmed hospital staff cases) + (Unreported cases)] × employment rate in Liverpool. It was assumed that the number of unreported cases of measles was 22.5% of all confirmed and potential reported cases of measles [12]. We multiplied the total case numbers by the employment rate in Liverpool [21], because if the measles cases were in an adult then they would be absent from work, and if it were in a child then their guardian would have to take time off work to care for their child. We assumed that a hospitalised confirmed case required two weeks of absence; a confirmed case without hospitalisation required three days of absence; and potential and unreported cases also required three days of absence (though this is likely to be an underestimate as HPA standard advice for exclusion of cases from school/workplace settings is four days [22]). We used the estimated absenteeism rate

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Box 1: Scope of the costs included in the model.

Broad category:	Sub-category:	Borne By:
Direct costs of the outbreak	Treatment of Cases	Primary care
		Secondary care
		Patients / carers
	Public Health Costs – Control & Containment	HPA, PCT, acute trusts, community trusts, and other relevant organisations, e.g. walk-in centre, out-of-hours services, etc.
		Local authority / schools
Productivity costs (indirect costs)		Secondary care (ward closures and cancelled admissions)
		Primary care (delayed and cancelled appointments)
		Patients / carers (work absence looking after an affected person or during recovery)
		Wider society (school / nursery closures)

multiplied by the average earnings rate for the region [21] adjusted for the length of absence.

2.4. Sensitivity analysis

A multi-variate deterministic sensitivity analysis was undertaken to account for the degree of uncertainty in costs based on assumptions, extrapolations or evidence from the literature. Where the cost information was provided from central records there has been no variation in the modelling. A list of the assumptions for the sensitivity analysis is shown in Tables 1 and 2.

2.5. Outcomes from the model

To compare against studies that only calculated control and management costs, a public health cost per case was calculated by dividing the modelled public health cost by the total number of confirmed and potential cases. For NHS treatment costs, a cost per patient admitted was calculated using admissions information.

Cost of achieving prevention was calculated assuming that herd protection against measles would require that 95% of eligible children receive 2 doses of the MMR vaccine. To achieve herd protection over the previous five years there was a need for a further vaccination of 11,793 children with MMR (8366 1st dose and 3427 2nd dose) [23]. The overall cost of delivering 11,793 MMR doses was estimated by assuming an administration and delivery cost of £7.64 per dose, plus the MMR vaccine cost of £6.37 per dose and a promotion cost at £1.50 per eligible child [24,25].

2.6. Modelling the cost of the entire outbreak period

The costs for the first four months of the outbreak were used to model the total cost of the outbreak running to 31st August 2013. Costs were divided into variable costs (dependent on case-load and outbreak duration including patient-facing activity in primary and secondary care institutions as well as public health activities such as contact tracing) and fixed costs (limited to the beginning of the outbreak including checking immunisation status of staff in primary and secondary care settings as this work was assumed to have taken place at the beginning of the outbreak, as well as the creation of the MMR Locally Enhanced Service for GPs).

The analysis was further informed by societal impact data from a study on the impact of measles infection, including factors such as absenteeism for individuals with confirmed measles and for their caregivers [26]. An individual in 63.1% of confirmed measles cases was assumed to take time off from work as a patient with a mean absence of 9.6 days (95% CI: 9.3–11.7), with 39.6% of individuals with confirmed measles requiring a caregiver for a mean time of 7.3 days (95% CI: 5.7–7.9) during infection.

3. Results

3.1. Costs for the outbreak period 1st February–31st May 2012

The estimated cost of the first four months of the outbreak was £1.4 million (sensitivity analysis £1.3 million to £1.6 million). Direct NHS healthcare costs were £292,000 (sensitivity analysis £282,000 to £306,000), 21% of the total cost. The majority of the total cost was due to direct public health costs £844,300 (60%) (sensitivity analysis £838,000 to £889,000). Productivity costs were

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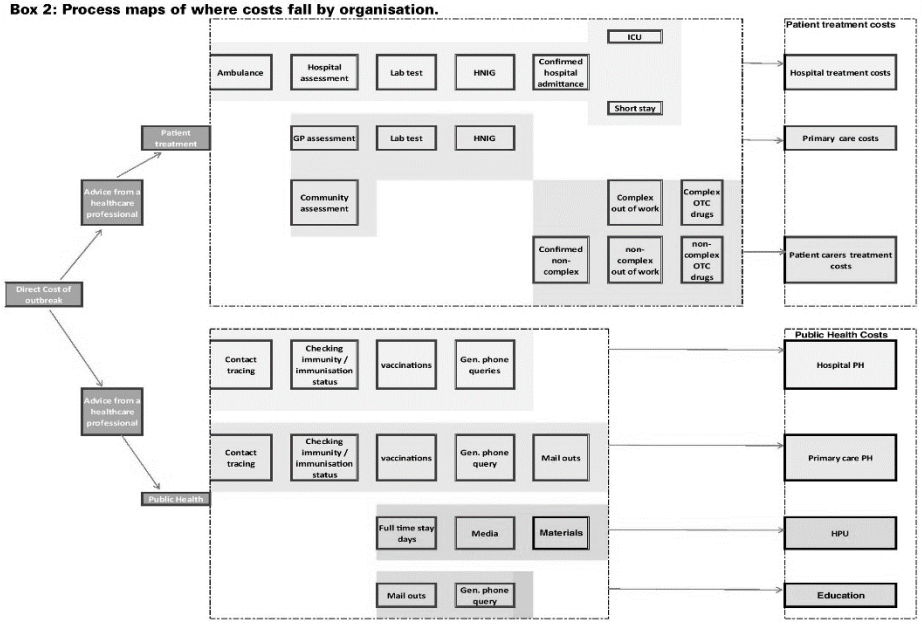
Box 2: Process maps of where costs fall by organisation.



Box 3: Process map of where cost fall by groups affected and activity.

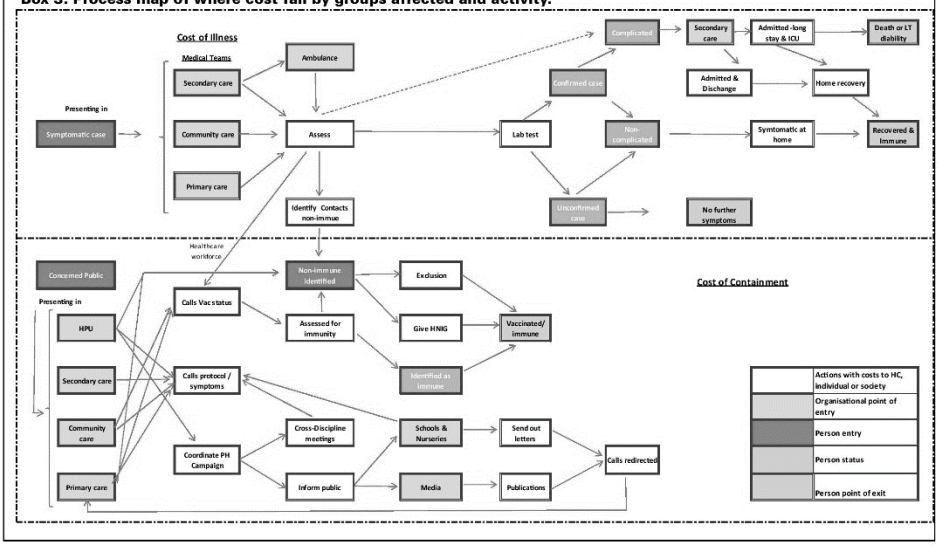


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Table 1
Parameters used in the sensitivity analysis for the calculated costs of the outbreak between 1st February 2012 and 31st May 2012.

	Lower end cost	Best estimate	Higher end cost
Costs of treatment per case in hospitals other than the two used to obtain the average cost	£1196	£1383	£1730
Cost of contact tracing in hospitals other than the two used to obtain the average cost	£0	Linked to Royal Liverpool estimate (£0.21 per worker at the hospital)	Linked to Royal Liverpool estimate (£0.21 per worker at the hospital)
Staff absence in hospitals other than the two used to obtain the average cost	£0	Linked to Royal Liverpool estimate (£537 per case of measles in the hospital)	Linked to Royal Liverpool estimate (£537 per case of measles in the hospital)
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

Unit costs rounded to the nearest £1.

Table 2
Parameters used in the sensitivity analysis for the modelled total costs of the full outbreak, 1st February 2012 to 31st August 2013.

	Lower end cost	Best estimate	Higher end cost
Costs of treatment in hospitals other than the two used to obtain the average cost	£1196	£1383	£1730
Cost of contact tracing in hospitals other than the two used to obtain the average cost	£0	Trust-specific, as provided by ICF report	1.5 × Trust-specific estimate from ICF
Staff absence in hospitals other than the two used to obtain the average cost	£0	Trust-specific, as provided by ICF report	1.5 × Trust-specific estimate from ICF
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

Unit costs rounded to the nearest £1.

£274,000 (sensitivity analysis £225,000 to £377,000), 19% of the total cost.

The highest proportion of the estimated cost of the initial outbreak period fell to secondary care organisations (37%) followed by the Health Protection Unit that coordinated the outbreak response (27%) (Table 3).

3.2. Costs of the full outbreak to 31st August 2013

The modelled cost of the full outbreak was £4.4 m (sensitivity analysis £3.9 m to £5.2 m). Of this, 15% (£678,300, between £644,000 and £707,800 from the sensitivity analysis) was attributed to direct NHS healthcare costs, 40% (£1,764,400, between £1,762,600 and £1,879,400 from the sensitivity analysis) attributed to direct public health costs and 44% (£1,952,700, between £1,443,900 and £2,564,800 from the sensitivity analysis) relate to productivity costs (Table 4).

Overall, 33% (£1,446,600) of the modelled total cost was related to activity concerning confirmed measles cases, and the remaining (£2,948,800) were related to both potential and unreported cases of measles (Table 5).

The direct hospital cost per admitted case was £1945 (£270,400/139). The direct public health cost per confirmed case was £2714 (£1,764,400/651).

3.3. Cost of achieving outbreak prevention through vaccination

The calculated overall cost of delivering 11,793 MMR doses over the previous five years to achieve herd protection across Cheshire and Merseyside was £182,909 (vaccine administration cost of £90,098, MMR vaccine cost of £75,121 and promotion cost of £17,690). This represents 4.2% of the modelled total cost of the outbreak.

4. Discussion

The modelled total cost of the 2012–13 Merseyside measles outbreak was substantial. In contrast, we estimated that 95% uptake of MMR could have been achieved by increasing uptake of those under-vaccinated children in recent five year cohorts of children in Cheshire and Merseyside at just 4.2% of the modelled total cost of the full outbreak.

4.1. Direct costs to healthcare providers

The modelled hospitalisation cost per patient admitted in Merseyside (£1945) was similar to those reported in three previous studies from Spain (£1521 per case in 2012 GBP) [14], Italy (£1614 in 2012 GBP) [13], and the USA (£2083 GBP in 2012 GBP) [17].

The overall hospitalisation cost is likely to be an underestimate, as the total number of admissions only includes those admissions at the time of notification and does not include those cases admitted following a later notification. The reported hospitalisation costs do not include any major measles-related complications as none were observed during this outbreak. It is 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 (£9798 per admission) and otitis media (£3057 per admission [27]) were not observed but would have substantially increased direct healthcare costs if they had occurred. Furthermore, conditions such as subacute sclerosing panencephalitis (SSPE)

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Table 3
Estimated costs[a] for the 2012–13 Merseyside measles outbreak, 1st February 2012 to 31st May 2012.

Organisation	Direct healthcare		Direct public health		Productivity		Total costs	
	Cost (£)	%	Cost (£)	%	Cost (£)	%	Cost (£)	%
Primary Care Trusts	0	0	90,100	11	0	0	90,100	6
Secondary Care	270,400	93	213,400	25	42,400	15	526,200	37
Community Care	0	0	43,000	5	0	0	43,000	3
General Practitioners	18,600	6	84,600	10	0	0	103,200	7
Cheshire & Merseyside Health Protection Unit	3000	1	368,800	44	0	0	371,800	27
Ambulance Service	0	0	1100	0	0	0	1100	0
MRI Laboratory costs	0	0	28,500	3	0	0	28,500	2
Society lost productivity	0	0	0	0	231,600	85	231,600	17
Local authority	0	0	14,800	2	0	0	14,800	1
Total cost	**292,000**		**844,300**		**274,000**		**1,410,300**	

[a] Estimated costs mainly consist of costs based on evidence provided by the relevant organisations. Costs are rounded to the nearest £100.

Table 4
Modelled total costs of the full outbreak by organisation type of cost (direct healthcare provision, public health, and loss of productivity), 1st February 2012 to 31st August 2013.

Organisation	Direct healthcare		Direct public health		Productivity		Total costs	
	Cost (£)	%	Cost (£)	%	Cost (£)	%	Cost (£)	%
Primary Care Trusts	–	0	223,000	13	–	0	223,000	5
Secondary Care	575,000	85	370,000	21	49,200	3	994,200	23
Community Care	–	0	91,400	5	–	0	91,400	2
General Practitioners	103,300	15	212,000	12	–	0	315,000	7
CMHPU	–	0	790,400	45	–	0	790,400	18
Ambulance Service	–	0	2300	0	–	0	2300	0
MRI Laboratory	–	0	60,500	3	–	0	60,000	1
Society Lost Productivity	–	0	–	0	1,903,500	97	1,903,500	43
Local Authority	–	0	14,800	1	–	0	14,800	0
Total	**678,300**		**1,764,400**		**1,952,700**		**4,395,400**	

Modelled total costs, rounded to the nearest £100.

which cost £6217 per admission [27] may take many years to develop, and therefore the treatments costs associated with the outbreak may increase if assessed over a longer period than this analysis. SSPE cases are also likely to require far more follow-up visits for specialist care, support, and longer period of home-care than otitis media resulting in more additional costs.

4.2. Direct costs to public health

Around 40% (£1,764,400) of the total costs related to direct public health activities. Overall, the 2012–13 outbreak has a lower public health cost per case (£2714) than four of five previous studies that reported on public health costs measles outbreaks, possibly due to the small number of cases in these studies – one with a total number of 3 cases found a cost of £31,260 (£33,424 in 2012 GBP) per case [16]; a second with a total number of 7 cases found a cost of £57,478 (£65,871 in 2012 GBP) per case [15]; a third with a total number of 12 cases found a cost of £5458 (£6215 in 2012 GBP) per case [28]; and a fourth with 1 case found a cost of £15,196 (£16,722 in 2012 GBP) per case [29]. It appears that the higher the number of cases, the lower the public health costs per case. This makes intuitive sense given that the more cases there are, the greater the chances of epidemiological links to reduce the need for further contact tracing and the fact that some costs (e.g. distributing leaflets) would be identical regardless of the case burden. This economy of scale effect explains why the public health costs per case in these studies are larger than in Merseyside. One other study with a total number of 40 cases found a similar cost per case of £2569 (£3155 in 2012 GBP) [30] to our estimate. The public health responses described in these studies were similar to that of the

Table 5
Modelled total costs of the full outbreak by organisation, 1st February 2012 to 31st August 2013.

Organisation	Confirmed cases modelled total cost		Confirmed, probable, and potential cases modelled total cost		Confirmed, probable, possible and unreported cases modelled total cost	
	Cost (£)	%	Cost (£)	%	Cost (£)	%
Primary Care Trusts	184,300	13	223,000	6	223,000	5
Secondary Care	347,300	24	994,200	25	994,200	23
Community Care	24,200	2	91,400	2	91,400	2
General Practitioners	248,500	17	315,300	8	315,300	7
CMHPU	220,600	15	790,400	20	790,400	18
Ambulance Service	600	0	2300	0	2300	0
MRI Laboratory Costs	16,000	1	60,500	2	60,500	1
Society Lost Productivity	390,300	27	1,549,000	38	1,903,500	43
Local Authority	14,800	1	14,800	0	14,800	0
Total	**1,446,600**	**100**	**4,041,000**	**100**	**4,395,400**	**100**

Modelled total costs, rounded to the nearest £100.

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Merseyside outbreak, indicating that the costs associated with the public health response were broadly proportionate to the size of the outbreak.

The number of contacts traced plays a substantial role in the public health response to an outbreak and therefore related public health costs. In the Merseyside outbreak attempts were made to identify all contacts during the early stages (1st February to 23rd 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 significant 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.

4.3. Productivity costs

The productivity losses accounted for 43% (£1,952,700) of the modelled total cost of the outbreak, and as the largest contributor to costs, our analysis suggests that it is important to include this societal perspective when assessing the impact of a measles outbreak. This is not an insignificant amount of money, especially given high levels of deprivation in the community. Only 2.5% of the productivity cost (£49,200) was attributed to staff absence in secondary care due to measles, with the remaining £1,903,500 attributed to work or school absence in the wider population costs. Previous studies reporting the cost of measles outbreaks did not include productivity costs so here we present new insight on the socio-economic impact of measles outbreaks.

4.4. Policy implications

There were few reported cases in vulnerable groups, such as immunosuppressed individuals or pregnant women, additionally there were no measles related deaths or serious complications at the time of writing this report. With this in mind, it is not unexpected that the cost of providing treatment was significantly less than the cost of the public health interventions. Therefore, it is important not to underestimate the impact of the public health activities such as raising awareness for timely vaccination of eligible individuals; identification and protection of individuals through timely contact tracing; immediate case isolation; enhanced infection control measures; and appropriate exclusion of suspected cases from schools, workplaces and other settings. It is paramount that these interventions are prioritised in any future outbreaks to limit onward transmission and protect public health.

An investment of an additional £1 on immunisation over the past five years to reach the herd protection threshold would have saved £23 incurred as a result of this outbreak had herd protection been achieved. These stark figures suggest that it is important to prioritise and aim to achieve high MMR uptake levels (95%) consistently across all localities and sectors of the population in order to prevent widespread measles outbreaks occurring. Although vaccinating eligible children to 95% would not impact on uptake of others who are susceptible within local communities, nevertheless preventing spread among children would limit the spread in communities.

The overall investment in the childhood vaccination programme will be undermined and its full benefits unrealised if herd protection is not achieved, as a costly outbreak of measles occurring in areas with low uptake is a distinct possibility. It is therefore important for immunisation commissioners to commission a well-resourced, co-ordinated and robust vaccination programme that consistently achieves MMR uptake of 95% and above.

4.5. Strengths and limitations

This study has some limitations. Firstly, no attempt was made to estimate any additional opportunity cost of the outbreak to organisations (beyond staff salary costs) to avoid double counting. Nor was an attempt made to estimate the effects on staff welfare, or to estimate a value of lost leisure time as it is complex to assign monetary values to these. Using wages as a measure of productivity is a conservative method of estimating loss of productivity, therefore the overall cost estimate was assumed to be conservative.

Secondly, more organisation-specific quantifications of costs could have been made by consulting with more of the organisations affected by the outbreak (including all of the hospitals admitted cases, PCTs and GP practices, rather than those which were affected most), and surveying measles cases and their caregivers to estimate the duration of work/school absence.

Thirdly, it is likely that we have underestimated the total cost of implementing a vaccination programme to reach herd protection in the area. Our estimated cost of this programme included vaccine administration costs, promotion costs and the cost of vaccine stock. Additional promotion costs may be required to persuade strongly vaccine-hesitant parents and guardians to vaccinate their children, including more labour-intensive approaches in reaching this community. However, it is apparent that any additional resources used to achieve herd protection are likely to be significantly lower than the costs associated with managing any future measles outbreaks.

MMR vaccination coverage in Cheshire and Merseyside is unlikely to be homogeneous and some communities in the area may already have higher vaccination coverage than the 95% threshold. Heterogeneous vaccination coverage may lead to widespread outbreaks in the community if some areas have a coverage level sufficiently low to fuel transmission with clusters of susceptible individuals [31], indeed outbreaks have been reported in other countries due to clusters of susceptible individuals residing in areas with otherwise very high vaccination coverage [32,33]. The herd protection threshold target of 95% uptake should be a target for homogenous coverage, rather than an average across the community with heterogeneous uptake.

Given the constraints, we consider that this study provides a robust estimate of the cost of the 2012–13 Merseyside measles outbreak. Furthermore, the study has provided information on the impact and cost to the NHS and wider economy of not achieving uptake targets detailed in the Public Health Outcomes Framework required to achieve herd protection [34].

5. Conclusions

The total cost of the 2012–13 Merseyside measles outbreak is higher than suggested in previous research, as a wider range of costs associated with the outbreak have been modelled. Despite this, the total cost is still likely to be an underestimate, as it is difficult to quantify the full societal impact. This study illustrates the importance of prevention through MMR vaccination and achieving herd protection, compared to the costs and resource implications of managing an outbreak. We recommend that immunisation commissioners seek to commission a well-resourced, co-ordinated and robust vaccination programme that consistently achieves MMR uptake rates of 95% and above across all communities of the population.

Research in context

Evidence before this study:

Several studies have investigated the economic cost of measles outbreaks in different countries. Such studies have reported a mean

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cost per measles case; the mean cost per hospitalised measles case, both with and without measles-related complications; and the estimated cost of preventing a single case. Additionally, some studies estimated the public health costs of managing and containing measles outbreaks. However, no studies have presented the wider socio-economic cost of a measles outbreak that considers direct healthcare costs, direct public health costs and the cost of the loss of productivity to the affected communities.

Added value of this study:

This study provides estimates of the socio-economic cost of the 2012–13 measles outbreak in Merseyside, UK. Direct NHS healthcare costs were sourced directly from General Practice surgeries, NHS Trust databases and Accident and Emergency units. Direct public health costs were sourced from Primary Care Trusts and other organisations involved in the containment of the outbreak, taking data on staff time, vaccination and prophylaxis administration, contact tracing and other containment activities. Productivity loss costs were sourced from staff absenteeism records from organisations involved in the outbreak management, along with estimates of school and work absenteeism in the community combined with adjusted mean earnings rates sourced from local government data.

Implications of all the available evidence:

The total cost of the 2012–13 Merseyside measles outbreak is higher than suggested in previous research of measles outbreaks, as a wider range of costs have been estimated than in previous research. In contrast, the estimated additional cost of achieving herd protection for the community through the MMR vaccination programme would have been just 4.2% of the estimated total cost, demonstrating both the importance and value of a well-resourced, co-ordinated and robust preventative vaccination programme.

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