Mathematical modelling and cost-effectiveness of future RSV intervention strategies

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A thesis submitted for the degree of Doctor of Philosophy

August 2020
Declaration

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

I would like to express my deep gratitude to Dr Katherine Atkins, Dr Marc Baguelin, Dr Jasmina Panovska-Griffiths, and Dr Richard Pebody, my research supervisors, for their patient guidance, enthusiastic encouragement and useful critiques of this research work. I would also like to thank Dr Dominic Thorrington and Dr Albert van Hoek, for their advice and assistance in conducting the RSV cross-sectional survey. I also wish to thank my parents, Mark and Helen, my sister Emma, and friends Zainab, Matt, Chris, Phil, Ed, and Hannah, for their support and encouragement throughout my studies. Finally, I would also like to thank the Medical Research Council and CoMPLEX for funding this work.
New Respiratory Syncytial Virus (RSV) prophylactics are likely to be licensed in the next few years. Such prophylactics, including long-acting monoclonal antibodies and new vaccines, will aim to either replace or supplement the current monoclonal Palivizumab programme. This thesis explores the implications of these changes to RSV health policy by developing and using a novel mathematical model for RSV transmission and evaluating the impact of potential intervention programmes. The model will be combined with an economic analysis and a cross-sectional survey of RSV burden in England and Wales. Specifically, this thesis is split into six chapters which outline different topics of RSV research which are used collectively to inform RSV policy decision making in England and Wales. Chapter 1 provides the background information, giving context for the chapters that follow, as well as the aims and objectives of the thesis. Chapter 2 outlines a study that determines the health burden due to RSV in England and Wales through a cross-sectional survey performed in the winter of 2016/17. Chapter 3 describes a review of existing transmission models outlining the key epidemiological features that characterise RSV transmission and determines gaps in the current literature. Chapter 4 then presents a novel mathematical model for RSV transmission, parametrised and calibrated to seven years of historical epidemiological data using a Bayesian approach. Impact projections of the model for different RSV intervention programmes are given in Chapter 5. Finally, Chapter 6 combines the impact projections with an economic model to showcase the cost-effectiveness and affordability for a suite of RSV intervention programmes. The results of the calibrated model suggest that maternal protection of infants is seasonal, with 2-14% of infants born with protection against RSV. Further, the economic analysis found that to cost-effectively and affordably replace the current monoclonal antibody Palivizumab programme with long-acting monoclonal antibodies, the purchase price per dose would have to be less than around £4,350 but dropping to £200 for vaccinated heightened risk infants or £90 for all infants. A seasonal maternal vaccine would have to be priced less than £85 to be cost-effective and affordable. While vaccinating pre-school and school-age children is likely not cost-effective relative to elderly vaccination programmes, an elderly vaccination programme is not likely to be affordable. Conversely, vaccinating infants seasonally at two months of age would be cost-effective and affordable if priced less than £80. In a setting with seasonal RSV epidemiology, maternal protection conferred to newborns is also

Abstract

New Respiratory Syncytial Virus (RSV) prophylactics are likely to be licensed in the next few years. Such prophylactics, including long-acting monoclonal antibodies and new vaccines, will aim to either replace or supplement the current monoclonal Palivizumab programme. This thesis explores the implications of these changes to RSV health policy by developing and using a novel mathematical model for RSV transmission and evaluating the impact of potential intervention programmes. The model will be combined with an economic analysis and a cross-sectional survey of RSV burden in England and Wales. Specifically, this thesis is split into six chapters which outline different topics of RSV research which are used collectively to inform RSV policy decision making in England and Wales. Chapter 1 provides the background information, giving context for the chapters that follow, as well as the aims and objectives of the thesis. Chapter 2 outlines a study that determines the health burden due to RSV in England and Wales through a cross-sectional survey performed in the winter of 2016/17. Chapter 3 describes a review of existing transmission models outlining the key epidemiological features that characterise RSV transmission and determines gaps in the current literature. Chapter 4 then presents a novel mathematical model for RSV transmission, parametrised and calibrated to seven years of historical epidemiological data using a Bayesian approach. Impact projections of the model for different RSV intervention programmes are given in Chapter 5. Finally, Chapter 6 combines the impact projections with an economic model to showcase the cost-effectiveness and affordability for a suite of RSV intervention programmes. The results of the calibrated model suggest that maternal protection of infants is seasonal, with 2-14% of infants born with protection against RSV. Further, the economic analysis found that to cost-effectively and affordably replace the current monoclonal antibody Palivizumab programme with long-acting monoclonal antibodies, the purchase price per dose would have to be less than around £4,350 but dropping to £200 for vaccinated heightened risk infants or £90 for all infants. A seasonal maternal vaccine would have to be priced less than £85 to be cost-effective and affordable. While vaccinating pre-school and school-age children is likely not cost-effective relative to elderly vaccination programmes, an elderly vaccination programme is not likely to be affordable. Conversely, vaccinating infants seasonally at two months of age would be cost-effective and affordable if priced less than £80. In a setting with seasonal RSV epidemiology, maternal protection conferred to newborns is also
seasonal, an assumption not previously incorporated in transmission models of RSV. For a country with periodic RSV dynamics like England, seasonal programmes rather than year-round intervention programmes are always optimal.
Impact statement

There are several specific aspects of the thesis which will have beneficial use both inside and outside academia. First, this thesis is the first to estimate the health burden of RSV in terms of Quality Adjusted Life Years lost. As this metric is the standard used for cost-effectiveness analysis, these values will be used by academics, public health researchers and policy decision makers in future RSV-related cost-effectiveness analyses. Second, in the course of this thesis a novel mathematical model for RSV transmission and vaccination has been designed, parametrised and calibrated to incidence data from England and Wales and combined with an economic analysis. Furthermore, the numerical code of this model is readily available as open-source software and this has the potential to be used by policy decision makers in the future. Therefore our work has the potential, in future, to be expanded to other intervention scenarios of different countries. Third, from an epidemiological prospective, this thesis shows that maternal protection in infants born in England changes seasonally, with low protection occurring before the start of the RSV season, and peak protection occurring just after the RSV season. This observation contrasts the assumption that RSV maternal protection is constant throughout the year as assumed in previous mathematical models and could be used as evidence to influence the design of future epidemiological studies. Finally, our work is the first modelling work to estimate the cost-effective purchasing price per course for RSV intervention programmes by combining an RSV transmission model with an economic analysis informed from the National Institute of Clinical Excellence guidelines. As such, the model framework presented in this thesis it remains the most comprehensive transmission model study to inform policy decision making on the cost-effectiveness of future RSV intervention programmes in England and Wales to date.
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Chapter 1

Background

Respiratory Syncytial Virus (RSV), causes acute lower respiratory tract infections (ALRT) predominately in young children. With a suite of new preventative measures against RSV disease on the horizon, public health bodies need to decide if the health benefit acquired from administering these measures warrants the cost of delivery (i.e. are cost-effective). However, as the health burden and transmission dynamics of RSV are not fully understood, evaluating the cost-effectiveness of potential measures is difficult and speculative results are highly uncertain. This PhD thesis evaluates the impact of these potential measures in light of current evidence and determines which are likely to be cost-effective in England and Wales. To do this, I explore the transmission dynamics of RSV by building a mathematical model of its transmission in England and Wales and parameterise it by considering observational epidemiological studies and using Bayesian inference. I also conduct a cross-sectional survey to determine the health burden associated with RSV in England and Wales. Finally, using the derived mathematical transmission model and the estimates of health burden, I evaluate the impact and cost-effectiveness of potential intervention programmes for RSV in England and Wales, giving specific guidelines on the cost-effective purchasing price per dose.

1.1 Virology and Immunology

RSV is a cytoplasmic enveloped RNA virus which predominately infects humans. It is a member of the family Paramyxoviridae, which includes parainfluenza viruses, mumps virus and measles virus. The viral envelope of RSV contains two large virally encoded transmembrane surface proteins: the G attachment protein and the F fusion protein, which are important for immunity and pathology. Extensive antigen differences observed on the
G protein only has lead to two antigenic subgroups of RSV, A and B, being defined.\textsuperscript{2} RSV is spread through either a) close contact with an infected person or b) by direct contact of contaminated surfaces with nasal or conjunctival mucosa. Once the virus reaches a mucosal surface, it replicates by infecting epithelial cells using the G attachment protein. Then, through a processes mediated by its F fusion protein, neighbouring epithelial cells fuse together, forming multi-nucleated cell masses called syncytia. Replication of RSV in epithelial cells causes an innate immune response and an adaptive immune response which helps clear the infection and forms the clinical features of RSV disease. For example, immune responses to viral replication in the nasopharynx cause excessive production of mucus, resulting in symptoms such as rhinitis. In addition, inflammatory responses to viral replication in the bronchioles or alveoli can cause much more severe clinical disease, including a bronchiolitis and pneumonia.\textsuperscript{3}

Despite the fact that RSV infection creates an effective humoral response, RSV persistently causes symptomatic reinfection, even with the same strain of virus, throughout life.\textsuperscript{4} The exact mechanisms which causes this ability to persistently reinfect hosts is not clear and remains an active area of research. Several identified characteristics of RSV which could speculatively contribute to lack of long-term immunity include i) the ability of virally-secreted G proteins to bind to antigen, allowing evasion of antibody-mediated clearance,\textsuperscript{5} and ii) RSV-specific viral tropism, which restricts the exposure of viral antigen to the host’s immune system.\textsuperscript{6} Frequent reinfection with RSV means most individuals are susceptible to infection each winter, regardless of whether they were infected in the previous season.\textsuperscript{7}

Young infants are born with maternally-acquired neutralising IgG antibodies against RSV.\textsuperscript{8} The immunological effects of maternally-acquired neutralising IgG are poorly understood, however, high levels of these antibodies in infants results in a reduction of RSV-associated bronchiolitis and hospitalisation cases when compared to infants with low levels of RSV neutralising antibodies, suggesting a protective effect for up to 6 months.\textsuperscript{9–11} Maternally-acquired RSV-neutralising IgG titre in infants has been shown to vary seasonally, peaking at the end of the RSV season.\textsuperscript{10,12,13} In addition, birth-cord RSV neutralising IgG titre levels correlates with that of the mother.\textsuperscript{14} This suggests that the increased antibody levels in in pregnant women who have recently experienced an RSV infection could be transferred their new born, providing boosted seasonal protection.
1.2 Epidemiology

RSV is estimated to annually cause 33.1 million ALRT, in children under 5 years of age and is the most significant pathogen which causes ALRT in young children globally.\textsuperscript{15} The most common clinical feature of RSV infection in infants is bronchiolitis—a swelling in the bronchioles caused by mucosal inflammation which makes it difficult to breathe.\textsuperscript{3} RSV infections are very closely associated with bronchiolitis, causing between 50-80\% of bronchiolitis cases globally.\textsuperscript{16} Clinical features of RSV infection in older children and adults are much milder, including symptoms such as rhinitis and coughing, and are often asymptomatic.\textsuperscript{17,18} Risk factors for severe RSV infection include congenital chronic conditions (including lung disease, neuromuscular disease, heart disease, immunodeficiency, and chromosomal abnormalities) and acquired chronic conditions (including liver disease, epilepsy).\textsuperscript{19} Household structure is also a risk factor for severe RSV infections, with increasing risk correlated with an increasing number of siblings sharing a household with an infant.\textsuperscript{20} This is because infants have been shown to be the main disseminators of disease within a household in both high-income and low-income countries.\textsuperscript{21,22} Though ubiquitous globally, RSV displays great heterogeneity in its seasonal pattern of incidence, severity and prevalence across the world.\textsuperscript{23} These differences in RSV seasonal activity have been speculated to be part effected by latitude, relative humidity, temperature and social behaviour, but is likely to be driven by a complex interplay between these location-specific factors.\textsuperscript{24}

RSV has a high burden in England and Wales, where it has been recently estimated to be responsible for approximately 46,000 hospitalisations and 900,000 GP consultation each year.\textsuperscript{25–27} The majority of the hospitalised cases are due to RSV bronchiolitis, a condition which, in 2011, accounted for 5\% of all hospital admissions in infants (an increase from 3\% in 2004\textsuperscript{28}) and is the most common reason for hospital admission for infants in the UK.\textsuperscript{28} The majority of these cases occur in the winter months in the UK, with a very reliable peak of RSV activity occurring every December.\textsuperscript{29} Though there are disease-related risk factors for RSV infection in the UK, between 85 and 95\% of hospitalised infants have no known predisposing risk factors for RSV infection.\textsuperscript{30,31} In fact, recent studies suggest that the month of birth is the most important factor in determining susceptibility to severe RSV infection,\textsuperscript{29} with children born just prior to RSV seasonal incidence starting being at a significantly higher risk of severe infection. In addition to infants, there is also a notable
RSV burden in the vulnerable elderly population in the UK with an estimated 13,000 hospitalisations and 180,000 GP consultations occurring annually. Consequently, RSV infections in the UK are persistent and increasing, making it a huge public health burden in infants and the elderly.

1.3 Intervention programmes

Options for prevention and control of RSV are limited. Vaccines against RSV have been unsuccessful and have an unfortunate history, with a formalin-inactivated vaccine increasing the incidence and severity of RSV infection in clinical trials performed in infants during the 1960s. This unfortunate event highlights the complexity of RSV immunopathogenesis, which even today is not fully understood. Further, as RSV can only infect humans, determining the safety and efficacy of potential vaccines using animal or in vitro models doesn’t guarantee success in human trials, with many promising candidates eventually failing in vivo. To date, there is no commercial vaccine against RSV. The only RSV-specific preventative measure available is monoclonal antibodies—Palivizumab. Administration of monoclonal antibodies introduces immunoglobulin G-1 (IgG-1) monoclonal antibody that binds to the F-protein of RSV into the host, providing immediate, but short lived protection from RSV infection. The seminal IMPACT study showed that giving monthly intramuscular injections of Palivizumab to premature infants (<35 weeks) significantly reduces both the rate of RSV-related hospitalisation and the number of RSV-related hospital days. However, because monthly injections are needed to maintain a serum antibody concentration at a protective level, administration of Palivizumab is logistically difficult and expensive (a single course can cost up to £5000). Due to its high cost, the eligibility criteria for Palivizumab in the UK is very specific, and includes only infants who:

1. are born at less than 34 weeks gestation age and Bronchopulmonary dysplasia (BPD)/Congenital Heart Disease (CHD) and who are <9 months at the start of the RSV season

2. have respiratory diseases who are not necessarily pre-term but who remain in oxygen at the start of the RSV season

3. have Severe Combined Immunodeficiency Syndrome (SCID)

These guidelines are stricter than other high-income countries, leaving the majority of the population of the UK vulnerable to RSV infection each season. In particular, there
are a number of infants with congenital conditions such as Cystic Fibrosis and Down’s Syndrome and infants with acquired conditions such as Epilepsy and liver disease, who are particularly susceptible to severe RSV infection but are left unprotected. Though the protection due to Palvizumab is effective, it’s lack of availability makes it an ineffective product for preventing RSV infection at the population level. However, recent advancements in monoclonal antibody research has produced promising alternative products to Palvizumab, including MEDI8897, which provides similar levels of protection to Palvizumab for up to five months (without the need for monthly doses). This product will be easier to administer and cheaper than the Palvizumab course, with the potential for an augmented eligibility criteria, providing protection to more infants.

Although there are no commercial vaccines against RSV, technological and biological advancements mean vaccines are close to commercial availability, with over 40 vaccines and new monoclonal antibodies currently undergoing pre-clinical and clinical trials. The most promising of these includes a vaccine composed of recombinant RSV F nanoparticles, aimed at pregnant women, developed by Novavax called ResVax. ResVax targets pregnant women during their third trimester to boost the concentration of RSV F-protein IgG antibodies in both the mother’s serum and their newborns serum’s. A boost in similar RSV-neutralising antibodies titres has been shown to decrease rates of hospitalisation and bronchiolitis and therefore could protect infants at their most vulnerable. The stage 3 clinical trial for ResVax (called the Prepare Trial) recruited 4,636 maternal – infant pairs across 3.5 years and 11 countries. The results of Prepare Trial suggested the RSV F vaccine was well-tolerated by pregnant women and safe, with efficient antibody transferral from pregnant women to new born. The observed efficacy of the vaccine strategy across all sites was 39.4% against the primary endpoint (medically-significant RSV LRTI), which did not meet the required threshold of 40.0%, but observed efficacy was greater against more severe endpoints: including RSV LRTI with hospitalization (44%) and RSV LRTI with severe hypoxemia (48%). However, there was some variation in efficacy observed in timing of vaccination by gestational age (increased efficacy less than 33 weeks) and huge variation depending on location (11.6% in USA vs 42.5% South Africa against medically-significant RSV LRTI). These inconsistencies in efficacy, mean further research is needed to determine if its eligible for licensure. Vaccines aimed at pregnant women also see low uptakes rates in the UK, with year-round maternal vaccination such as Pertussis seeing uptakes of 60%, and seasonal maternal vaccination programmes for Influenza reaching
about 40%. Vaccines aimed at young infants are slower to progress due to the previously unsuccessful formalin-inactivated vaccine. In addition there are reduced immune responses to RSV infection early in life, due to immunological immaturity and immunosuppressive effects of maternal antibodies. Consequently, vaccines aimed at young infants require special consideration to balance the safety and efficacy of vaccinating such a vulnerable age group. Other possibilities for vaccination include targeting school age children, as they have been identified as the major disseminators of disease within households. With these vaccines on the horizon, the RSV public health policy landscape will significantly change and evidence is required to inform public health bodies of the dynamics and feasibility of implementing a RSV vaccine programme in the UK.

1.4 Outline of PhD

In light of these new potential preventative measures, the research aim of my PhD is to evaluate the cost-effectiveness of potential intervention strategies against RSV in England and Wales. To achieve this research aim I outline five main objectives:

1. **Objective 1**: Determine the health burden due to RSV infection in England and Wales

2. **Objective 2**: Gain an overview of the current RSV modelling landscape

3. **Objective 3**: Develop a new mathematical model of RSV transmission in England and Wales

4. **Objective 4**: Evaluate the impact of potential RSV intervention programmes

5. **Objective 5**: Evaluate the cost-effectiveness of potential RSV intervention programmes

Next, I describe these objectives in more detail.

**Objective 1: Determine the health burden due to RSV infection in England and Wales**

Cost-effectiveness analyses require accurate measures for both the cost and health benefit of an intervention programme. The metric used for quantifying health benefit is Quality Adjusted Life Years (QALYs). QALYs take into account both the morbidity during the infection, in the form of Health-Related Quality of Life (HR-QoL), and time over which
this morbidity is experienced. In order to determine the HR-QoL, standardised instruments such as EQ-5D forms are used—providing a mapping from qualitative descriptions of disease severity into a single quantitative measure of morbidity. No such measures for HR-QoL loss currently exist for RSV infection. Therefore this objective is an essential step in ensuring that the cost-effectiveness analysis, which is described later in the thesis, is accurately evaluating the effects of potential intervention programmes.

**Objective 2: Gain an overview of the current RSV modelling landscape**

Mathematical models make it possible to understand how infectious diseases spread throughout a population. To ensure these models are accurate, they should include disease-specific transmissions characteristics informed from epidemiological studies. To understand which RSV-specific model structures help improve the accuracy of these mathematical models, a systematic review of existing mathematical models of RSV transmission is performed. This review gives an overview of the current RSV modelling landscape, including potential intervention programmes which have been evaluated, inspiring the mathematical model outlined in the next chapter.

**Objective 3: Develop a new mathematical model of RSV transmission in England and Wales**

A dynamic transmission model is developed, where the probability of transmission is proportional to the number of infected persons in a population at any time, to model the spread of RSV in England and Wales. Using this type of model allows for the indirect effects (i.e. herd immunity) of an intervention programme to be evaluated, and is therefore much preferred over other mathematical models. The model is parametrised through a critical analysis of the epidemiological observation studies of RSV disease and calibrated to RSV surveillance data specific to England and Wales using Monte Carlo Markov chain (MCMC) Bayesian inference techniques, to obtain a set of posterior distributions for the inferred parameters. These posterior distributions are then used together with the mathematical model to produce the model-estimated incidence of RSV disease in England and Wales.
Objective 4: Evaluate the impact of potential RSV intervention programmes

Using the projected incidence of RSV from the mathematical model of RSV transmission I evaluate the impact of potential intervention programmes. This is done by adapting the existing mathematical model to include specific immunological responses associated with each prophylactic. The impact of these programmes are measured in terms of cases of RSV-related symptomatic infection, GP consultation, hospital cases, hospital bed days and deaths averted. As these outcomes can be converted into costs and QALYs, this objective is an important intermediate stepping stone towards evaluating the cost-effectiveness analysis.

Objective 5: Evaluate the cost-effectiveness of potential RSV intervention programmes

Cost-effectiveness analyses (CEA) are an important part of the healthcare decision-making process. The basic idea behind a CEA is to check that the increased health benefit from implementing a new intervention programme is enough to warrant any increased costs. The guidelines for how this analysis is performed in England and Wales are outlined in the National Institute of Clinical Excellence’s (NICE) reference case, which I follow throughout this thesis. As the price of the potential intervention strategies is not yet available, this objective provides a list of maximum purchasing costs per course of treatment for which each intervention programme would remain cost-effective.

This thesis comprises of five further research chapters, each addressing each of the objectives, followed by a chapter about the open source software which was created as a result of this thesis, and finally a summary chapter. In Chapter 2 Objective 1 is achieved. Here, I describe the methods and results of a cross-sectional survey, conducted in the winter of 2016-17 to ascertain QALY loss due to acute RSV infection in infants who are hospitalised and also RSV infections in the household members of these infants. In Chapter 3, Objective 2 is achieved by presenting a systematic review of the existing transmission models of RSV and summarises the key model characteristics which are important in capturing the transmission dynamics of RSV. Objective 3 is achieved in Chapter 4 which outlines the transmission model of RSV used throughout this thesis and includes a summary of the studies used to parameterise the model and the MCMC methods used to calibrate the
epidemiological parameters in the model. **Objective 4** is achieved in **Chapter 5** where I outline the promising prophylactics currently in clinical trials that I wish to evaluate. In addition, I describe the impact of all the relevant intervention programmes associated with these prophylactics. Finally, **Objective 5** is achieved in **Chapter 6**, where the QALY loss (from **Chapter 2**) is paired with both the UK-specific costs from 2018 and the impact estimated in **Chapter 5** to determine the maximum purchasing price per course for these programmes to remain cost-effective. A summary of how the contents of the chapters in this thesis are related to each other is contained in **Figure 1.1**.

This work in this thesis has generated two publications, one based on Chapter 2, and another based on Chapter 4–6.44,45

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**Figure 1.1**: Summary of how the contents of the chapters in this thesis are related to each other
Chapter 2

Estimating the health burden due to RSV

2.1 Introduction

To determine the health burden due to RSV infection, I conducted a cross-sectional survey to measure the morbidity of acute RSV infection in infants and adults during the winter of 2016 and 2017 for use in a cost-effectiveness analysis. Cost-effectiveness analyses rely on the existence of measures for morbidity associated with RSV episodes and is routinely expressed in terms of Quality of Life Year (QALY) loss. QALY loss for a single RSV episode is calculated by integrating the loss of Health-Related Quality of Life (HR-QoL) over the duration for which the symptoms are experienced. HR-QoL is evaluated through the use of standardised and validated instruments, such as EuroQol’s EQ-5D that considers the physical, mental and emotional effects of an illness. Despite RSV vaccine strategy cost-effectiveness analyses being published validated QALY estimates for RSV infection in either children or adults do not exist. Moreover, EQ-5D methods do not reliably capture the HR-QoL in very young children, in whom severe RSV episodes predominantly occur.

In this chapter, I outline the methodology and report the results of a cross-sectional survey which determines the HR-QoL loss due to an RSV episode in individuals aged five years and older with suspected RSV using EQ-5D questionnaires. Using the results of the cross-sectional survey, I developed a statistical model to predict the HR-QoL loss as a function of responses from a broader health and healthcare-seeking questionnaire. The statistical model was able to predict the estimated QALY loss for children and adults.
over five years of age. Finally, using the statistical model parameterised with responses from the broader health and healthcare-seeking questionnaire administered to caregivers of children aged younger than five with recently confirmed RSV infection, I calculated the QALY loss per RSV episode for children less than five years of age, for which there are no standard instruments to measure HR-QoL loss.\textsuperscript{53}

2.2 Methods

2.2.1 Study recruitment

During the 2016-17 RSV season, confirmed cases of RSV in children under the age of 5 years from the previous two weeks were extracted on dates 13th December, 25th December 2016, and 3rd January 2017 from the Public Health England (PHE) Respiratory DataMart surveillance (RDMS) system.\textsuperscript{57} For all the confirmed cases for whom name, date of birth and National Health Service (NHS) number were provided, home addresses were obtained from the PHE Patient Demographic Service. For all these home addresses, a questionnaire pack addressed to the parent or guardian of the confirmed case, was sent the day after its extraction date from the PHE RDMS system. Each questionnaire pack consisted of three questionnaires, an information sheet, and a stamped addressed return envelope. The Index Questionnaire requested information about the recent RSV episode in the confirmed case. The other two questionnaires requested information about suspected RSV episodes in older household members; those aged 5-14 years (5-14 Questionnaire) and those aged 15 years or older (15+ Questionnaire). Suspected RSV cases were defined as persons who share a household with the confirmed case and who experienced an onset of RSV-like symptoms (runny or blocked nose, fever, coughing, and/or a sore throat) between five days before and five days after the onset of symptoms in the confirmed case (five days being the average latency period for RSV).\textsuperscript{58,59}

2.2.2 Questionnaire information

The Index Questionnaire was completed by a parent or guardian on behalf of the confirmed case, the 5-14 Questionnaire on behalf of or by the child themselves and the 15+ Questionnaire by the adolescent or adult. The Index Questionnaire requested information on (i) the age of the child, (ii) the confirmed case’s symptoms (runny/blocked nose, fever, coughing, sore throat), (iii) the healthcare seeking behaviour (no healthcare sought,
contacted or visited GP, visit to Accident and Emergency department, admission to hospital), (iv) coughing severity (mild/no coughing, severe coughing) and (v) a Visual Analogue Scale (VAS) for the worst day of the recent infection and the day of questionnaire completion. A VAS was presented for health from 0 (worst health) to 100 (best health) for both days and the difference between the VAS scores was defined as the VAS score loss due to an RSV episode. In addition to the questions asked in the Index Questionnaire, the 5-14 and the 15+ Questionnaires also asked (vi) the time taken off school/work due to symptoms (productivity) and (vii) EuroQol EQ-5D-3L-Y\textsuperscript{54–56} (for 5–14 year olds)\textsuperscript{49} or EQ-5D-3L\textsuperscript{54,55} (for 15+ year olds) questionnaires to determine Health-related Quality of Life (HR-QoL) weight at baseline and on the worst day of suspected RSV infection. I did not ask questions about the health or economic impact of an infant’s infection on (a) parent(s) as cost-effectiveness guidelines in the UK recommend including the direct effects of an infection only.\textsuperscript{60} See Supplementary material S1.2 for full questionnaire packs.

The EuroQol ED-5D-3L-Y\textsuperscript{54–56} and EQ-5D-3L\textsuperscript{54,55} questionnaires use a UK-specific Time Trade-Off scoring tariff to determine the HR-QoL weight according to five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. I refer to this HR-QoL weight on the worst day of infection as the peak HR-QoL weight from the data and the difference in the HR-QoL weights between the baseline and the worst day of infection as the peak HR-QoL loss from the data.

### 2.2.3 Statistical model to estimate HR-QoL

EQ-5D questionnaires are not validated for children under five years of age so it is not possible to obtain estimates for the peak HR-QoL loss from the data in the confirmed cases. Therefore, using the responses from the suspected cases, I fitted a regression model to predict the (model-estimated) peak HR-QoL loss, as a function of questionnaire variables: age (5–14 years, 15 years and older), coughing severity, healthcare seeking behaviour, productivity and VAS score loss.

#### Model selection

To inform the structure of the regression model, I first determined whether the peak HR-QoL loss sampled from the data was likely drawn from a bimodal or unimodal distribution using an F-test-based hypothesis test.\textsuperscript{61} The variance for the bimodal distribution is calculated by dividing the data with values below and above a fixed value $h^*$ and finding
the mean of the two variances of the two groups. The degrees of freedom for an estimate of
the variance of the unimodal sample is 72, and the degrees of freedom for an estimate of
the variance of the bimodal sample is 69. Therefore by varying \( h^* \) within the range 0
to 1, I calculated the \( h^* \) that minimised the F-test value with 72 degrees of freedom in the
numerator and 69 degrees of freedom in the denominator.

To parameterise a regression model, I use a mixture-model approach that uses three
sub-models. Specifically, I estimate three response variables (a) the probability that a
disease episode is severe, and the “model-estimated” peak HR-QoL loss for (b) mild \( (Y_M) \)
and (c) severe \( (Y_S) \) disease respectively. Therefore, the full mixture model I develop to
determine the model-estimated peak HR-QoL loss for a symptomatic infection, \( Y \), is given
by

\[
Y = pY_S + (1 - p)Y_M
\]  

(2.1)

Where \( p, Y_S, Y_M \) are estimated response variables.

**Mixture model structure**

*Probability of severe disease*: To estimate the probability \( (p) \) of a disease episode being
severe I use a logistic regression analysis because the response variable is binary (severe
or mild).

*Model-estimated peak HR-QoL loss for severe and mild disease*: I initially fit \( Y_S \) and
\( Y_M \) as linear regression models. However, in the case of \( Y_M \) linear regression resulted
in unrealistic negative values. To overcome this, I used a log-transformed model instead
for \( Y_M \). For consistency, I then considered both the linear and log-transformed regression
models for \( Y_S \) and chose the better fitting model based on the Akaike Information Criterion
(AIC).

Overall, for our mixture-model approach, I therefore fit three regression models: a
logistic regression model to predict the probability of a disease episode being severe \( (p) \),
a log-transformed linear model to predict the model-estimated peak HR-QoL loss when
disease is mild \( (Y_M) \), and a linear model to predict the model-estimated peak HR-QoL
loss when disease is severe \( (Y_S) \).
Explanatory variables

I used the following five explanatory variables \( x = (x_1, \ldots, x_5) \) and level stratification (listed below in curly brackets). I performed the regression analyses for each of the six combinations of the explanatory variable level stratifications (three stratifications for coughing severity and two stratifications for age). The number of levels for both variables were chosen based on the AIC.

Healthcare-seeking behaviour \( (x_1) \): No healthcare sought, healthcare sought, No healthcare sought, A+E or GP consultation but no hospital admission and admission to hospital, No healthcare sought, A+E but no hospital admission, GP but no hospital admission, and admission to hospital.

Coughing severity \( (x_2) \): None/mild coughing, severe coughing, No coughing, mild coughing, and severe coughing.

Age \( (x_3) \): 5-14 years, 15+ years.

Productivity \( (x_4) \): no time off work or school, time off work or school.

VAS score loss \( (x_5) \): integer value as the difference between score reported on worst day subtracted from score reported on the day of questionnaire completion.

Backwards stepwise regression

For each model I performed a backwards stepwise regression by estimating all five coefficients and intercept and eliminating the explanatory variable with the highest P-value above 0.05. I continued this process of fitting the regression model and eliminating one explanatory variable until all the remaining variables have a P-value less than 0.05. A stringent threshold value of 0.05 was chosen to encourage a simpler model.

Estimating the variance

Using the backward stepwise regression, I estimated the functions \( E[Y_S], E[\log(Y_S)], \) and \( E[p] \) as a function of the significant explanatory variables. Therefore, for an arbitrary point \( x^* = x_1, \ldots, x_5 \), the uncertainty around the estimates is given by

\[
Y_S = Ax^* + \epsilon_S
\]
$$\log(Y_M) = Bx^* + \epsilon^*_M$$  \hspace{1cm} (2.3)  

$$p = \sigma(Cx^* + \epsilon^*_p)$$  \hspace{1cm} (2.4)  

Where $\epsilon^*_j \sim N(0, \sigma^*_j)$, $j \in \{S, M, p\}$ is the error associated with the prediction at point and $A = \{a_0, \ldots, a_5\}$, $B = \{b_0, \ldots, b_5\}$, $C = \{c_0, \ldots, c_5\}$. I choose $\sigma^*_S$ and $\sigma^*_M$ to provide 95% confidence intervals that are consistent with the 95% prediction intervals from linear model fit and I choose $\sigma^*_p$ to provide 95% confidence intervals that match the 95% confidence interval of the generalised linear model fit output. I take 10,000 samples from the distributions for $Y_S$, $Y_M$ and $p$ and substitute these values into the equation for $Y$ 10,000 times to get the empirical distributions for $Y$. The 95% CIs are found by ordering the data and taking the 250th and 9750th sample.

**Data used to fit the mixture model**

To fit the three regression models for $Y_S$, $Y_M$ and $p$ I use three datasets derived from the observation data and consist of a response variable associated with the peak HR-QoL loss from the data and the explanatory variables, $x = (x_1, \ldots, x_5)$. For the log-transformed linear regression model, which predicts the model-estimated peak HR-QoL loss for mild disease, I used observational data for which the peak HR-QoL loss is below and equal to $h^*$. Similarly, for the linear regression model which predicts the model-estimated peak HR-QoL loss for severe disease, I use observational data for which the peak HR-QoL is above $h^*$. For the logistic regression model which predicts the probability of an infection being severe, $p$, I use all the observation data, and transform the peak HR-QoL loss from the data into a binary response variable which is 0 when the peak HR-QoL loss is below $h^*$ and 1 when the peak HR-QoL loss is above $h^*$.

All analysis was performed in R (v. 3.3.2) and plotting was performed in Mathematica (v.10.3.0.0).

**2.2.4 Quality-adjusted life year (QALY) loss due to an RSV episode**

I estimated each respondent’s QALY loss by multiplying their model-estimated peak HR-QoL life loss by (i) a pooled duration of coughing distribution and (ii) a fixed scaling factor for disease severity throughout the illness. Multiplying the model-estimated peak HR-QoL by the duration of coughing only gives an estimated QALY loss which assumes that an individual experiences their worst symptoms everyday of their infection.
As symptoms of infections usually build to a peak and then subside, this calculation is likely to overestimate the true QALY loss due to RSV infection. Therefore, I multiply this value by a fixed scaling factor for disease severity (a value between 0 and 1) to capture heterogeneity in HR-QoL life loss over the course of an infection.

**Duration of symptoms**

Due to a poor response rate for reporting the duration of symptoms in our questionnaire (67%), calculating the QALY loss only for the responses which provided a duration of symptoms would lead to a substantial waste of data. Therefore, I pooled the responses for the duration of symptoms. Thus, to evaluate the QALY loss for each model-estimated peak HR-QoL loss, I then sampled a duration from this pooled distribution. In estimating the pooled coughing duration distributions, I excluded responses that did not indicate a duration of coughing and those that indicated a duration of more than 22 days as this is longer than the maximum duration of RSV symptoms reported in previous studies.58

To compare using one pooled distribution to multiple distributions, stratified by respondent characteristics, I performed a backwards stepwise linear regression analysis using the duration of symptoms as the response variable and age group (<5, 5–4, 15+ years), coughing severity (severe coughing or no/mild coughing), and VAS score loss as independent variables. I found that VAS score loss was unlikely to account for any of the variance in duration symptoms (P = 0.53), I pooled responses by age and coughing severity (P = 0.14, P = 0.08, respectively). Therefore, I calculated six pooled distributions for the duration of symptoms (Figure 2.4). For each included individual respondent in the analysis, I then randomly sampled their respective symptom duration from their respective pooled distribution based on their age group and whether they reported severe coughing.

**Scaling factor for disease severity**

I estimated the scaling factor for disease severity using daily EQ-5D questionnaires from individuals participating in the Flu Watch study.62 Flu Watch is a community cohort study in which householders were asked to prospectively record all respiratory illnesses and submit a nasal swab for Polymerase Chain Reaction (PCR) based identification of respiratory viruses over winter seasons. In 2010/11 participants (or adult carers) were also asked to complete a one-off baseline EQ-5D questionnaire at the start of the study as well as daily EQ-5D questionnaires throughout any respiratory illness to measure their daily
HR-QoL. Using the daily EQ-5D questionnaires from the Flu Watch study, I calculated the HR-QoL loss throughout an RSV episode relative to the worst day of infection for five of the nine confirmed infections. Three people were excluded as they indicated no HR-QoL loss over their infection; and one person was excluded because their base HR-QoL was lower than during the RSV episode—leading to negative HR-QoL loss values. The remaining five patients were aged between 16–45 years.

2.2.5 Ethics approval

In accordance with The Health Service (Control of Patient Information) Regulations 2002 No. 1438 Section 251 Regulation 3, Public Health England may process confidential patient information with a view to monitoring and managing; outbreaks of communicable disease; incidents of exposure to communicable disease and the delivery, efficacy and safety of immunisation programmes. All questionnaires that were returned from households and stored at PHE had no identifying information.

2.3 Results

2.3.1 Questionnaire responses

I sent out 770 questionnaire packs between 15 December 2016 and 4 January 2017 and received 122 responses by 28 February 2017 (response rate of 16%). I found that, when stratified by year of age, the age distribution of the confirmed cases who responded was similar to the age distribution of the contacted confirmed RSV index cases. However, when stratified by month of age in the first year of life, I oversampled infants aged 3–4 months old and undersampled infants aged 1–2 months old (Figure 3.1). In the 122 households, suspected cases were reported in 33 (27.0%) persons aged 5–14 years old and 54 (44.2%) of persons aged 15 years and older.

After selecting questionnaire responses according to the inclusion criteria, I determined the model-estimated peak HR-QoL loss for 108/122 (88.5%) of confirmed cases in children less than five years of age, and for 21/33 (63.6%) and 40/54 (74.1%) of suspected cases aged 5–14 years and 15 years and older, respectively. Duration of coughing was provided for 98/122 (80.3%) and 43/87 (49.4%) of confirmed and suspected cases respectively.
Figure 2.1: Age of confirmed RSV samples in PHE database (N=770, black) and of the returned questionnaires for analysis (N=122, gray).

In the questionnaire responses from the suspected cases, I found that 21/33 (63.6%) of children aged 5-14 years old, and 43/54 (79.9%) of persons aged 15 years and older did not seek healthcare due of their suspected RSV episode (Table 3.1). Further, I found that 17/33 (51.5%) children aged 5–14 years took time off school and 9/54 (16.6%) of persons aged 15 years and older took time off work or school due to their suspected RSV infection, both with a median time off of 2 days (range 1–10 days) (Table 3.1). The EQ-5D-Y questionnaires suggested that for children aged 5-14 years old RSV mostly affected usual activities (72%), caused pain/discomfort (76%) and anxiety/depression (84%). The EQ-
5D-3L responses for respondents aged 15 years and older suggested similar results with RSV affecting respondents’ usual activities (54.2%), causing pain/discomfort (36.0%) and anxiety and depression (32.0%) (Figure 2.2). Converting these EQ-5D and EQ-5D-3L responses using the UK TTO scoring tariff, the median peak HR-QoL weight from the data for children aged 5–14 years old and persons 15 years and older was 0.689 (range 0.170–1.000) and 0.752 (range 0.166–1.000) respectively. These weights led to a median peak HR-QoL loss from the data of 0.456 (range 0.0–1.170) and 0.358 (range 0–0.998) for 5-14 and 15 years and older respectively. As there was no significant difference between the peak HR-QoL loss from the data between 5–14 years old and persons 15 years (Kolmogorov-Smirnov test, p = 0.291), all HR-QoL and QALY results were pooled for ages 5+ years for further analysis.

For individuals seeking healthcare, I found that cases in children under the age of five years were more severe when compared with suspected cases in persons aged five years and older as evidenced by a higher VAS score loss (median 65 vs 40) and the proportion of persons with severe coughing (0.76 vs 0.18).
Figure 2.2: Responses from the EQ-5D-3L-Y and EQ-5D-3L questionnaires on the day of completion (Base) and the worst day of health during a suspected infection for respondents aged 5-14 years old (top) and 15+ years old (bottom).
CHAPTER 2. ESTIMATING THE HEALTH BURDEN DUE TO RSV

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Aged 0–4 years (n=122) (%)</th>
<th>*Aged 5–14 years (n=33) (%)</th>
<th>Aged 15 years and older (n=54) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny/blocked nose</td>
<td>96 (78.7)</td>
<td>28 (84.8)</td>
<td>43 (79.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>70 (57.4)</td>
<td>18 (54.5)</td>
<td>22 (40.7)</td>
</tr>
<tr>
<td>Coughing</td>
<td>110 (90.2)</td>
<td>27 (81.8)</td>
<td>51 (94.4)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>36 (29.5)</td>
<td>17 (51.5)</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>Number of responses</td>
<td>121 (99.1)</td>
<td>33 (100.0)</td>
<td>54 (100.0)</td>
</tr>
</tbody>
</table>

| Coughing severity                                                       |                            |                             |                                   |
| No effect on daily activities                                           | 16 (13.1)                  | 10 (30.3)                   | 8 (14.8)                          |
| Mild effect on daily activities                                         | 34 (27.9)                  | 15 (45.5)                   | 32 (59.3)                         |
| Severe effect on daily activities                                       | 93 (76.2)                  | 4 (12.1)                    | 8 (14.8)                          |
| Number of responses                                                     | 116 (95.1)                 | 28 (84.8)                   | 46 (85.2)                         |

| Coughing severity duration                                              |                            |                             |                                   |
| No effect on daily activities (median, range)                           | 4 days (1–14)              | 10 days (10–10)             | 14.5 days (1–28)                  |
| Mild effect on daily activities (median, range)                         | 3.5 days (1–14)            | 3 days (1–9)                | 5.5 days (1–28)                  |
| Severe effect on daily activities (median, range)                       | 6.5 days (1–35)            | 3 days (1–4)                | 7 days (3–10)                     |
| Number of responses                                                     | 98 (80.3)                  | 12 (36.6)                   | 31 (57.4)                         |

| Health seeking behaviour                                               |                            |                             |                                   |
| Phone/email NHS 111/NHS 24/NHS choices                                  | 39 (32.0)                  | 2 (6.1)                     | 2 (3.7)                           |
| Phone/email GP—response from the receptionist                          | 20 (16.4)                  | 2 (6.1)                     | 2 (3.7)                           |
| Phone/email GP—response from the nurse/doctor                           | 20 (16.4)                  | 2 (6.1)                     | 2 (3.7)                           |
| Visit a GP or nurse                                                     | 83 (68.0)                  | 10 (30.3)                   | 10 (18.5)                         |
| Visit A& E department                                                   | 71 (58.2)                  | 3 (9.1)                     | 1 (1.9)                           |
| Admitted to hospital                                                    | 103 (84.4)                 | 1 (3.0)                     | 1 (1.9)                           |
| None                                                                    | 0 (0.0)                    | 21 (63.6)                   | 43 (79.6)                         |
| Number of responses                                                     | 121 (99.1)                 | 33 (100.0)                  | 54 (100.0)                        |

| Productivity                                                            |                            |                             |                                   |
| Individuals reporting taking time off work or school                     | —                          | 17 (51.5)                   | 9 (16.7)                          |
| Duration of time off work or school (median, range)                     | —                          | 2 days (1–10)               | 2 days (1–7)                      |

| VAS score loss                                                          |                            |                             |                                   |
| Baseline (median, range)                                                | 90 (30–100)                | 95 (10–100)                 | 95 (50–100)                       |
| Worse day (median, range)                                               | 20 (0–85)                  | 50 (5–85)                   | 50 (0–90)                         |
| Loss (median, range)                                                    | 65 (10–100)                | 38 (0–90)                   | 35 (10–85)                        |
| Number of responses                                                     | 120 (98.4)                 | 32 (97.0)                   | 54 (100.0)                        |

| Number of responses used calculate peak HR-QoL loss                     | 108 (88.5)                 | 21 (63.6)                   | 40 (74.1)                         |

Table 2.1: Summary of index, 5-14, and 15+ Questionnaire responses. Numbers in parentheses is the percentage unless otherwise stated. VAS, visual analogue scale. * Conditional on ascertaining a confirmed case through GP/hospitalisation.
2.3.2 Model-estimated peak HR-QoL loss

Model selection

The F-test-based hypothesis test value was minimised at \( h^* = 0.6 \) where \( F_{73.69} = 4.35 \) and \( P < 0.001 \), suggesting that the peak HR-QoL loss from the data were sampled from two independent distributions. Intuitively, therefore, this result is consistent with RSV disease being classed as either mild (typically with a peak HR-QoL loss from the data below the threshold value, \( h^* = 0.6 \)) or severe (typically with a peak HR-QoL loss from the data above the threshold value, \( h^* = 0.6 \)) (Figure 2.3).

![Figure 2.3: Histogram of the peak HR-QoL loss due to RSV from the responses of the 5-14 and 15+ Questionnaire with the threshold value, \( h^* \) (dashed lined), region of mild disease (green) and region of red disease (red).]

Regression analysis

Using a backwards stepwise regression approach, this statistical model found that the peak HR-QoL loss from the data was parsimoniously predicted by three factors: the VAS score loss, whether healthcare was sought, and the presence of severe coughing (Supplementary material S1.1).

This statistical model predicted the model-estimated peak HR-QoL loss in suspected cases aged five years and older who did and did not seek healthcare as 0.616 (95% CI 0.155–1.371) and 0.405 (95% CI 0.111–1.137) respectively. I found that the questionnaire data were well predicted by the model, with no evidence to suggest the peak HR-QoL
loss from the data and the model were different (Kolmogorov-Smirnov test, p = 0.111, (Figure 2.5)). Applying this statistical model to those under five for whom HR-QoL loss could not be directly estimated, I found a model-estimated peak HR-QoL loss of 0.820 (95% CI 0.222–1.450). Finally, assuming the ratio of HR-QoL loss for healthcare-seeking cases to non-health-seeking cases is independent of age, I estimated a model-estimated peak HR-QoL loss for under fives as 0.539 (95% CI 0.144–0.952, Table 3.1).

2.3.3 Quality-Adjusted Life Years loss

The daily RSV HR-QoL weights from Flu Watch62 suggest that for the first half of symptom duration, the HR-QoL weight decreases linearly to its minimum before linearly rebounding to baseline health. There is no reported reduction of HR-QoL weight during the second half of symptom duration. To account for the changing severity of symptoms across the entire RSV episode, I calculated the weighted HR-QoL loss by multiplying the HR-QoL loss by a constant scaling factor of 0.25. Finally, to calculate the estimated QALY loss per RSV episode, I multiplied the weighted HR-QoL loss per RSV episode by the duration of symptoms reported in the questionnaire responses. The duration of symptoms in children aged 5-14 years was shorter (median 3 days, (range 1–10)) than both the duration of symptoms in children under five years old (median 5 days (range 1–21)) and in persons aged 15 years and older (median 5 days (range 1–21)) (Figure 2.4). This calculation led to an estimated QALY loss per healthcare seeking RSV episode in children less than five years old of $3.823 \times 10^{-3}$ (95% CI $0.492 \times 10^{-3}$–$12.766 \times 10^{-3}$, Tables 2.3)—approximately twice that for persons aged five years and older ($1.950 \times 10^{-3}$ (95% CI $(0.185 \times 10^{-3}$–$9.578 \times 10^{-3}$)). For individuals who did not seek healthcare, the QALY loss per RSV episode was $3.024 \times 10^{-3}$ (95% CI $0.329 \times 10^{-3}$–$10.098 \times 10^{-3}$) for under fives and $1.543 \times 10^{-3}$ (95% CI $0.136 \times 10^{-3}$–$6.406 \times 10^{-3}$) for those five years and older (Table 2.3).
Figure 2.4: The distribution of duration of coughing symptoms for all respondents with no severe coughing (upper panel) and with severe coughing (lower panel). For each sample, the whiskers (vertical line) indicates the range, the box indicates the interquartile range, and the horizontal line is the median.
Figure 2.5: The peak HR-QoL loss from the EQ-5D questionnaires (dark gray) and estimated using the statistical model (light gray). The dashed line shows the mean, and solid thin lines indicate the upper and lower 95% confidence interval.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Peak HR-QoL loss from the EQ-5D questionnaires (Mean and 95% CrI)</th>
<th>Peak HR-QoL loss from statistical model (Mean and 95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All responses</td>
<td>0.392 (0.034–1.136)</td>
<td>0.332 (0.131–0.955)</td>
</tr>
<tr>
<td>5-14 yrs</td>
<td>0.456 (0.035–1.283)</td>
<td>0.327 (0.131–0.990)</td>
</tr>
<tr>
<td>15+ yrs</td>
<td>0.358 (0.028–1.020)</td>
<td>0.335 (0.130–0.932)</td>
</tr>
<tr>
<td>Mild coughing</td>
<td>0.298 (0.017–1.029)</td>
<td>0.237 (0.129–0.395)</td>
</tr>
<tr>
<td>Severe coughing</td>
<td>0.818 (0.214–1.274)</td>
<td>0.766 (0.445–1.110)</td>
</tr>
<tr>
<td>No time off</td>
<td>0.322 (0.026–0.964)</td>
<td>0.278 (0.128–0.756)</td>
</tr>
<tr>
<td>Time off</td>
<td>0.626 (0.043–1.448)</td>
<td>0.517 (0.135–1.099)</td>
</tr>
<tr>
<td>No healthcare sought</td>
<td>0.306 (0.016–0.979)</td>
<td>0.284 (0.129–0.862)</td>
</tr>
<tr>
<td>Healthcare sought</td>
<td>0.596 (0.057–1.329)</td>
<td>0.450 (0.122–1.046)</td>
</tr>
</tbody>
</table>

Table 2.2: The peak HR-QoL loss from the EQ-5D questionnaires and estimated using the statistical model.
### Chapter 2. Estimating the Health Burden Due to RSV

**Table 2.3:** HR-QoL, QALD, and QALY loss for the confirmed cases in children less than five years of age, and in the suspected cases in children five years and older.

*Estimated by assuming the proportional reduction in HR-QoL loss and QALY loss between those who seek healthcare and those who do not is the same as observed in suspected infections in persons over five years of age.

#### 2.3.4 Healthcare-seeking and total disease burden

The total number of annual GP consultations and hospital admissions due to RSV in England is 855,000 and 375,000-383,000 for persons aged 5 years and older and less than 5 years, respectively. Combining these numbers with our QALY loss estimates for individuals seeking health care in England resulted in a mean annual QALY loss of 3,120–3,141, 54% of which is attributable to those 5 years and older. Our questionnaire responses indicated that 25% of individuals aged 5 years and older seek health care during an RSV episode. Using this proportion, we estimated that there are approximately 2.6 million symptomatic RSV infections in England annually that will not be captured in a healthcare surveillance system. The mean annual QALY loss associated with these non-healthcare-seeking episodes for persons 5 years and older is around 4,011, approximately 29% of the QALY loss in this age group.
2.4 Discussion

In this chapter, I presented the findings of a cross-sectional survey which estimated the RSV burden in terms of QALY loss per infection. For children over five years old and adults, my statistical model showed that the QALY loss can be accurately predicted by whether there was severe coughing, whether healthcare was sought, and Visual Analogue Scale score loss. The model could evaluate the QALY loss in children under five years old, in whom the majority of severe RSV episodes occur but for whom QALY loss cannot be estimated directly. For those who seek healthcare, I found the QALY loss in children under the age of five years is $3.823 \times 10^{-3}$ (95% CI $0.492 \times 10^{-3} - 12.766 \times 10^{-3}$), double that for those five years and older ($1.950 \times 10^{-3}$ (95% CI $0.185 \times 10^{-3} - 9.578 \times 10^{-3}$)).

This cross-sectional survey has some limitations. First, because the confirmed cases were recruited into the study conditional on them seeking healthcare, I could not directly estimate the QALY loss in children less than five years old who did not seek healthcare from the statistical model. To overcome this limitation, I assume that the ratio of QALY loss for people over five years who do not seek healthcare to those that do is the same independent of age. However, using this ratio may overestimate the QALY loss of non-healthcare-seeking cases in children less than 5 years of age, as healthcare-seeking cases in persons aged five years and older are generally milder than healthcare-seeking confirmed cases in infants less than five years old (with decreases in VAS score loss, coughing severity, and the proportion admitted to hospital). To collect data directly on the QALY loss in children under five who do not seek healthcare would require a much larger and more intensive community-based study with frequent testing throughout an RSV season. Second, suspected cases may have experienced non-RSV respiratory disease. However, previous studies have shown that around 50% of households experience a secondary infection in either siblings or parents during the same time as an infection in the infant, therefore it is reasonable to assume that the majority of suspected cases are in fact RSV. Finally, completing questionnaires some days after symptoms may be subject to recall bias. The estimates for the peak HR-QoL life loss for persons aged 15 years and older (0.452 (95% CI 0.177–1.222)) are larger than the peak HR-QoL loss estimated in the Flu Watch study (range 0.107–0.309), however this latter estimate may be imprecise due to the small sample size.
This study is the first to estimate the QALY loss due to acute RSV infection. Two previous studies have also estimated the HR-QoL due to RSV infection both of which suffer from shortcomings. The first study a Time Trade-off study which estimated HR-QoL loss using responses from participants about a hypothetical illness that they, or their child, had not experienced. Unlike this study I calculated the HR-QoL loss for people who have had, or suspected to have had, a recent RSV infection. The second study estimated the HR-QoL using EQ-5D questionnaires for children with RSV-associated sequelae. Sequelae included chronic conditions such as persistent coughing and/or wheeze so HR-QoL loss estimates are likely to differ substantially from those associated with acute RSV symptoms. For accurate evaluations, I recommend that future cost-effectiveness analyses use directly obtained HR-QoL loss estimates for RSV episodes, such as those presented in this paper, in addition to HR-QoL loss associated with sequelae.

The RSV-related QALY loss estimate for people aged five years and over is consistent to the estimates of a prospective study that estimated QALY loss across people of all ages with non-confirmed Influenza who reported Influenza-like illness (ILI) (mean $2.6 \times 10^{-3}$ (range $-69.2 \times 10^{-3}$–$39.7 \times 10^{-3}$)). Similarly, for the under fives, these estimates are similar to non-Influenza episodes who suffer ILI who present at a hospital or GP ($4.0 \times 10^{-3}$ (range $3.4 \times 10^{-3}$–$4.6 \times 10^{-3}$)). In contrast, I find that the QALY loss estimates for RSV episodes in the under fives who seek healthcare are less severe than hospitalised Influenza episodes, (QALY loss of $6.0 \times 10^{-3}$ (range $5.1 \times 10^{-3}$–$6.9 \times 10^{-3}$)). These comparisons suggest that, although Influenza has a higher QALY loss per episode, the QALY loss due to an RSV episode is comparable to previous QALY loss estimates for persons with general ILI.

I estimated that 54% of the QALY loss associated with healthcare seeking episodes was attributable to individuals aged five years and older. This result suggests that neglecting QALY loss in older children and working-age adults might substantially underestimate the impact of a potential RSV vaccine programme. Further, these results are consistent with previous studies that suggest that RSV is characterised by high levels of household transmission. Together, these data suggest that integrating transmission models—that capture both the direct and indirect effects of immunisation—into economic evaluations will be crucial to accurately estimate the impact of potential vaccine programmes.

From the questionnaires, I am unable to estimate the proportion of healthcare seeking in children younger than five years with symptomatic RSV. However, I expect this propor-
tion to be higher than the 25% reported in those aged five years and older for two reasons: infections in infants are generally more severe, with higher rates of symptomatic infections,\(^{17}\) and a tendency for increased parental healthcare seeking in infants compared to older children.\(^{69}\) However, the healthcare seeking behaviour for both children and adults will likely depend on the country and I suggest caution in translating the total RSV burden estimates for England presented in this study to other countries.

To summarise, in this chapter I estimated the RSV burden quantified by QALY loss due to an RSV episode in confirmed cases in children less than five years old and suspected cases in persons aged five years and older. Despite severe RSV being associated with infants, I found that RSV infections in individuals aged five years and older account for 54% of the annual QALY loss attributable to healthcare seeking episodes in England. Consequently, in future chapters, I will use this information to undertake an economic evaluation of potential vaccine programmes and consider their effect on not only where the severe disease burden lies, but across the whole population. To evaluate the effect of potential vaccination programmes across the whole population, it is necessary to develop a dynamic mathematical model of RSV transmission capable of evaluating each intervention programme. The motivation for structure of such a mathematical model is outlined in Chapter 3 and the model structure itself is outlined fully in Chapter 4.
Chapter 3

Review of RSV transmission models

3.1 Introduction

Mathematical models are used to help understand how infectious diseases spread in a population. These models can be either static, where the probability of transmission is constant, or dynamic, where the probability of transmission is proportional to the number of infected persons at specified point in time. Dynamic mathematical models are preferred because they evaluate the impact of an intervention programme against an infectious disease both on the individuals targeted (the direct effects) and the impact on the remaining population through intervention-induced changes in transmission (the indirect effects). To ensure the transmission dynamics are accurately evaluated, the model must capture the transmission pathways specific to RSV across the population. Therefore, evaluating and comparing existing frameworks which model RSV transmission can provide a useful baseline for determining which pathways are important in the transmission of RSV for England and Wales.

In this chapter I perform a literature review to identify mathematical models of RSV transmission. The purpose is twofold. First, the identified models can be used to understand which model characteristics best capture the transmission dynamics of RSV. By comparing the model structures, I gain insights into the optimal structural characteristics of RSV transmission models and provide a set of guidelines for future transmission models of RSV which ensure that the dynamics are appropriately captured. The second aim is to synthesise evidence from these models on the impact of potential intervention
programmes, and outline gaps in epidemiological and prophylactic-related knowledge regarding the impact of likely intervention programmes against RSV.

### 3.2 Search criteria for literature review

I am searching for *mathematical models* of the *transmission* of *RSV*. Therefore, I identify three different search concepts. The first is RSV, which we search for as either *RSV* or *Respiratory Syncitial Virus*. The second search concept specifies the need for a model, which I search for using the term *model* or *network*. The final search concept specifies the nature of the model, where I specify that the model should be either *mathematical*, capture *transmission* or be *dynamic*.

With this search criteria, I searched Web of Science and Pubmed for articles published up to 30 September 2018 using the search terms:

(RSV>Title OR "Respiratory Syncytial Virus"[Title]) AND (Model* OR Network) AND (Transmission OR Mathematic* OR Dynamic*)

The total number of studies found between the two search engines after duplicates were removed was 88. Then, by screening the studies by title I removed 58 studies which were either excluded because they were an in-host or bovine-RSV models (56) or excluded because they were not an original research article (2). Of the 30 remaining articles I removed 7 because the models were not parameterised or calibrated using any epidemiological data and 1 because it was not in English. (Figure 3.1)

The search returned 22 studies between 2001-2018 that fit our inclusion criteria.

The studies contained mathematical models of RSV transmission which employed similar basic epidemic compartmental structures, but varied in the study setting, parameterisation, and model structure (Table 3.1). Regarding the variation in setting, the studies were calibrated to data from ten different countries of varied geographical location, five of the countries were from a temperate setting and five were from a tropical setting (Table 3.1). The models were parameterised using either frequentist or Bayesian approaches to estimate the value or assess the uncertainty in transmission parameters.
Records identified in database, Web of Knowledge, $n = 77$

Records identified in database, PubMed, $n = 58$

Records after duplicates removed $n = 88$

Records screened by title $n = 88$

Records excluded $n = 58$

Excluded because in-host model or non-hRSV $n = 57$

Excluded because not original research article $n = 2$

Full-text articles assessed for eligibility $n = 30$

Full-text articles excluded $n = 8$

Excluded because it is not parameterised to data $n = 7$

Excluded because not in English $n = 1$

Records included in review $n = 22$

**Figure 3.1:** Schematic of paper selection progress based on PRISMA template
<table>
<thead>
<tr>
<th>Study</th>
<th>Model structure</th>
<th>Region</th>
<th>Long-term cumulative immunity</th>
<th>Data to calibrate model</th>
<th>Calibrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>White 2005</td>
<td>SIS*S</td>
<td>England/Wales, and Finland</td>
<td>None</td>
<td>Number of RSV associated hospital cases. Weekly. All ages.</td>
<td>Point est.</td>
</tr>
<tr>
<td>White 2007</td>
<td>SIS</td>
<td>Various</td>
<td>Number of RSV associated hospital cases. Monthly-except West Midlands UK is weekly. All ages.</td>
<td>Point est.</td>
<td></td>
</tr>
<tr>
<td>Arenas 2009</td>
<td>SIRS</td>
<td>Valencia, Spain.</td>
<td>None</td>
<td>Number of RSV associated hospital cases. Monthly Children ≤4yrs.</td>
<td>Fixed-point est. w. 95% CI non-Bayesian methods (parameter variation.)</td>
</tr>
<tr>
<td>Capistran 2009</td>
<td>SIS*</td>
<td>Gambia, Finland.</td>
<td>None</td>
<td>Number of RSV hospital admission due to RSV. Monthly.</td>
<td>Point est.</td>
</tr>
<tr>
<td>Acedo, Dies 2010</td>
<td>SIRS &lt;1, &gt;1yrs</td>
<td>Valencia, Spain.</td>
<td>None</td>
<td>Number of RSV associated hospital cases. Monthly Children ≤4yrs.</td>
<td>Point est.</td>
</tr>
<tr>
<td>Leecaster 2011</td>
<td>SEIRS &lt;2, &gt;2yrs</td>
<td>Salt Lake County, UT, USA</td>
<td>None</td>
<td>Number of RSV associated hospital cases. Daily. Children.</td>
<td>Point est.</td>
</tr>
<tr>
<td>Pitzer 2015</td>
<td>SIS 0-1, 1-4, 5-9, 10-19, 20-39, years, 40-59, years, and 60+ years old</td>
<td>United States</td>
<td>Exposure 4. Rel. sus., rel. Inf. and duration of inf.</td>
<td>Number of RSV associated hospital cases. RSV positive samples from labs. All ages.</td>
<td>Point est.</td>
</tr>
<tr>
<td>Kinyanjui 2015</td>
<td>MSIRS 99, 24 months from birth, 75 years therefore until 77+.</td>
<td>Kilifi, Kenya</td>
<td>Exposure 3. Rel. sus., rel. Inf. and duration of inf.</td>
<td>Number of RSV associated hospital cases. Monthly Children ≤5yrs.</td>
<td>Point est. w. 95% CI non-Bayesian methods (Hosian)</td>
</tr>
<tr>
<td>Yamin 2016</td>
<td>MSIARS 0-0.5, 0.5-5, 5-24, 24-49, and 50yrs</td>
<td>Texas, California, Colorado, and Pennsylvania</td>
<td>Exposure 2. Rel. Inf. and duration of inf. Age: 8. rel. sus. and prob of asymp</td>
<td>RSV positive samples from labs. Weekly. All ages.</td>
<td>Texas—Prospective study of RSV. Point est.</td>
</tr>
<tr>
<td>Pan-Ngum 2017</td>
<td>SAI and MSIRS 99, 24 months from birth, 75 years therefore until 77+.</td>
<td>Kilifi, Kenya</td>
<td>Exposure 3. rel. inf., rel. sus. and duration of inf.</td>
<td>Number of RSV associated hospital cases. Monthly Children ≤5yrs.</td>
<td>Point est. w. 95% CI non-Bayesian methods (Hosian)</td>
</tr>
<tr>
<td>Pan-Ngum 2017</td>
<td>BWIS/SIS 15.12 monthly from birth, 2-5yr 6-10yrs, 10-75yrs</td>
<td>Kilifi, Kenya</td>
<td>Severity of inf (asymp,URTI, LRTI, SLRTI,H) 4. rel. inf., rel. us. and duration of inf.</td>
<td>Number of RSV associated hospital cases. Monthly Children ≤5yrs.</td>
<td>Point est. w. 95% CI non-Bayesian methods (Hosian)</td>
</tr>
<tr>
<td>Hogan 2017</td>
<td>SEIRS, 75, 60 months from birth, five years thereafter.</td>
<td>Western Australia</td>
<td>Age: 2. rel. infectiousness (&gt;10yr)</td>
<td>RSV positive samples linked to hospital records.</td>
<td>RSV positive samples linked to hospital records.</td>
</tr>
</tbody>
</table>

Table 3.1: Transmission models of RSV grouped by their underlying epidemiological assumptions. Individuals are classified as maternally protected (M), susceptible (S), infected but not infectious (E), infected and infectious (I), recovered (R), or susceptibility-reduced (S*).
3.3 Results 1: Capturing RSV transmission dynamics

This section will first outline epidemiological model structures which are common to many/all infectious disease transmission models and then it will outline model structures which are specific to capturing RSV infection.

3.3.1 Basic compartmental structure of existing RSV transmission models

Compartmental models imitate the propagation of RSV by splitting the population into epidemiological groups associated with different stages of infection and monitoring the proportion of the population in each group over time. These groups include: those susceptible to becoming infected (S); those infected but not yet infectious (E); those infected and infectious (I); and those who have recovered and are immune to infection (R). The rate at which persons who are susceptible to infection become infected is assumed to be proportional to the number of infected persons in the population at a specific point in time. The time spent in the other compartments is modelled assuming an exponential distribution with rate, \( r \), which is to be determined by synthesising existing epidemiological evidence, or through model calibration. An SEIR structure, which is commonly used to model infectious diseases, can be manipulated to better capture transmission dynamics specific to RSV. For example, there is a period of temporary immunity that is experienced following an RSV infection because disease-induced heightened RSV-antibody levels eventually start to wane until they reach similar levels to pre-infection.\(^{59,92}\) To capture this transmission dynamic in mathematical models, I assume recovered persons (R) experience a period of temporary immunity, which is lost with rate \( \omega \)—after which individuals are susceptible to reinfection (Figure 3.2). Another common method of manipulating SEIR structure to better capture transmission dynamics is to include more epidemiologically-specific components. For example, maternally-derived passive antibodies provides neonates with temporary protection to RSV infection. The duration and magnitude of protection to RSV from maternal passive immunity is not clear, but is related to RSV-neutralising IgG cord titre at birth which wane exponentially over time.\(^{9,10,12,93,94}\) RSV transmission models incorporate protection due to maternal passive immunity by assuming that all neonates are born with complete but temporary protection to RSV, which is lost at rate \( \xi \)—the rate of loss of maternal passive immunity, after which they are susceptible to infection.\(^{70,84,87}\) There is also evidence to suggest that levels of maternally-derived antibodies in infants
varies seasonally (so protection varies seasonally) and between infants, however no model has explored this feature. Manipulating SEIR structure to include RSV specific dynamics such as the period of maternal protection and waning immunity are examples of RSV-specific model characteristics that ensures that the transmission dynamics are accurately captured.

3.3.2 Region-specific transmission dynamics

RSV epidemiology varies significantly across the globe. Some countries experience distinct annual outbreaks (usually in temperate places), and other countries experiencing irregular outbreaks (usually in tropical settings). The mechanisms causing country-specific seasonal RSV outbreaks patterns is not known but is likely to be a combination of region specific social and climatic factors. As the transmission of infectious diseases is related to social contact structure within a population, some models used region-specific contact surveys to determine the average number of contacts made between two different subpopulations and estimate the probability of infection per infectious contact \( q \). Models which use these contact patterns find that the transmission patterns are highly dependent on the contact structure used, even when fitted to the same data. Climatic factors are difficult to incorporate because there is no clear consensus on which factors significantly influence outbreak patterns. In modelling, it is best to incorporate an absolute forcing parameters which oscillates throughout the year or use climatic factors to determine a relative variation in transmission capacity over time. All parameters in the model associated with social and climatic factors should be parameterised to region-specific datasets so that the region-specific transmission dynamics are captured.

3.3.3 Different model structures for capturing RSV transmission dynamics

In this section, I outline the model structures identified in the review models which capture the RSV transmission dynamics. Model structures arise to capture the heterogeneity in the transmission dynamics which occur due to factors such as variability in symptomatic expression of disease; the duration of infection; the quantity of virus shed; social behaviour (number of contacts made) and susceptibility to infection of RSV. I identify four different model structures from the review models that capture the observed heterogeneity in transmissive capacity for RSV; symptomatic dependent, age dependent, exposure dependent, and strain dependent models (Figure 3.2–3.6).
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(A) No dependencies

\[ \mu_B \quad \xi \quad M \quad S \quad E \quad \lambda(t) \quad \sigma \quad I \quad \gamma \quad R \]

Figure 3.2

(B) Symptomatic dependency

\[ \mu_B \quad \xi \quad M \quad S \quad E \quad \lambda(t) \quad I_a \quad I_b \quad I_c \quad I_d \quad R \]

Figure 3.3

(C) Age dependency

\[ \mu_B \quad \xi \quad M \quad S^1 \quad E^1 \quad I^1 \quad \gamma^1 \quad R^1 \quad S^2 \quad E^2 \quad I^2 \quad \gamma^2 \quad R^2 \]

Figure 3.4

(D) Exposure dependency

\[ \mu_B \quad \xi \quad M \quad S_0 \quad E_0 \quad I_0 \quad R_0 \quad S_1 \quad E_1 \quad I_1 \quad R_1 \]

Figure 3.5
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(E) Strain dependency

\[
\begin{array}{ccc}
S & \xrightarrow{\mu_B} & S \\
\lambda_A & \xrightarrow{I_A} & I_A \\
\lambda_{het} & \xrightarrow{\gamma} & \lambda_{het} \\
I_A & \xrightarrow{\gamma} & I_B \\
\lambda_{hom} & \xrightarrow{\gamma} & \lambda_{hom} \\
I_B & \xrightarrow{\gamma} & I_{A,B} \\
\end{array}
\]

\[
\begin{array}{ccc}
I_A & \xrightarrow{\gamma} & I_A \\
\lambda_{het} & \xrightarrow{\gamma} & \lambda_{het} \\
I_{A,B} & \xrightarrow{\gamma} & I_{A,B} \\
\lambda_{hom} & \xrightarrow{\gamma} & \lambda_{hom} \\
I_{B, A} & \xrightarrow{\gamma} & I_{B, A} \\
\end{array}
\]

Figure 3.6

Symptomatic dependent model

Studies which evaluate the infection characteristics of asymptomatic infection suggest that up to 80% of RSV infections can be asymptomatic in adults (or as low at 5% in infants less than one year of age), and asymptomatic infections have a decrease in the duration of infection and viral load when compared to symptomatic infection.\(^{17,18}\) This evidence suggests that asymptomatic infections are less infectious than symptomatic infections. One model incorporates this difference in infectiousness by including two infection-epidemiological states: asymptomatic infection and symptomatic infection with the former associated with a scalar reducing the infectiousness.\(^{87}\) Symptomatic expression of RSV disease ranges from mild rhinitis to hospitalised Bronchiolitis requiring intensive-care treatment, (which can lead to death), and is dependent on age and exposure.\(^{95}\) However, it is not clear if the severity of infection changes the transmissive capacity of an individual. On one hand, severe infections might last longer and have a higher viral shedding—increasing the transmissive capacity of a host, on the other hand, social factors such as social withdrawal may decrease the transmission capacity. One model considered the effect of symptom severity on transmission by splitting the infectious category, \(I\), into distinct categories of severity, allowing parameters such as duration of infections and infectiousness to be symptom-specific (Figure 3.3).\(^{90}\) This model finds, through model calibration, that milder infections (Upper Respiratory Tract Infections) are less transmissive compared with more severe infection (Lower Respiratory Tract Infections). Understanding the difference in transmission capacity between mild infections and severe infections is particularly important in the evaluation of herd immunity as models which assume that homogenous transmission capacity between all infected persons, par-
particularly between asymptomatic and symptomatic infections, may overestimate the role of transmission in milder infections, leading to inaccurate quantification of the transmission dynamics.

**Exposure dependency model**

It has been shown from prospective cohort studies that the duration of infection, and susceptibility to infection decreases with repeated exposure, leading to changes in host transmission capacity. This is because a boost of levels of pre-existing RSV-neutralising antibodies acquired from previous RSV infections results in an increased immunological response to RSV decreasing the severity of subsequent infections. Models incorporate these observed changes in RSV severity by compartmentalising the population into the number of times they have been infected with RSV (exposure) allowing the rate of loss of infection, $\gamma_i$, and susceptibility to infection relative to primary infection $\delta_i$ to be dependent on the number of previous infections, $i$ (*Figure 3.4*). Understanding the relationship between exposure and transmission capacity is important when evaluating intervention programmes. For example, intervention programmes which provide passive protection will only delay onset of primary infection and thus will not change the infectiousness of an infection if exposure dependency models are considered on their own. Consequently when evaluating such intervention programmes, age-dependent contacts or additional model structures should supplement the exposure model.

**Age-dependent models**

Age physiological factors, such as underdeveloped lung composition and naïve immune system infants, and decreased T-cell response in the elderly, contribute to an increase in the severity of symptomatic expression of RSV.\(^{96}\) Therefore, age can indirectly influence the transmission dynamics of RSV through changes in symptomatic expression of disease. Despite this observation, some models have transmission parameters dependent on age which are not associated with disease severity, including the rate of loss of infection, $\gamma_i$, and susceptibility to infection relative to primary infection $\delta_i$ to be dependent on the number of previous infections, $i$ (*Figure 3.5*). This is likely because many epidemiological studies do not account for both exposure and age, and therefore stratify their results usually by age only, meaning it is not possible to find information to best estimate for the exposure specific parameters despite this being the most immunological feasible way to parameterise the model. Understanding the complex relationship between age-related fac-
tors that affect disease severity; the resulting effect on transmission; and exposure effects on transmission, remains a big challenge in understanding RSV epidemiology. Many of the above model characteristics mentioned above can be combined to give rise to complex mathematical structures. For example, Yamin’s study\textsuperscript{87} uses age, exposure and symptomatic stratification to model RSV transmission, and Kinyanjui’s study\textsuperscript{84} uses exposure and age.

**Strain-dependent models**

Studies looking at strain-specific severity of RSV infections suggests that two main RSV stains co-circulate (RSV-A and RSV-B) with the dominant strain alternating over time. One model, which has included strain-dependent factors, including strain-specific susceptibility and transmission rates, found that RSV-A appears more frequently and is more transmissive than RSV-B.\textsuperscript{71} (Figure 3.6) Understanding strain-strain interactions and co-circulations dynamics could be useful in understanding region-specific transmission dynamics, however, current prophylactic candidates are likely to work equally well for both strains so it is unclear if including strain-strain interactions are necessary to evaluate the impact of intervention programmes.

### 3.3.4 Parameter estimation in identified transmission models

**Parameter estimation from epidemiological evidence**

The values of the epidemiological parameters of the RSV transmission model can be estimated from three different types of epidemiological RSV studies: prospective cohort studies, retrospective cohort studies and experimental challenge studies. Prospective cohort studies are useful for estimating parameters which depend on exposure, such as susceptibility and duration of infection, as the number of previous infections for each individual can be monitored. However, these studies are logistically difficult and expensive to implement and so the few studies that do exist only cover a specific subpopulation. Retrospective cohort studies recruit a patient when they present symptoms at either a GP clinic or a hospital, therefore it is not possible to know the number of previous RSV infections they have experienced. Consequently, retrospective cohort studies are only useful for estimating age-dependent parameters. In addition, careful attention must be given to bias that may arise from the recruitment process. Experimental reinfection studies gives accurate, controlled estimates for individual specific infections factors, allowing variables
such as duration of shedding, latency period, viral load to be estimated. However, such experiments can only be conducted in adults, and, because experimental reinfection is likely to be more aggressive than natural infections, some bias can be introduced towards more severe infections. A summary of the parameter estimates for each RSV transmission model, the papers they reference, and the type of study they are is given in Table 3.2.
<table>
<thead>
<tr>
<th>Model</th>
<th>Dur. of latency (1/(\sigma))</th>
<th>Dur. of mat. pro. (1/(\xi))</th>
<th>Dur. of immunity (1/(\omega))</th>
<th>Dur. of infection (1/(\gamma = \tilde{\gamma}))</th>
<th>Relative susceptibility ((\delta))</th>
<th>Relative infectiousness ((\alpha))</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>4 (95,97)</td>
<td>28 (97,99)</td>
<td>200 (98)</td>
<td>(\tilde{\gamma}) 10 (99)</td>
<td>(d_1) 0.5, (92,99,100)</td>
<td>(\alpha) 0.41 BF</td>
</tr>
<tr>
<td>71</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{1,000}) 0.35 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{1,000}) 0.84 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>4 (70)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>4 (70)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>200 (97)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>200 (76)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(\delta_{2}) 0.68 BF</td>
<td>(\alpha_1) 0.60 BF</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.2:** Table summarising numerical estimates for the epidemiological parameters used in the given mathematical transmission models of RSV. Boldface represents a value which is determined by model fitting and non-bold face is a parameter estimated from previous papers, given by references in superscript. BF: best fit, PM: posterior mean.
Model calibration

Model calibration is the process of determining values of the model parameters so the output of the model matches a specified dataset. The benefits of this are twofold. First, the model output is closer to the observed data, meaning the model can reproduce the data better, and second, parameters for which there is no prior knowledge of their value can be inferred from the model structure. Such parameters include the duration of maternal protection and duration of protection which, because they vary from region to region and in time, are difficult to estimate from epidemiological studies.

There are two types of datasets used to fit the review models: prospective surveillance data and hospital admission data. Prospective surveillance data gives an accurate representation of the burden of RSV, however, due to the difficulty and expense of these studies, they are not available in the majority of settings. Hospital admission data assesses the number of persons who are admitted to hospital or the number of positive RSV samples collected in a surveillance region. This data is often available from national surveillance programmes of disease, but it has severe limitations. They are often subject to bias as only severe infections are included, also heterogeneous healthcare seeking behaviour across a population may lead to bias burden estimates. Further, local differences in admission thresholds for RSV disease may introduce further bias. To overcome the limitations in using hospital admission data to calibrate the models, a non-constant reporting fraction—which is a constant which multiplies the model-predicted number of new infections to fit the reported observational data—is used. Two models estimate exposure- and age-dependent reporting fractions, to allow account for bias in reporting rates across the population. Techniques such as this give a fuller appreciation of the change in both disease severity through symptomatic expression and healthcare-seeking behaviour and appreciate inaccuracies in using bias surveillance data.

In calibrating parameters to observational data, identified transmission models have used both frequentist and Bayesian approaches. The frequentist approach uses a derived maximum likelihood to establish best-fit point-estimates and 95% confidence intervals for transmission parameters. Similarly, Bayesian approaches also used a derived likelihood to estimate the transmission parameters but with two distinct advantages. The first advantage, is the use of prior distributions associated with parameters to influence the likelihood of posterior estimates. This allows models to incorporate uncertainty in prior knowledge
about a parameter value, derived by synthesising all available epidemiological evidence, into the model predictions. The second advantage is the establishment of posterior distributions for the parameters, which give the reader the direct probability of an estimate equating the true value, and can be summarised by posteriors means and 95% credible intervals, which give a more intuitive interpretation of the estimates of the true value of the parameters than point estimates and 95% confidence intervals from frequentist likelihood estimates. Consequently, I suggest that future models use a Bayesian inference framework to allow for the uncertainty of parameter estimations to be taken into account.

The majority of the models found in the review provide a visual representation of the model fit by comparing the model-predicted incidence and the surveillance data. The models all appear to capture seasonal RSV incidence. Unfortunately, as no single study fits a model using both a frequentist and a Bayesian calibration technique, it is not possible to determine if one technique is better at fitting to the data than another.

### 3.3.5 Summary

After evaluating the evidence from all existing models of RSV transmission, I provide a list of desirable model structures that future RSV transmission models should include to ensure they accurately capture the transmission dynamics of RSV.

In this section, I analysed the key structural characteristic of the models which help to accurately capture the transmission dynamics of RSV. I found the basic compartmental structure of these models best captured observed RSV epidemiology by allowing hosts to become reinfected after a temporary period of immunity (an SIRS model) and also incorporating protection resulting from maternally derived immunity. In addition, models include complex methods for capturing the observed heterogeneity in host transmission capacity of RSV, including dependencies on the number of exposures, age of hosts, symptomatic expression of disease, and RSV strains. In particular, I highlight the importance of using regional specific data sources to capture regional specific seasonality, particularly social contact structures and estimate probability of transmission per daily contact. In addition, I give an overview of parameter estimation in the models and describe how to overcome limitations in current observation data used to calibrate such models, including the use of Bayesian inference to appreciate uncertainty in specific parameters such as duration of short-term immunity; duration of maternally-derived immunity; reporting
<table>
<thead>
<tr>
<th>Model structure</th>
<th>Evidence</th>
<th>Incorporation in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waning post-infection immunity</td>
<td>RSV infected individuals can become reinfected with RSV, even within the same season with the same strain.⁴, ⁹⁸</td>
<td>Individuals in the recovered epidemiological compartment, R, wane exponentially with rate ω to the susceptible group, S.</td>
</tr>
<tr>
<td>Waning maternal-immunity in neonates which varies seasonally.</td>
<td>Heightened levels of RSV neutralising cord-titre reduces risk of hospitalisation.⁹, ¹⁰, ¹² The peak age for RSV incidence in England and Wales is 2 months of age.⁵⁹ RSV-neutralising cord titre varies seasonally.¹²</td>
<td>A proportion of neonates, which varies with the season, are born into a protective category, M, which they leave exponentially with rate ξ into a susceptible group, S.</td>
</tr>
<tr>
<td>Decreased transmissible capacity after primary infection</td>
<td>A boost of levels of pre-existing RSV-neutralising antibodies acquired from previous RSV infections results in an increased immunological response to RSV.³</td>
<td>Stratify population into the number of times they have acquired infection and allow parameters such as duration of infection, and susceptibility to infection decrease to be dependent on the number of times they have been infected.</td>
</tr>
<tr>
<td>Regional specific heterogeneous contact structure</td>
<td>Previous studies have linked contact structure to transmission pathways for infectious disease¹⁸, ¹¹³</td>
<td>Into the force of infection by allowing probability of transmission to be ( c_{a,b} \cdot q ) where ( c_{a,b} ) is the number of contacts between made by age group a with age group b and q is the probability of transmission.</td>
</tr>
<tr>
<td>Regional specific incidence data for calibration</td>
<td>RSV epidemiological varies globally so each model should calibrate parameter values specific to each region.²³</td>
<td>Compare model predicted incidence with RSV incidence data from a specific region and link through the observational model.</td>
</tr>
<tr>
<td>Bayesian inference methods</td>
<td>Allows to for the uncertainty in specific parameters to be properly appreciated. Also can incorporate prior knowledge into the uncertainty of estimation.</td>
<td>Derive posterior distributions for each parameter though MCMC sampling methods</td>
</tr>
</tbody>
</table>

**Table 3.3:** Set of guidelines for future models to help capture RSV-specific transmission dynamics.
fraction; relative infectiousness. Ensuring that mathematical models accurately capture the transmission dynamics of RSV and give a full appreciation to the uncertainty in the regional-specific data used to calibrate the models and ensures that total impact of intervention programmes is correctly quantified.
3.4 Results 2: Evaluating potential intervention programmes

In this section, after providing motivation for the potential RSV intervention delivery strategies, I first consolidated evidence from the transmission model which have evaluated the impact of RSV interventions programmes and then discussed what I can infer from their results the impact of the aforementioned potential RSV intervention delivery strategies.

3.4.1 Potential prophylactic strategies

I identified four prophylactic strategies for reducing the disease burden of RSV; active direct protection; passive direct protection; indirect untargeted protection and indirect targeted (or cocooning) Table 3.5. These prophylactic strategies reduce the disease burden of RSV by reducing incidence in either adults aged 65 years and over (as in active direct protection) or children less than one year of age (as in active direct protection, passive direct protection, and indirect untargeted protection and cocooning) through either direct protection or altering transmission pathways to reduce overall burden (indirect protection). For each of the prophylactic strategies, I provide motivation for their potential effectiveness at curtailing RSV infection and give examples of potential vaccination programmes.
### Prophylactic Strategy

<table>
<thead>
<tr>
<th>Prophylactic Strategy</th>
<th>Example Subpopulations</th>
<th>Prophylactic Example</th>
<th>Motivation</th>
<th>Importance of Dynamic Transmission Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active direct protection</td>
<td>Infants &lt;1yrs</td>
<td>rBCG-N-hRSV (Pontifica Universidad Catolica Chile) and ChAd155-RSV (GSK)</td>
<td>These subpopulations have the highest observed disease burden.</td>
<td>Importance is unclear. Studies have shown that vaccination of infants less 1 years of age confers substantial herd protection, but this is highly dependent on social contact structure.</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
<td>MVA-BnN RSV (Bavarian Nordic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive direct protection</td>
<td>Pregnant women</td>
<td>RSV F nanoparticles (Novavax)</td>
<td>Elevated RSV MatAB cord-titres at birth decreases the risk of incidence of RSV in neonates during the first year of life29–34. Therefore, vaccination of pregnant women during the third trimester could boost cord titres and confer protection in neonates, transplacentally through cord blood (antenatal protection) or through breast milk (postpartum protection). Similar programmes that vaccinate pregnant women against pertussis have been effective in the US.</td>
<td>Importance depends on the efficacy of maternally derived protection. High efficacy means that the neonate confers a large degree of protection, and so indirect protection from cocooning is negligible. Similarly low efficacy implies that the neonate confers a little protection, and so indirect protection from cocooning is more important.</td>
</tr>
<tr>
<td></td>
<td>Neonates</td>
<td>MEDI8897 (MedImmune)</td>
<td>Infants in the first few months of life are the most at risk of severe complications (Bronchiolitis) due to RSV infection.</td>
<td>Importance is unclear. Studies have shown that vaccination of infants less 1 years of age confers substantial herd protection, but this is highly dependent on social contact structure.</td>
</tr>
<tr>
<td>Indirect untargeted protection</td>
<td>School-age children</td>
<td>None</td>
<td>School children are the main disseminators of respiratory disease such as flu; likely to be a similar case for RSV. Cohort studies of RSV transmission suggest that a significant proportion of infants acquire their infection from household-sharing older siblings.</td>
<td>Important. Highly dependent on evaluating contact-dependent transmission so the effect of herd immunity can be assessed.</td>
</tr>
<tr>
<td>Indirect targeted protection (cocooning)</td>
<td>Family members of vulnerable infants</td>
<td>None</td>
<td>Cohort studies of RSV transmission suggest that a significant proportion of infants acquire the infection from household family members, specifically older siblings. Targeting these household members could reduce incidence infants.</td>
<td>Important. Highly dependent on evaluating contact-dependent transmission so the effect of herd immunity can be assessed.</td>
</tr>
</tbody>
</table>

**Table 3.4:** Summary of potential prevention strategies against RSV.
**Active direct protection**

Active direct protection refers to intervention programmes which aim to vaccinate individuals which have the highest disease burden. For RSV, these individuals are children under the age of one year (infants), and adults aged 65 years and older (elderly). For active direct protection to be effective in infants, vaccines must be administered as early as possible to prevent infections during peak incidence during 1-4 months of age. Vaccinating infants in the first few months of life causes additional challenges in vaccine production compared to older age groups as initiating an effective immunological response in naïve immune systems in infants is difficult. For active direct protection to be effective in the elderly, programmes are likely to be either universal, as in the case of Influenza, or targeted at high-risk persons. To evaluate the effect of active direct protection vaccination strategies, static mathematical transmission models suffice as the small number of contacts that infants and the elderly have means there is likely to be significant degree of herd immunity acquired from vaccination.

**Passive direct protection**

Passive direct protection refers to intervention programmes which aim to provide passive immunity to individuals which have the highest observed disease burden. I outline two mechanisms through which passive immunity is administered to infants. The first mechanism aims to augment the period of maternally acquired immunity in neonates by vaccinating pregnant women in their third trimester. Though the exact mechanism by which protection is conveyed through passive immunity is not known, it has been observed that neonates with high levels of maternal-derived antibodies to RSV in cord titre are less likely to be hospitalised due to RSV in the first year of life than neonates with lower levels of maternal-derived antibodies to RSV in cord titre. Therefore, vaccines could boost RSV antibodies levels in pregnant women with the expectation that it will result in higher levels of protection in neonates. There are difficulties associated with the implementation of maternal vaccination however, with low coverage levels observed for Influenza in the UK, which may render maternal programmes less effective. The second mechanism through which passive immunity is administered to infants is by directly giving a passive immune agent to the neonate at birth. This strategy provides extra protection to infants during the first few months of life as it increases the concentration of RSV antibodies, causing primary infections to occur later in life, which leads to lower rates of severe infection and
of hospitalisation. Dynamic mathematical models are required to accurately evaluate the
effects of passive direct protection strategies in the case of pregnant women. Specifically,
there is an element of herd immunity acquired from vaccinating pregnant women as they
have a high number of daily contacts with their neonate (cocooning).

**Untargeted indirect protection**

Indirect protection refers to vaccination programmes which aim to vaccinate individuals
who are likely to be the main drivers of disease transmission, reducing the transmission of
RSV to vulnerable populations through herd immunity. Herd immunity can be an effec-
tive strategy as curtailing the transmission of infectious diseases, as has been shown with
vaccination of school-age children to reduce the incidence of influenza in the elderly.\textsuperscript{114,115} Though no vaccine candidate in clinical trials has the specific aim to target individuals
such as school-age children, most of the vaccines which are aimed at vulnerable popula-
tions have been tested on, (during intermediate phases trails) healthier adults beforehand.
Therefore, if there is evidence to suggest that vaccination of school-age children is a cost-
effective strategy at curtailing RSV infection, vaccine candidates could easily alter their
trial trajectory accordingly to test for efficacy and safety in healthy school-age children.

**Targeted Indirect protection**

Indirect targeted protection, or cocooning, are vaccination programmes which aim to vaccinate specific members of the population who have a close relationship with persons
who are vulnerable to RSV infection. For example, vaccinating household members of
neonates could be effective at reducing incidence owing to the observation that 50% of
infections in infants come from household members.\textsuperscript{68} Similar to untargeted indirect pro-
tection, no vaccine candidates have strategy in mind, however, overwhelming evidence
which suggests that this is a cost-effective vaccine could alter clinical trial testing tra-
jectory. For both targeted and untargeted indirect protection, mathematical models are
very important in their evaluation because transmission is highly dependent on contact
structures within a population. Therefore models which evaluate indirect protection vac-
cination scenarios should include heterogeneous contact structure specific to the modelled
region to accurately evaluate the effect of acquired herd immunity.
3.4.2 Overview of mathematical models of RSV vaccination

I identified seven models which evaluate the effectiveness of potential vaccination programme (Table 3.5). All seven models include a SIRS structure, allowing short-term immunity to occur and consider the effect of seasonality through seasonal forcing. Four of these models also include heterogeneity in disease severity, contact structure, and two of these include altered transmission dynamics due to asymptomatic infection. Maternally derived immunity is considered in three of the models. Models are all calibrated to the number of RSV hospitalisations due to RSV, with Poletti et al. being additionally calibrated to RSV infections rates from a prospective cohort study of RSV in infants. Three of the vaccination models estimate point values for fitted parameters, and two models use Bayesian inference to derive models posterior distributions for fitted parameters.
### Outline of vaccination strategies

<table>
<thead>
<tr>
<th>Vaccine effect</th>
<th>Target</th>
<th>Coverage</th>
<th>Uptake</th>
<th>Duration of protection</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete immunity</td>
<td>Neonates</td>
<td>85%</td>
<td>Instantaneous at birth</td>
<td>100%</td>
<td>Same as normal infection</td>
</tr>
<tr>
<td>Complete immunity</td>
<td>Elderly</td>
<td>90%</td>
<td>Continuous moved when they reach specific age</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Complete immunity</td>
<td>Pregnant women</td>
<td>80%</td>
<td>1st January instantaneous</td>
<td>3 or 6 months</td>
<td></td>
</tr>
<tr>
<td>Reduction in i) risk of primary inf; ii) duration of infection; iii) infectiousness</td>
<td>Neonates</td>
<td>90/100%</td>
<td>2 or 3 doses &lt;6 mo</td>
<td>Waning vaccine effect, 1 or 2 years, considers interaction with natural immunity</td>
<td></td>
</tr>
<tr>
<td>Reduction in primary infection</td>
<td>Pregnant women</td>
<td>90/100%</td>
<td>Continuous over year</td>
<td>Maximum duration 6 months (4 and 3)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3.5: Summary of potential vaccine strategies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Neonates</th>
<th>Elderly</th>
<th>Pregnant women</th>
<th>Neonates (passive)</th>
<th>School-age children</th>
<th>Cocooning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acedo 2010</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Kinyanjui 2015</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Poletti 2015</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Yamin 2016</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Jornet-Sanz 2017</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Pan-Ngum 2017</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hogan 2017</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Active direct protection

Active direct protection can be used to lower RSV burden by targeting the infants and/or the elderly. There are six transmission models that consider the impact of infant vaccination on either the overall incidence of RSV\textsuperscript{85,87} or the number of RSV-associated hospitalisations.\textsuperscript{76,84,89,90} Poletti et al.’s study\textsuperscript{85} shows that vaccinating infants at three months of age results in a 40% decrease in overall RSV incidence in children less than one year old (assuming 100% coverage). Yamin et al.’s study\textsuperscript{87} shows that vaccinating all children less than 5 years old, results in 70-80% decrease in incidence in this age group (assuming a coverage of 80% coverage). Pan-Ngum et al.’s\textsuperscript{90} study suggest vaccination infants at 2 and 4 months of age reduces incidence in children under 5 years by 60% (assuming 90% coverage) and Kinyanjui et al.’s\textsuperscript{84} study suggests that vaccinating infants at 6 month of age provides a 63% reduction in the overall of RSV incidence across all ages (assuming a 90% coverage). Overall, these models suggest that vaccination programmes which target infants are effective at reducing RSV incidence providing they are highly efficacious (>90%) and are able to maintain a high level of coverage (>90-100%). Though high coverage levels are feasible in this age group (as observed with MMR); high efficacy may be difficult to achieve given the complex and poorly understand immunopathogenesis of RSV, which has caused a troubled history of vaccine development. In evaluating the impact of active direct protection in the elderly, Yamin et al.’s study\textsuperscript{87} shows that vaccinating the elderly results in a 20-30% decrease in overall incidence (with 80% coverage)—three times less than the overall proportional reduction if children less than five were vaccinated. This suggests that vaccination strategies which target infants are more effective at preventing population-level incidence of RSV than vaccination strategies targeting the elderly.

Passive direct protection

Passive direct protection can be conveyed to infants through two mechanisms; vaccination of pregnant women and passive immunity directly given to neonates. There are three models which consider the effect of vaccinating pregnant women.\textsuperscript{85,90,91} Poletti et al’s study\textsuperscript{85} suggests that vaccinating pregnant women results in a proportional reduction in incidence of 31.5% (95% CI 30.7-37.5%), (under the assumption that maternally acquired immunity is complete and vaccination extends it from 4 months to 8 months at 100% coverage). Pan-Ngum et al.’s\textsuperscript{90} study suggests vaccinating pregnant women reduces the number of hospitalisations in infants by 7-14% (under the assumption that maternally
acquired immunity is complete and vaccination extends it from 2 months to 3 months at 50% coverage). Hogan et al.’s study suggests vaccination of pregnant women results in a 26% reduction in hospitalisation for infants aged 0-2 months old and a 40% reduction in hospitalisation for infants aged 3-5 months old (under the assumption that maternally acquired immunity is partial and vaccination extends it from 3 months to 6 months at 50% coverage). Poletti et al.’s study additionally shows that the effect of herd immunity acquired from vaccinating pregnant women on preventing infections in infants is negligible (i.e. vaccinating pregnant women with no increase in maternally derived immunity has no effect on incidence of RSV in infants). These models cumulatively suggest that large increases in the duration of maternally derived immunity results in an effective vaccination scenario for reducing RSV burden in infants. Therefore, this evidence suggests that maternal vaccination is likely to be effective, providing that it can provide a boost in immunity in neonates. There is no study that evaluates the effect of passive immunity through direct injection of neonates with monoclonal antibodies, except existing Palivizumab studies.

**Untargeted indirect protection**

Untargeted indirect protection is likely to be effective through vaccination of school-age children. Three models evaluate the indirect effect of vaccinating school-age children on incidence in infants and the elderly. Yamin et al.’s study shows that vaccinating children between the ages of 6 months and 5 years reduces RSV incidence in the elderly by 70-80%—twice as effective at reducing incidence in the elderly than vaccination of persons aged 5-24 yrs (assuming 80% coverage). Vaccination of persons aged between 5-24 yrs is less effective at reducing incidence in children less than 5 years old, with around 20% reduction in incidence (assuming 80% coverage). Poletti et al.’s study suggests that vaccination of 5-14 years offers a 35.6% (95% CI 13.7–89.4%) proportion reduction in infections in infants (assuming 100% coverage). Kinyanjui et al.’s study suggests that vaccination of infants aged between 5-10 months is the most effective method at reducing incidence in infants less than 6 months, and the majority of this protection is from herd immunity. These results imply that vaccination of school-age children may be an effective measure at reducing disease burden in the elderly and in infants, however a finer stratification of age groups when considering vaccination programmes might provide a clearer understanding of the transmission pathways which are being targeted.
Targeted indirect protection (cocooning)

Poletti et al’s study\(^8\) is the only identified model which considers the effect of cocooning in reducing transmission of RSV, finding that vaccinating siblings or mothers (at the birth of neonate) cohabiting with vulnerable infants, showed no proportional reduction in incidence in infants under the age of one year.

3.4.3 Summary of results of existing intervention models

In this section, I outlined four RSV vaccine strategies which are likely to be effective at reducing RSV burden (active direct protection, passive direct protection, and indirect untargeted protection and cocooning). To ascertain the impact of these strategies I consolidated the results of seven existing mathematical models which evaluated the effect of various RSV vaccination programmes. I found that active direct protection strategies are likely to be an effective strategy at preventing RSV infection providing the vaccines are highly efficacious and are able to reach a high level of coverage. Further, passive direct protection acquired through vaccination of pregnant women is likely to be highly effective providing the acquired maternal protection in infants is increased twofold. Finally, untargeted indirect protection administered through vaccination of school-age children is likely to provide some protection to both the elderly and to infants. It is not clear whether passive direct protection acquired through vaccination of neonates, or if untargeted indirect protection are effective strategies. The former has not been evaluated in existing modelling papers, and the latter has only been evaluated in one study. Further work is certainly needed to evaluate these intervention programmes.

3.5 Conclusions

In this chapter I ascertained what I can infer from existing mathematical models of RSV transmission about how to construct a model of RSV transmission which both accurately captures RSV transmission patterns and accurately evaluates the impact of relevant potential vaccination scenarios. To achieve this I performed a review of mathematical models of RSV transmission, and found 22 models which varied in setting and structure. By critically analysing these models I found specific ways to capture the transmission dynamics of RSV and discovered the large variety in parameter estimation means that Bayesian inference methods are important to allow full uncertainty in their values to be appreciated. Further, by synthesising evidence from models which evaluate the impact of potential
vaccination programmes, I gained a clearer understanding of the effectiveness of vaccine
delivery strategies. Finding the conditions under which direct protection and maternal
vaccination are likely to be effective, and highlighting the need for more models which are
evaluating passive immunity and cocooning effects. Using all this evidence I provided a
set of guidelines for models to follow which ensure that future studies evaluate the impact
of potential intervention programmes effectively and accurately. In the next chapter I use
this knowledge and outline a mathematical model for the transmission of RSV in England
and Wales.
Chapter 4

Development of a model for RSV transmission in England and Wales

4.1 Introduction

The previous chapter suggests that more mathematical models are required which capture RSV-specific transmission characteristics. These transmission characteristics include waning post-infection and maternal immunity, decreasing transmission capacity after primary infection and regional-specific contact patterns. In this chapter a mathematical model of RSV transmission is developed which includes these transmission characteristics. There are three steps to building this model. First, I describe the mathematical model which includes the important transmission characteristic and the associated fitted parameters. Second, I describe the data sources used to determine the prior distributions for the fitted parameters in the mathematical model. Finally, I outline the Bayesian inference methods used to calibrate the model and determine the posterior distributions which capture the dynamics of RSV given the Respiratory DataMart System surveillance data.

The mathematical model outlined in this chapter is a compartmental-type deterministic model. The large size of the population considered (approximately 55 million people in England and Wales) means this type of model is less computationally intensive than an agent-based model, where each person’s transmission dynamics must be specified and tracked individually. In order to capture the heterogeneity in transmissive capacity across the population, the model stratifies the population into age groups. Similar to other mathematical models of disease transmission, the transmissive capacity of each age group is dependent on i) the number of infected people in other age groups, iii) the number
of contacts they make with other age groups and ii) the severity of the infection in the individual. Using Bayesian inference methods outlined in this chapter is preferable over non-Bayesian methods as it allows for the uncertainty in all the parameters estimates to be fully incorporated, leading to more realistic predictions about the impact of potential programmes.

4.2 Description of the model

The model tracks the number of individuals in six different epidemiological states ($M$, $S$, $E$, $I$, $A$ and $R$). When a susceptible individual ($S$) acquires infection, they move to an exposed but not infectious state ($E$) for an average of $1/\sigma$ days, after which they become infectious with either symptomatic ($I$) or asymptomatic ($A$) infection. After an infectious period of $1/\gamma$ days, individuals move to a protected state ($R$) for a period of $1/\omega$ days, after which they become susceptible to reinfection ($S$). A proportion of new-borns are assumed to be born with high levels of RSV neutralising antibodies, $p_R$, granting maternally-derived protection ($M$) for a period of $1/\xi$ after birth (See Section 4.2.2 for the two different parameterisations). The number of individuals that have experienced zero, one, and two or more previous infections (denoted by the subscripts 0, 1, 2, 3) are also tracked. Consistent with empirical data, I assume that the proportion of individuals who experienced asymptomatic infection is dependent on age$^{17}$ and the duration of infection and susceptibility to infection are dependent on the number of previous RSV infections.$^{92,95}$ A summary of the model variables that show different epidemiological states are contained in Table 4.1 and a schematic of the epidemiological model is shown in Figure 4.1. The parameters of the model are contained in Table 4.2 and the full system of model equations of are shown in Equation 4.1.
Figure 4.1: The relationship between the mathematical model state variables ($M$: protected due to maternal antibodies, $S$: susceptible, $E$: exposed but not infectious, $I$: infectious and symptomatic, $A$: infectious and asymptomatic, $R$: recovered and protected) for each of the four exposure levels (subscript $i = 0, 1, 2, 3$). For maternal immunity, the parameters are $\mu$ the daily birth rate, $p_R$ the proportion of neonates born with protection and $\xi$ the rate of loss maternal immunity. For each exposure level $i$, $\lambda_i$ is the force of infection, $\sigma$ is the rate of loss exposure to infection, $p^a$ is the probability that an RSV infection is asymptomatic in age group $a$, $\gamma_i$ is the rate of loss of infectiousness, and $\omega$ is the rate of loss of post-infection immunity.
### State Description

<table>
<thead>
<tr>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M(t)$</td>
<td>Number of individuals at time $t$ who are completely protected from infection due to maternally-derived antibodies.</td>
</tr>
<tr>
<td>$S_i(t)$</td>
<td>Number of individuals at time $t$ who are susceptible to acquiring an RSV infection, who have experienced $i$ previous infections.</td>
</tr>
<tr>
<td>$E_i(t)$</td>
<td>Number of individuals at time $t$ who are infected with RSV but are not yet infectious (i.e. exposed), who have experienced $i$ previous infections.</td>
</tr>
<tr>
<td>$A_i(t)$</td>
<td>Number of individuals at time $t$ who are infected with RSV, infectious and have no symptoms of RSV-related respiratory disease, who have experienced $i$ previous infections.</td>
</tr>
<tr>
<td>$I_i(t)$</td>
<td>Number of individuals at time $t$ who are both infected with RSV, infectious and have symptoms of RSV-related respiratory illness, who have experienced $i$ previous infections (not including the current infection).</td>
</tr>
<tr>
<td>$R_i(t)$</td>
<td>Number of individuals at time $t$ who are completely protected from infection due to immunity acquired from natural-infection, who have experienced $i$ infections (not including the one just experienced).</td>
</tr>
<tr>
<td>$Z(t)$</td>
<td>Cumulative number of new RSV infections at time $t$</td>
</tr>
</tbody>
</table>

**Table 4.1:** Description of the epidemiological state variables of the RSV model, where $i \in \{0, 1, 2, 3\}$. 
## Table 4.2: Prior distributions of the parameters in the mathematical model. Subscript $i$ indicates exposure level and superscript $a$ indicates age group.

The ODEs of the mathematical model for RSV transmission for age group $a$ are:
CHAPTER 4. DEVELOPMENT OF A MODEL FOR RSV TRANSMISSION IN ENGLAND AND WALES

\[
\begin{align*}
\dot{M}_a &= \rho_R \dot{I}_1(a) - \xi \dot{M}_a - \eta^a \dot{M}_a + \eta^{a-1} \dot{M}_a^{-1} \\
\dot{S}_a &= (1 - \rho_R) \mu \dot{I}_1(a) + \xi \dot{M}_a - \lambda_a(t) \dot{S}_a^a - \eta^a \dot{S}_a^a + \eta^{a-1} \dot{S}_a^a^{-1} \\
\dot{E}_a &= \lambda_a(t) \dot{S}_a^a - \sigma E_a \\
\dot{A}_a &= \rho^a \sigma E_a - \gamma_a A_a \\
\dot{I}_a &= (1 - \rho^a) \sigma E_a - \gamma_a I_a \\
\dot{R}_a &= \gamma_a A_a + \omega R_a - \omega R_a \\
\dot{S}_a &= \omega R_a^a - \lambda_a(t) S_a^a \\
\dot{E}_a^1 &= \lambda_1(t) S_a^a - \sigma E_a^1 \\
\dot{A}_a^1 &= \rho^a \sigma E_a^1 - \gamma_1 A_a^1 \\
\dot{I}_a^1 &= (1 - \rho^a) \sigma E_a^1 - \gamma_1 I_a^1 \\
\dot{R}_a^1 &= \gamma_1 A_a^1 + \gamma_1 I_a^1 - \omega R_a^1 \\
\dot{S}_a^1 &= \omega R_a^1 - \lambda_2(t) S_a^1 \\
\dot{E}_a^2 &= \lambda_2(t) S_a^2 - \sigma E_a^2 \\
\dot{A}_a^2 &= \rho^a \sigma E_a^2 - \gamma_2 A_a^2 \\
\dot{I}_a^2 &= (1 - \rho^a) \sigma E_a^2 - \gamma_2 I_a^2 \\
\dot{R}_a^2 &= \gamma_2 A_a^2 + \gamma_2 I_a^2 - \omega R_a^2 \\
\dot{S}_a^2 &= \omega R_a^2 + \omega R_a - \lambda_3(t) S_a^2 \\
\dot{E}_a^3 &= \lambda_3(t) S_a^3 - \sigma E_a^3 \\
\dot{A}_a^3 &= \rho^a \sigma E_a^3 - \gamma_3 A_a^3 \\
\dot{I}_a^3 &= (1 - \rho^a) \sigma E_a^3 - \gamma_3 I_a^3 \\
\dot{R}_a^3 &= \gamma_3 A_a^3 + \gamma_3 I_a^3 - \omega R_a^3 \\
\dot{Z}_a &= \sigma (E_a + E_a^1 + E_a^2 + E_a^3) 
\end{align*}
\]

where an overdot refers to differentiation with respect to \( t \), \( \dot{I}_1(a) \) is the indicator function (non-zero at \( a = 1 \)). The value of \( \rho_R \) depends on the maternal protection model (see Section 4.2.2) and \( \lambda_t(a) \) is the force of infection for age group \( a \) (see Section 4.2.4).

### 4.2.1 Age stratification

In order to capture the heterogeneity in transmissive capacity across the population, I stratified the model into age groups (indicated by the superscript \( a \)). 25 age groups were considered, allowing for the dynamics of RSV incidence in infants to be closely monitored (age groups: <1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 months, and 1, 2, 3, 4, 5–9, 10–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75+ years). The number of individuals, \( N_a \), in each age group, \( a \), is calculated by multiplying the daily birth rate in 2018 for England and Wales, \( \mu = 1863 \) live birth per day, by the number of days spent in each age group \( (d_a) \). Individuals in an epidemic compartment move to the next age group \( (X_a \rightarrow X_{a+1}) \).
CHAPTER 4. DEVELOPMENT OF A MODEL FOR RSV TRANSMISSION IN ENGLAND AND WALES

at rate $\eta^a = 1/(365 d_a)$.

4.2.2 Maternal protection model

I considered two different model structures to capture the dynamics of maternal protection. The first, static immunity model, $\mathcal{M}^1$, assumes that all neonates are born with protection, ($p_R = 1$). The second, dynamic immunity model $\mathcal{M}^2$, assumes that the proportion of infants born with protection is equal to the proportion of women of child bearing age (15-44 years) who are in epidemiological state, $R$ (i.e. recently experienced RSV) at time $t$, $p_R(t) = \frac{\sum_{a=19}^{21} R^a(t)}{\sum_{a=19}^{21} N^a}$. The dynamic immunity model was chosen due to the observation that i) RSV neutralising cord titre correlates with maternal RSV neutralising antibodies levels, and ii) RSV neutralising cord titre changes seasonally (Figure 4.2).

\[
\begin{align*}
\text{Static immunity (M}^1\text{)} & \quad \mu \quad \xi \\
\text{Dynamic immunity (M}^2\text{)} & \quad p_R(t)\mu \\
\end{align*}
\]

Figure 4.2: Two models of maternal protection where $\mu$ is the daily birth rate, $\xi$ is the rate of loss of maternal-derived immunity, and $p_R(t)$ is the proportion of infants born with protection at time $t$.

4.2.3 Contact matrices

I assume that the contact rate between two age groups is proportional to the mean number of daily physical and conversational contacts made between those age groups. To estimate the number of contacts between age group $a$ and $b$, I combined the results of two contact surveys. The first study (Study A), was conducted as part of the EU funded POLYMOD study from 2008—a large pan-European survey with 7,290 participants who recorded 97,904 contacts across all age groups. The second study (Study B), is a smaller study in the United Kingdom in 2013 with 122 number of participants (all under the age of one year) who recorded 758 contacts. Both studies provided estimates for the number of daily household/non-household contacts and daily physical/conversational contacts made between each age group. Therefore, to estimate the total number of daily physical/conversational contacts made between age group $a$ and $b$, ($p^{a,b}$ and $c^{a,b}$ respectively), I
used Study A for participants less than 1 year of age, and Study B for older participants. 
To ensure this symmetry occurs in the contact matrices, I calculated the weighted mean 
number of contacts made between age $a$ to age group $b$ for conversational contacts (same 
formula for physical contacts) as:

$$c_{a,b} \leftarrow \frac{1}{N^a + N^b} \left( c_{a,b} N^a + c_{b,a} N^b \right)$$

where $N^a$ is the population size for age group $a$. The resulting symmetric contact 
matrices for $p_{a,b}$, $c_{a,b}$ are plotted in Figure 4.3.
Figure 4.3: Top: Number of daily physical contacts made between age group \( a \) and age group \( b \). Bottom: Number of daily conversational contacts made between age group \( a \) and age group \( b \). White squares indicate no reported contacts between age groups. In these surveys, this means there were no reported physical contacts within infants less than 1 years old, and between infants ages 1-4 years and the elderly (65 years and older).
4.2.4 Force of infection

The probability of transmission for a contact made between two age groups is \( q_p \) if the contact is physical and \( q_p q_c \) if the contact is conversational, where \( 0 < q_c < 1 \) is the reduction in infectiousness of conversation contacts relative to physical contacts. Further, due to climatic factors, I assumed that the probability of transmission is seasonally forced according to a normal distribution, with peak transmission occurring at \( \phi \), mean \( b_1 \) and standard deviation \( \psi \). Finally, because asymptomatic infections are shorter and have a lower viral load than symptomatic infection, I assume the infectiousness of asymptomatic infections is reduced by a factor of \( 0 < \alpha < 1 \). The equation for the force of infection is therefore:

\[
\lambda^a_i(t) = q_p (1 + b_1 \exp((t - \phi)^2/(2\psi^2))) \prod_{i'=0}^{i} \delta_{i'} \sum_{b=1}^{25} \frac{(p^{a,b} + p^{e,a,b})}{\bar{N}^b} \left( A^b_i \alpha + I^b_i \right) \tag{4.2}
\]

4.2.5 Initial conditions

For each age group \( a \), I estimated i) the initial proportion of persons who still have maternally derived immunity, \( p^{a}_\xi \), (by assuming loss of immunity is exponentially distributed with rate \( \xi \)) and ii) the initial proportion of persons who have experienced \( k \) number of previous infections \( p^{a}_k \) (assuming acquisition of infection is Poisson distributed with rate 1 per year). The initial proportion of persons in each exposure level who are not infected is therefore given by \((1 - l_1)\), and of this proportion, \( l_2 \) are in epidemiological group \( R_i \), with the rest in epidemiological group \( S_i \). Of the infected proportion, \( l_1 \), the initial proportion in state \( E \), is the average amount of time within that epidemic group \((\sigma/(\sigma + \gamma_i))\). Following a similar argument, the formulae for the initial proportion of the infected persons who are in the asymptomatic and symptomatic state is \( \sigma/(\sigma + \gamma_i) p^a \) and \( \sigma/(\sigma + \gamma_i)(1 - p^a) \) respectively (Figure 4.4).
The equations for the initial conditions are:

\[
M^a(0) = N p^a_\xi
\]

\[
S^a(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_0 \right] (1 - l_1) (1 - l_2)
\]

\[
E^a(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_1 \right] \left( \frac{\sigma}{\tau + \sigma} \right) l_1
\]

\[
A^a(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_2 \right] \left( \frac{\gamma^a_0}{\tau + \gamma^a_0} \right) (1 - p^a) l_1
\]

\[
R^a(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_3 \right] (1 - l_1) l_2
\]

\[
S^a_1(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_1 \right] (1 - \delta_1 l_1) (1 - l_2)
\]

\[
E^a_1(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_2 \right] \left( \frac{\sigma}{\tau + \sigma} \right) \delta_1 l_1
\]

\[
A^a_1(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_3 \right] \left( \frac{\gamma^a_0}{\tau + \gamma^a_0} \right) (1 - p^a) \delta_1 l_1
\]

\[
R^a_1(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_4 \right] (1 - \delta_1 l_1) l_2
\]

\[
S^a_2(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_1 \right] (1 - \delta_2 l_1) (1 - l_2)
\]

\[
E^a_2(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_2 \right] \left( \frac{\sigma}{\tau + \sigma} \right) \delta_2 l_1
\]

\[
A^a_2(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_3 \right] \left( \frac{\gamma^a_0}{\tau + \gamma^a_0} \right) (1 - p^a) \delta_2 l_1
\]

\[
R^a_2(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_4 \right] (1 - \delta_2 l_1) l_2
\]

\[
S^a_3(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_1 \right] (1 - \delta_3 l_1) (1 - l_2)
\]

\[
E^a_3(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_2 \right] \left( \frac{\sigma}{\tau + \sigma} \right) \delta_3 l_1
\]

\[
A^a_3(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_3 \right] \left( \frac{\gamma^a_0}{\tau + \gamma^a_0} \right) (1 - p^a) \delta_3 l_1
\]

\[
R^a_3(0) = \left[ N \left( 1 - p^a_\xi \right) p^a_4 \right] (1 - \delta_3 l_1) l_2
\]

where \( N = N^a \); the equation for \( p^a_\xi \), the initial proportion of persons in age group \( a \) (age range, \([n^{a-1}, n^a] \), \( n^{a-1} < n^a \) ) who still have maternal protection given a rate of loss of maternal protection parameter, \( \xi \), is:

\[
 p^a_\xi = \frac{1}{(n^a - n^{a-1})} \int_{n^{a-1}}^{n^a} \exp(-365\xi x) \, dx
\]

and the equations for \( p^a_k \), the initial proportion of persons in age group \( a \) who have experienced \( k \) number of previous infections assuming no cumulative protection follows a
Poisson distribution, is:

\[ p^a_k = \frac{1}{(n^a - n^{a-1})} \int_{n^a-1}^{n^a} \frac{(x)^k \exp(-x)}{k!} \, dx, \quad k = 0, 1, 2 \]

\[ p^a_0 = 1 - (p^1_0 + p^1_1 + p^2_2) \]  \hspace{1cm} (4.5)

4.2.6 Number of new infections

The output of the mathematical model is the number of new infections \( Z^{M^m,a}_{w_t, a} \) in age group \( a \), maternal model \( m \), per week \( w_t \) and the formula is:

\[ Z^{M^m,a}_{w_t, a} = \frac{Z^{M^m,a}(t)}{dt} \bigg|_{t=w_{k-1}} \]  \hspace{1cm} (4.6)

where \( Z^{M^m,a}(t) \) is the cumulative number of new infections at time \( t \) under maternal immunity model \( m \).
4.3 Parametrisation of the model

This section outlines the studies used to derive the prior distributions for the fitted parameters in the mathematical model.

4.3.1 Duration of immunity

It is unclear what the period of naturally-acquired immunity is for RSV, however, observational cohort studies suggest that reinfection is possible after 60 days and it is also reasonable to assume that some hosts are susceptible again at the start of an RSV season (on average 200 days later). Therefore, I assumed the prior distribution for the duration of protection of $N(130,35)$ so that the 95% CI corresponds with 60 and 200 days.

For duration of maternal protection, it has been shown that higher titres of RSV IgG neutralising antibodies in cord at birth causes i) a significant decrease in disease incidence during in the first 6 months of life and ii) a decrease in risk of hospital admission. Therefore, the duration of maternal protection is assumed to be no shorter than 14 days and no longer than 6 months, giving a prior of $U(14,180)$.

4.3.2 Duration of symptomatic infection

For the prior for the duration of the latency period ($1/\sigma$), an experimental challenge study was used to estimate the mean and standard deviation as 4.0 and 1.5 days respectively. Using the formula

$$\text{Gamma}\left(\frac{\mu^2}{s^2}, \frac{s^2}{\mu}\right)$$

(4.7)

where $\mu$ is the mean and $s^2$ is the variance, the fitted distribution for $1/\sigma$ is Gamma(7.111, 0.563). To ensure that the duration of infection decreased with repeated exposure, I found prior distributions for the duration of primary infection, $1/\gamma_0$, and the decrease in duration of infection relative to the previous infection, $g_i$ such that $\gamma_1 \equiv \gamma_0 (g_1)^{-1}$, $\gamma_2 \equiv \gamma_0 (g_1 g_2)^{-1}$, and $\gamma_3 \equiv \gamma_0 (g_1 g_2 g_3)^{-1}$. The mean and 95% confidence interval for primary and subsequent infection from a prospective cohort study were the convolution distributions: 5.1 (95% CI 4.2–6.2) + $U(0,7)$ and 4.0 (95% CI 3.3–4.9) + $U(0,7)$ respectively where the uniform distribution arises to account for left-censoring in weekly collection protocol. The empirical sample for the prior distributions for $1/\gamma_0$ is found by sampling from 5.1 (95% CI 4.2–6.2) + $U(0,7)$ and fitting the sample to a probability distribution. The method of
fitting an empirical sample to a probability distribution, I refer to as **Fitting procedure 1**:

**Fitting procedure 1** To fit an empirical distribution to a probability distribution the maximum likelihood method was used to estimate the parameters of the i) Gamma$(k, \theta)$, ii) LN$(\mu, \sigma)$, and iii) $W(\lambda, k)$, and choose the probability distribution with the highest likelihood.

**Fitting procedure 1** gives a probability distribution of $W(4.137, 8.303)$ for $1/\gamma_0$. For $g_1$ I divided the samples from 5.1 (95% CI 4.2–6.2) + $U(0, 7)$ by the samples from 4.0 (95% CI 3.3–4.9) + $U(0, 7)$ and used **Fitting Procedure 1** on the resulting sample to get a probability distribution of $W(34.224, 0.879)$ for $g_1$. For $g_2$, I used an experimental reinfection study to find a mean and standard deviation for $\gamma_2$ of 3.6 and 1.1 days respectively (Gamma(10.71, 0.34) from Equation 4.7). Dividing ordered samples from this distribution by the ordered empirical sample for $\gamma_0$ multiplied by $(g_1)^{-1}$ gives an empirical sample for the prior distribution for $g_2$ which, from **Fitting procedure 1**, has a probability distribution LN($-0.561, 0.163$). As there is no evidence to suggest the duration of infection decreases further after tertiary infection, $g_3 = 1$.

### 4.3.3 Susceptibility to infection

The prior distribution for the reduction in susceptibility to infection, $\delta_i$, assuming $i$ number of previous infections, is determined using two prospective cohort studies which estimated the average proportion of individuals who become infected when challenged with RSV for secondary, tertiary and subsequent infections, relative to their previous infection, as 0.757, 0.878 and 0.322 respectively (with sample sizes of 47, 26 and 19). Using the formula

$$B(\mu n, (1 - \mu)n)$$

where $\mu$ is the mean, and $n$ is the sample size, I estimated the probability distributions for these observations as $B(35.583, 11.417)$, $B(22.8293, 171)$ and $B(6.117, 12.882)$ for susceptibility to secondary and tertiary and subsequent infection, relative to previous infection.

### Asymptomatic infection

The proportion of infections which are asymptomatic is estimated from a prospective cohort study which showed, for ages <1, 1-4, 5-14, and 15 years and over, the mean prob-
ability of asymptomatic infection is 0.091, 0.173, 0.521, and 0.765, for the sample sizes is 33, 52, 73, and 47 respectively (giving $B(3.003, 29.997)$, $B(8.996, 43.004)$, $B(38.033, 34.967)$ and $B(35.955, 11.045)$ from the formula Equation 4.8). Though exiting studies have estimated the difference in viral load and the duration of shedding between asymptomatic and symptomatic infection, it is unclear how these differences alter the infectiousness of a host.\(^{17}\) Therefore, as there is no strong evidence otherwise, I assumed the prior distributions for $\alpha$ of $U(0, 1)$.

### 4.3.4 Transmission and initial parameters

Finally, as they cannot be estimated from epidemiological data, the prior distributions for the transmission probability per contact physical contact $q_p$, relative reduction in transmission due to conversational contact $q_c$, the relative seasonal amplitude $b_1$, the offset $\phi$ and the width of heightened transmissive season $\psi$ all have prior distributions of $U(0, 1)$. A summary of all the prior distributions described above associated with the mathematical model is given in Table 4.2.
CHAPTER 4. DEVELOPMENT OF A MODEL FOR RSV TRANSMISSION IN ENGLAND AND WALES

4.4 Calibration of the model

This section outlines the Metropolis-Hasting algorithm and the virological surveillance data used to calibrate the mathematical model.

4.4.1 Detection model

The virological surveillance data used to calibrate the mathematical model is the Respiratory DataMart System (RDMS). RDMS is a laboratory-based virological sentinel surveillance system, which systematically collects data on the number of RSV positive and negative clinical respiratory samples from 14 Public Health England (PHE) and National Health Service (NHS) laboratories in England and reports them weekly. These laboratories represent all 9 regions of England, however it does not have samples from Wales and it is not possible to determine the proportion of the population these samples cover. Though there are areas which these laboratories do not cover, I assume that these reported samples are representative of all of England and Wales. For the majority of laboratories, the source data is not available, and for those where it is, the majority of the samples are from hospital inpatients. From RDMS, I extracted the total number of weekly laboratory-confirmed cases of RSV from July 2010 and up until June 2017 for each age group. The number of positive samples for age group \( a \) and week number \( w_t \) is given by \( d_{a,w_t} \in D \), where \( D \) is the set of all samples.

Only a small proportion of the total RSV infections will be detected by the RDMS. This is because RSV infections which are included are only those in which the infected individual:

1. acquired infection in a region which is covered by the surveillance system
2. consulted healthcare at some clinical interface
3. the health care profession offering a test
4. the test is accurate in detecting the RSV virus

As severity of RSV infection depends on age, points 2) and 3) imply that the proportion of total RSV infections which are present in the RDMS is likely to be dependent on age. Therefore, I assumed that the per-infection detection probability by the RDMS surveillance system, \( \epsilon^a \), could be depende/textbfnt on age (note that \( Z_{w_t}^a \epsilon^a \approx d_{w_t}^a \)).
Due to lack of direct information for estimates of the detection probability I had to make several assumptions. First, I estimated an approximate value, \( \bar{\epsilon}^a \) by dividing the proportion of the population which are reported in the dataset \( p^a \) by an estimate for the attack rate in age group, \( r^a \) (Figure 4.5). The estimate for the attack rate is found from a prospective cohort study\(^{118} \) for children less than 5 years, and for individuals greater than 5 years I used the attack rate from the aforementioned prospective cohort study for the first year, under the assumption all infants are fully susceptibility, and multiplied it by the prior distribution for the relative reduction in susceptibility \( \delta_i \). The approximate values for the detection probability, \( \bar{\epsilon}^a = p^a / r^a \), are plotted in Figure 4.5. By defining the total number of positive samples for age group \( a \) per year from RDMS as \( D^a \), the weighted proportion of samples for each age group is given by \( w^a = D^a / \Sigma D_a \).

Assuming that each age group has a unique detection probability could over fit the model, however, using too few detection probabilities lead to a poorly fitted model. I

---

**Figure 4.5:** Top: Schematic showing the multiplicative relationship in age group \( a \) between the estimated attack rate \( r^a \), the detection probability \( \epsilon^a \), and the proportion of the population caught in the RDMS surveillance dataset, \( p^a \). Bottom: For each age group \( a \), this plot shows the estimated value for the detection probability \( \epsilon^a \), and the number of positive RSV samples from the RDMS dataset \( D^a \) which is proportional with the radius of the point marker.
chose the optimal number of age dependent detection rates by performing a formal model comparison using Akaike Information Criteria (AIC) to choose between 5 models which vary in the number of detection probabilities used between ages 0-4 years. The first age structure ($E^1$) assumed the same detection probability value for all 0–4 year olds. The second, third and fourth structures ($E^2, E^3$ and $E^4$) assumed that the 0–4 age groups is parameterised by 2, 3 and 4 different detection probabilities. To find the optimal age stratification for each of these three structures, I fitted the values of $\bar{\epsilon}^j$ to a discrete-valued function using a weighted least squares method (using the weights $w^j$) for all possible stratifications of this age group and then chose the age stratification with the smallest corresponding AIC. This method gave the optimal age stratifications of $\{0–2\text{mo},3\text{mo–}4\text{yrs}\}$, $\{0–2\text{mo}, 3–7\text{mo}, 8\text{mo–}4\text{yrs}\}$ and $\{0–2\text{mo}, 3–5\text{mo}, 6–11\text{mo,}1–4\text{yrs}\}$ for the three structures respectively. For the fifth structure, I assumed that the values of detection probability are parameterised according to an exponential decay $\exp(ax + b)$, where $a$ and $b$ are parameters be estimated.

For detection models $E^j, j = \{1,2,3,4\}$, the prior distribution for each of the detection probabilities $\epsilon^j$, were found by calculating the weighted mean and standard deviation of the estimated detection probabilities values $\bar{\epsilon}^j$ contained within the age range of the stratification and then fitting these moments (through Equation 4.7) to a Gamma distribution. For $E^5$, the detection probability for age group $j$, is given by fitting a non-linear weighted least squares with the exponential function of the form $\exp(ax + b)$ to the estimated detection probabilities values between 0 and 4 years. The mean and standard deviations of the parameters of the fitted exponential ($a$ and $b$) are then then assumed to follow a normal distribution. A summary of all the age stratifications and prior distributions for all five of the model structures are given in Table 4.3.
Parameter | Prior distribution | Source
--- | --- | ---
Detection model structure 1, $\mathcal{E}^1 = \{\epsilon_1, \epsilon_2, \epsilon_3\}$
$\epsilon_1$ | $0$–$4$ yrs | $\text{Gamma}(1.4278, 0.0050)$ | $\tau^a$

Detection model structure 2, $\mathcal{E}^2 = \{\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4\}$
$\epsilon_1$ | $0$–$2$ mo | $\text{Gamma}(10.9978, 0.0013)$ | $\tau^a$
$\epsilon_2$ | $3$–$8$ mo | $\text{Gamma}(11.9721, 0.00045)$ | $\tau^a$

Detection model structure 3, $\mathcal{E}^3 = \{\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5\}$
$\epsilon_1$ | $0$–$2$ mo | $\text{Gamma}(10.9978, 0.0013)$ | $\tau^a$
$\epsilon_2$ | $3$–$8$ mo | $\text{Gamma}(11.9721, 0.00045)$ | $\tau^a$
$\epsilon_3$ | $9$mo–$4$ yrs | $\text{Gamma}(2.16447, 0.00063)$ | $\tau^a$

Detection model structure 4, $\mathcal{E}^4 = \{\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6\}$
$\epsilon_1$ | $0$–$2$ mo | $\text{Gamma}(10.9978, 0.0013)$ | $\tau^a$
$\epsilon_2$ | $3$–$6$ mo | $\text{Gamma}(27.1392, 0.00024)$ | $\tau^a$
$\epsilon_3$ | $7$–$11$ mo | $\text{Gamma}(19.8873, 0.00018)$ | $\tau^a$
$\epsilon_4$ | $1$–$4$ yrs | $\text{Gamma}(7.64267, 0.00012)$ | $\tau^a$

Detection model structure 5, $\mathcal{E}^5 = \{\epsilon_1, \epsilon_2, \ldots, \epsilon_{17}, \epsilon_{18}\}$, $\epsilon_S = \exp(a + b \cdot j)$
$a$ | $0$–$4$ yrs | $\mathcal{N}(-3.9885, 0.1357)$ | $\tau^a$
$b$ | | $\mathcal{N}(-0.1794, 0.0413)$ | $\tau^a$

Common to all model structures, $|\mathcal{E}^k| = A_k$
$\epsilon_{S_{A_k-1}}$ | $5$–$54$ yrs | $\text{Gamma}(35.0678, 2.61628 \times 10^{-6})$ | $\tau^a$
$\epsilon_{S_{A_k}}$ | $55+$ yrs | $\text{Gamma}(59.2461, 2.28079 \times 10^{-6})$ | $\tau^a$

Table 4.3: Prior distributions for the parameters in the five detection models.

4.4.2 Calibration outline

I performed inference on the parameter set:

$$\theta^{m,e} = \mathcal{M}^m \cup \mathcal{E}^e$$

where $m \in \{1, 2\}$ and $e \in \{1, 2, 3, 4, 5\}$ are the possible maternal protection and detection model structures. For each model structure, the mathematical model estimated the number of new infections per week $Z_{a,w}$ and the detection model estimated the age-dependent probability of being reported in the RDMS dataset, $\epsilon^a$. I assume that year-to-year changes in the number of RSV positive samples are due to i) changes in sampling protocol, ii) hospital admission thresholds being lowered (particularly in the younger infants) and/or iii) failure to manage these acute illnesses in the community care setting. Therefore, to account for these year-to-year changes I normalise the number of RSV positive samples in age group $a$ during year $y$ relative to year 7 (2016–17) so that each year
has the same total number of positive samples in age group \( a \). Mathematically, for the number of positive samples \( d^a_{w_t} \) for age group \( a \) during week number \( w_t \), I define

\[
D^a_y = \sum_{t=1+52\times6(y-1)}^{52+52\times6(y-1)} d^a_{w_t}
\]  

(4.9)

Then, the normalised data \( \bar{d}^a_{w_t} \) during year \( y \), is given by

\[
\bar{d}^a_{w_t} = \frac{d^a_{w_t} D^a_y}{D^a_y}
\]  

(4.10)

By treating each infection in age group \( a \) as a Bernoulli trial, which has probability of success (being detected in the normalised RDMS dataset \( D \)) of \( \epsilon^a \), the likelihood function for the parameter set \((\theta^m,e)\) for week \( w_t \) and age group \( a \) is given by the binomial distribution \( \bar{d}^a_{w_t} \sim \text{Bin}(Z^{M^m,a}_{w_t}, \epsilon^a) \). Fitting the output for each age group over to seven years of weekly incidence data, the full likelihood is the product of each age and weekly binomial likelihood function:

\[
L(D|\theta^m,e) = L(D|M^m, \epsilon_e) = \prod_{a=1}^{25} \prod_{t=1}^{7\times52} \text{Bin}(Z^{M^m,a}_{w_t}, \epsilon^a)
\]

Using this likelihood and the prior distributions, the posterior distributions for the parameters in the model are determined using an adaptive parallel tempering Metropolis Hastings algorithm with a temperature ladder consisting of 12 chains and an adaptive covariance matrix. The proposal distribution was a multivariate truncated normal distribution \((TN)\), with the boundaries of the distributions equal to the support for each parameter. Thus, for each of the 12 chains, given a Markov chain of length, \( i \), \( \{\theta_t\}_{t=0} \) the equation of the acceptance probability of a new position, \( \theta' \sim TN(\theta_i, \Sigma_i) \) is

\[
a(\theta_i, \theta') = \frac{L(D|\theta') \mathcal{N}(\theta_i|\theta', \Sigma_i)}{L(D|\theta_i) \mathcal{N}(\theta'|\theta_i, \Sigma_i)}
\]  

(4.11)

Further details of the Metropolis Hastings algorithm are outlined in Supplementary material S2.1.

Model choice

To determine which of the model structures (maternal protection model \( m \) and detection model \( e \)) best estimates the incidence of RSV given the RDMS data, I calculated a Deviance Information Criterion (DIC) given by
$(4.12)$

where $L(D|\bar{\theta})$ is the likelihood of the mean of the posterior samples and $L(D|\theta)$ is the mean of the likelihood of the posteriors samples.

**Posterior distributions**

Each of the 12 Markov chains ran for 50,000 steps, where the first 25,000 steps were the burn-in and the final 25,000 steps were the empirical samples for the posterior distributions for each of the parameters. The final posterior samples were thinned every 20 steps, given an empirical sample of 1,250 values for the joint posterior distribution.

**Implementation**

The mathematical model ODEs were solved using the Euler method in Ascent package in C++, using a time step of 1 day over a 8 year period, (1 year to reach a steady state and 7 years to calculate the likelihood).

The binomial likelihood function leads to computationally unmanageable values, therefore I consider the log likelihood. The equation for the log likelihood function is therefore:

$$
\log L(D|\theta) \approx \begin{cases}
\sum_{a=1}^{25} \sum_{t=1}^{52 \times 7} -Z_{w_i} \epsilon^a, & \text{when } \bar{d}_i^a = 0 \\
\sum_{a=1}^{25} \sum_{t=1}^{52 \times 7} \bar{d}_i^a \log(Z_{w_i} \epsilon^j) - nZ_{w_i} \epsilon^j - \sum_{k=1}^{d_i^a} \log(k), & \text{when } \bar{d}_i^a > 0
\end{cases}
$$

and the acceptance probability can be calculated:

$$
a(\theta_i, \theta') = \exp(\log L(D|\theta') + \log(p(\theta')) - \log L(D|\theta_i) - \log(p(\theta_i))) + \log(TN(\theta_i|\theta', \Sigma_i) - TN(\theta'|\theta_i, \Sigma_i))
$$

Evaluating the correction constant is computationally difficult as it involves evaluating two points from multivariate truncated normal distributions in a high number of dimensions. Therefore, to evaluate a this term, I implemented a novel approach using an expected propagation method outlined in Cunningham et al.\textsuperscript{120}
4.5 Exemplar results

4.5.1 Model choice

Model comparison analyses (via DIC calculation) suggested that maternally-derived immunity in neonates was conferred seasonality according to the prevalence of recently infected pregnant women (Figure 4.6) with around 3% of neonates born into the maternally-derived protection group $M$, (i.e. are born with high levels of RSV neutralising antibodies) just prior to an epidemic in November, and 15% being born into the maternally-derived protection group $M$ at the end of an epidemic in March. Furthermore, I found that there is a likely exponential decrease in the reporting rates between the ages of 0–4 years, and fixed reporting rates for 5–54 years and 55 years and over. This is consistent with the assumption that it is rate of consulting healthcare due to RSV at clinical interface is likely to decrease with increasing age due to the reduction in the severity of infection and changes in parental concern. The corresponding values for $p_R$ and the detection probabilities are given in (Figure 4.8). The results which follow this section all refer to this model choice.

![Figure 4.6: DIC for the 5 detection model structures, and the 2 maternal immunity model structures. Best fitting model is the exponential detection model ($E^5$) with the dynamic maternal immunity model ($M^2$).](image-url)
CHAPTER 4. DEVELOPMENT OF A MODEL FOR RSV TRANSMISSION IN ENGLAND AND WALES

Figure 4.7: Top: The proportion of infants born with protection ($p_R$) over an epidemic season for the dynamic maternal immunity model. Bottom: A comparison of the posterior distributions for the detection model, $E^5$, where black points indicates the mean values and the red points indicated the lower and upper credible intervals.

4.5.2 Model fit

The calibrated model is able to reproduce the age and seasonal distribution of RSV incidence in England and Wales. A comparison between the model-predicted number of detected samples ($Z_{ij}, e^j$) and the annual number of positive samples from RDMS ($d_{w1}$) for each age group is shown (Figure 4.8-4.9). It is worth noting that there is not an even number of samples in each age groups, and although age groups 10 month, 11 months, and 2 years seem to fit poorly, they only amount to 5% of the total samples.
Figure 4.8: A comparison between the model-predicted number of detected samples during week $t$, $(Z^a_{w_t} e^z$, red line), estimated from averaging 1,000 samples from the posterior distribution during the third year of simulation, and the annual number of positive samples from RDMS ($d^a_{w_t}$, black dots) for age group $a$. 
As the force of infection is dependent on the number of infected persons in each age group, I can monitor its value over a season and determine what percentage of its value is attributable to each age group (Figure 4.10). This analysis finds that adults aged 15-64 years are the major source of infection for each age group, ranging from 37% in 5-14 year-olds and 71% in 15–44 year-olds. Infections which are attributable to parental contacts is commensurate to the proportion of parents, except in <1-year-olds where parents account for 65% of the infections acquired from 15-44 year olds. In addition, for children aged 5-14, other children of the same age account for the majority of infection (52%) suggesting a large amount of transmission occurs from within this age group.

Figure 4.9: The mean annual incidence of RSV per 100,000 persons (black line) with 95%Cr I (red region). The average number of contacts made per day for each age group shown in gray bars.
CHAPTER 4. DEVELOPMENT OF A MODEL FOR RSV TRANSMISSION IN ENGLAND AND WALES

Demographic group

<1 1–4 5–14 15–44 (non-mat)
15–44 (mat)
45–64 65+

Proportion of force of infection

0.0 0.2 0.4 0.6 0.8 1.0
<1 1–4 5–14 15–44 15–44 (mothers) 15–44 (non-mothers) 5–14 1–4 <1

Figure 4.10: Top: the source of the infection for each age group in the analysis. Bottom: The magnitude of the force of infection relative to age group 1. The force of infection for both Figures was estimated using the third year of simulation.

4.5.3 Posterior distributions

Using the calibration method, I was able to estimate parameters that have been difficult to evaluate directly from epidemiological studies. I estimated the average duration of maternal immunity and post-infection immunity as 134 days (95% CrI 120–146) and 359 days (95% CI 351–365), respectively and that asymptomatic infections are 63% (95% CrI 54%–72%) as infectious as symptomatic infections Figure 4.11–4.12. The duration of infections, duration of latency period and the relative susceptibility to infection corresponding with literature and are similar to the proposed prior distribution.
Model parameters ($\mathcal{M}^2, \mathcal{E}^5$)

Figure 4.11: Smooth histogram plots comparing the prior (gray) and the posterior (red) distributions for each of the inferred parameters.
Figure 4.12: Box and whisker plots of the posterior distributions for some of the model parameters. The whiskers represent the posterior range, the box is the interquartile range, and the horizontal line is the mean.
4.5.4 Estimated burden

The model predicts that between 68-81% of infants experience an RSV infection in their first year of life, with subsequent infection risk generally decreasing with age (Figure 4.13). Deviations away from this decreasing trend occur in age groups which have the highest number of daily contacts.

![Figure 4.13: The mean annual incidence of RSV per 100,000 persons (black line) with 95% Cr I (red region). The average number of contacts made per day for each age group shown in gray bars.](image-url)
4.6 Discussion

This chapter outlines the design, parametrisation, and fitting to available RSV data of a novel mathematical model for RSV transmission. The novelty of this mathematical model is the exploration of the hypothesis that maternal protection to new-borns is seasonal, contrary to the routine assumption in previous models in which all babies are born with protection to RSV. Epidemiological evidence for seasonal changes in maternal protection has also been provided in studies looking at seasonal changes in RSV-specific antibody level from cord titres at birth. As cord titre influences the rate of severe infections in the first year of life, seasonal changes could indicate temporal vulnerability in the infant population. The model also tested the hypothesis that detection of positive samples in infants less than 5 years of age is lost exponentially, contrary to the assumption that detection rates are fixed across age groups. The DIC analysis suggests that age-dependent factors which make up the detection probability decrease exponentially with age, which could be possibly due to the significant increase in disease severity in these age groups and parental concern for ill new-borns.

The posteriors distribution for the immunity parameters suggest that the average duration of maternal immunity is 132 days (95% CrI 118–146) or around four months. This duration is similar to observations from epidemiological studies, which show that heightened maternally-derived RSV neutralising IgG levels in infants can provide protection from infection for between four to six months. The posterior distribution for the average duration of naturally acquired protection is longer than suggested in experimental reinfection studies at 361 days (95% CrI 350–365) (implying around 40% of persons at the start of the season still have protection to RSV). This implies than 15%, 40% and 64% of person are susceptible after 2 months, 6 months and 12 months respectively. The discrepancy between the model estimated value and the experimental reinfection studies, which suggest frequent reinfection is common around 6 months, could be due to the increase in the probability of successful infection that comes from virological challenge in comparison to natural exposure to RSV. The estimated burden is also higher than suggested in a Kenyan study which looks at serological prevalence of RSV infection over a number of years. However, these difference could be explained by a number of factors. First, there is a difference in the epidemiology of RSV in Kenya and England and Wales, (e.g. Kenya has irregular and aperiodic epidemic peaks, primary infection occurs later) which makes it
difficult to compare incidence rates.\textsuperscript{121} Second, the study design of the Kenya study was very small, and it only tested for RSV strain A, and not RSV strain B, which are known to co-circulate in Kenya, therefore perhaps under reporting the true burden.\textsuperscript{4}

There are limitations in the epidemiological studies used to estimate the contact matrices and the attack rate. First, the POLYMOD survey,\textsuperscript{113} which was used to estimate the average number of daily contacts for persons over 1 years of age in the UK, is over ten years old, and there is emerging evidence which suggests that social contact patterns have changed in this time.\textsuperscript{122} These studies are still too small to fit large epidemic models such as the one presented in this chapter, but refitting the model to more recent contact matrices in the future may more accurately capture the current transmission dynamics of RSV. The epidemiological study used to estimate the attack rate, which was used to estimate the prior distribution rate for the detection probability, is also very old (over 40 years). The significant difference between the prior and posterior distributions for the detection probability suggests that the observations in this old epidemiological do not translate to recent times. More recent UK-specific prospective cohort studies would provide better estimates for the attack rate and improve the accuracy of prior distributions for the detection probability.

In the next chapter I will adapt the model to estimate the impact of potential intervention programmes. I will do this by comparing the projections of incidence from the yet-to-be described adapted model to the model projections in this chapter. By using this mathematical model of RSV transmission to evaluate the impact of potential intervention programmes, the direct and indirect effects of potential vaccination programmes can be properly quantified.
Chapter 5

Evaluating the impact of potential intervention programmes

5.1 Introduction

In the previous chapter I outlined the mathematical model for RSV transmissions and fitted it to historic RSV incidence data in England and Wales. In this chapter I adapt the model to evaluate the impact of potential intervention programmes at reducing RSV burden. I evaluated interventions programmes based on the RSV vaccines and monoclonal antibodies that are currently under development as outlined in Chapter 3. These intervention programmes are evaluated by modifying the existing transmission model in various ways. First, including stratification by clinical-risk group for infants less than one years of age, allowing intervention programmes which are aimed at different risk groups to be evaluated. Second, to properly evaluate the indirect protection which occurs from maternal vaccination, I consider stratification by family structure. Finally, I include additional compartments in order to model the immune dynamics associated with vaccines and monoclonal antibodies. By making these modifications and evaluating the model dynamically, I determine the number of cases averted per age and clinical-risk group for each intervention programme.

The impact is measured in terms of clinical outcomes associated with RSV disease, including symptomatic cases, hospital admission, deaths, GP consultations and number of hospital bed days averted across the whole population. These outcomes were chosen outcomes because both the age and risk-group specific QALY loss an the cost (in GBP) can be readily obtained. In addition, they also allow for a deeper understanding of intervention-
induced changes in transmission dynamics and the consequential direct and indirect effects on alleviating health-care outcomes across the population.

5.2 Adaptation of the model to incorporate intervention programmes

A summary of the adaptations made to the mathematical model to evaluate the intervention strategies is given in Table 5.2, the parameters associated with the intervention programmes are given in Table 5.1 and the equations of the adapted mathematical model are given in Supplementary material S3.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Fitted distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palivizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay between administration and protection</td>
<td>Immediate (fixed)</td>
<td>—</td>
<td>123</td>
</tr>
<tr>
<td>and protection (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average period of protection</td>
<td>150 (fixed)</td>
<td>—</td>
<td>123</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy on VHR infants (%)</td>
<td>33.8 (95% CI 0.0–66.6)</td>
<td>Gamma(3.7623, 0.08983)</td>
<td>23</td>
</tr>
<tr>
<td>Long-lasting mABs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay between administration and protection</td>
<td>Immediate (fixed)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>and protection (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average period of protection</td>
<td>250 (fixed)</td>
<td>—</td>
<td>38</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy against symptomatic infection (%)</td>
<td>70.1 (95% CI 52.3–81.0)</td>
<td>W(11.898, 0.732)</td>
<td>124</td>
</tr>
<tr>
<td>Efficacy hospitalised case</td>
<td>78.4% (95% CI 51.9–90.3)</td>
<td>W(11.611, 0.819)</td>
<td>124</td>
</tr>
<tr>
<td>Infant/childhood/elderly vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay between administration and protection</td>
<td>11.4 days (95% CI 2.8–22.1)</td>
<td>W(2.42, 12.87)</td>
<td>125</td>
</tr>
<tr>
<td>and protection (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of protection (days)</td>
<td>Same as post-infection immunity</td>
<td>See posterior</td>
<td>125</td>
</tr>
<tr>
<td>(1/\omega)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy against all infections (%)</td>
<td>83.0 (95% CI 75.0–88.0)</td>
<td>W(31.464, 0.845)</td>
<td>125</td>
</tr>
<tr>
<td>Novavax vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Period of protection (days)</td>
<td>Same as protected neonates (1/\xi)</td>
<td>See posterior</td>
<td>40</td>
</tr>
<tr>
<td>Efficacy against symptomatic infection (%)</td>
<td>41.4 (95% CI 4.1–64.2)</td>
<td>W(3.327, 0.461)</td>
<td>40</td>
</tr>
<tr>
<td>Efficacy against hospitalisations</td>
<td>53.5 (95% CI 23.0–71.9)</td>
<td>W(5.354, 0.58)</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 5.1: Description of the parameters associated with the prophylactics used in the intervention model.
### Chapter 5. Evaluating the Impact of Potential Intervention Programmes

<table>
<thead>
<tr>
<th>Intervention strategy</th>
<th>Further stratification</th>
<th>Additional compartments</th>
<th>Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current programme (Palivizumab)</td>
<td>0-8 month olds according to whether they are eligible for Palivizumab or not</td>
<td>$V_P$, protected due to Palivizumab</td>
<td>$S \rightarrow V_P$ instantly. $V_P \rightarrow S$ at rate $\omega_{pal}$</td>
</tr>
<tr>
<td>Long-acting monoclonal antibodies</td>
<td>i) 0-8 month olds according to whether they are eligible for Palivizumab. ii) 0-11 month olds according to whether they are high-risk or not high-risk</td>
<td>$V_M$, protected due to long-acting monoclonal antibodies</td>
<td>$S \rightarrow V_M$ instantly. $V_M \rightarrow S$ at rate $\omega_{mab}$</td>
</tr>
<tr>
<td>Infant, childhood and elderly vaccination</td>
<td>None.</td>
<td>None.</td>
<td>$S \rightarrow R$ takes on average 11.4 days. $R \rightarrow S$ at rate $\omega$</td>
</tr>
<tr>
<td>Maternal vaccination</td>
<td>15-44 year olds by parental status (not a parent $n$ or parent $p$) and infants and parents by whether they in programme c.</td>
<td>None.</td>
<td>Immunity from vaccination of pregnant women is same as immunity from vaccination of the elderly. Immunity in neonates assume all in c are born with protection (in group $M$).</td>
</tr>
</tbody>
</table>

**Table 5.2:** Summary of the adaptations made to the mathematical model to evaluate the intervention programmes
5.2.1 Current intervention programme (Palivizumab)

In order to evaluate the impact of the Palivizumab programme I stratified the infants aged between 0-8 months according to whether they are Palivizumab eligible (VHR) or not (indicated by the superscript, \( r \)). To estimate the proportion of infants who are eligible for Palivizumab in age group \( a \) \((p^{a,VHR})\), I first estimated the number of infants who receive Palivizumab per season in England from the number of Palivizumab units sold.\(^{126}\) I assumed this value is equal to the prevalence of infants who are eligible for Palivizumab in England and Wales. As the eligibility criteria for Palivizumab depends on age group \( a \) the start of the RSV season and on gestational age, I determined the proportion of infants, per gestational age, born with Chronic Lung Disease (CLD) and Chronic Heart Disease (CHD) using data from USA.\(^{127,128,36}\) This gives an estimate for the proportion of Palivizumab eligible persons of 0.00348, 0.00227 for infants aged < 1 and 1 month of age, 0.00066 for infants aged 2-5 months, 0.00002 for infants aged 5-8 months and zero otherwise. For these VHR infants, I assumed that 90% receive Palivizumab during the months of October of February inclusive (totalling 2128 courses), with 33.8% of these acquiring immediate protection which lasts for an average of \( 1/\omega_{\text{pal}} = 150 \) days, after which these individuals return to the primary susceptible compartment (\( S_0 \), Figure 5.1).\(^{123}\) I compare this status quo to the following three alternative intervention strategies.
Figure 5.1: The relationship between the state variables ($V_P$: protected due to Palivizumab antibodies) used in the Palivizumab intervention model. For Palivizumab the parameters are $\mu$, the birth rate, $p_R$ the proportion of infants born with protection due to maternal immunity, and $\phi_{P,pal}^{a,r}$ the proportion of infants in age group $a$, clinical risk group $r$ who are newly protected by Palivizumab at time $t$. The left schematic shows the rate of change between epidemiological groups when Palivizumab is administered at birth. The right schematic shows the rate of change between epidemiological groups when Palivizumab is given other age group. The rate of loss of immunity is given by $\omega_{pal}$ and shown by the dashed line. Rate of loss of maternal protection occurs at rate $\xi$ and is shown by a solid line.

5.2.2 Intervention strategy 1: Long-acting monoclonal antibodies

The first intervention strategy I consider is long-acting monoclonal antibodies. To evaluate this intervention strategy, I tracked the number of infants protected by long-acting monoclonal antibodies, $V_M$, who remain protected after birth for an average of $1/\omega_{mab} = 250$ days after which they return to $S_0$ (Figure 5.2). However, I relaxed this assumption in an uncertainty analysis. In order to evaluate the impact of long-acting monoclonal antibodies intervention programmes aimed at infants in different clinical risk groups, I stratified the infant population into demographic groups according to their clinical-risk status i) Palivizumab-eligible (VHR), ii) high-risk (HR), and neither (NR) (indicated by the superscript $r$). To estimate the proportion of infants who are high-risk, I assume the prevalence is 3.8% across each monthly age group up to 11 months. I evaluated three seasonal programmes that administer a single dose of long-acting monoclonal antibodies at birth i) to those who are currently eligible for Palivizumab (MAB-VHR-S), ii) to both VHR infants and HR infants (MAB-HR-S), iii) to all infants regardless of risk (MAB-ALL-S). I evaluated two additional seasonal programmes that extend administration (iv) to all VHR and HR infants under six months (MAB-HR-S+) and v) to all infants under
six months (MAB-ALL-S+) throughout October only\textsuperscript{33} I assume that these programmes would replace the existing Palivizumab programme; that they all achieve the same coverage as Palivizumab and that the efficacy per course is 70.1\% (95\% Confidence Interval (CI) 52.3–81.0\%).\textsuperscript{38,124} The monoclonal antibody programmes considered are summarised in Table 5.3.
<table>
<thead>
<tr>
<th>Intervention programme name</th>
<th>Prophylactic(s)</th>
<th>Eligible population</th>
<th>Window of administration</th>
<th>Coverage</th>
<th>Annual number of courses</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAB-VHR</td>
<td>La-mAB</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>11,679</td>
<td>Palivizumab</td>
</tr>
<tr>
<td>MAB-HR-S</td>
<td>La-mAB</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>MAB-VHR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR neonates</td>
<td>October-February</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAB-HR-S+</td>
<td>La-mAB</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>22,907</td>
<td>MAB-VHR</td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR neonates</td>
<td>October-February</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR 1-5 months</td>
<td>September-October</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAB-ALL-S</td>
<td>La-mAB</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>252,581</td>
<td>MAB-HR-S+</td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR and HR neonates</td>
<td>October-February</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAB-ALL-S+</td>
<td>La-mAB</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>547,818</td>
<td>MAB-ALL-S</td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR and HR neonates</td>
<td>October-February</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>La-mAB</td>
<td>HR and HR 1-5 months</td>
<td>September-October</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.3:** Summary of the characteristics of the intervention programmes which use long-acting monoclonal antibodies. La-mAB: Long-acting monoclonal antibodies
Figure 5.2: The relationship between the state variables ($V_M$: protected due to long-acting monoclonal antibodies) used in the long-acting monoclonal antibodies intervention model. For long-acting monoclonal antibodies the parameters are $\mu$, the birth rate, $p_R$ the proportion of infants born with protection due to maternal immunity, and $\phi_{P,mab}^a,r$ the proportion of infants in age group $a$, clinical risk group $r$ who are newly protected by long-acting monoclonal antibodies at time $t$. The left schematic shows the rate of change between epidemiological groups when monoclonal antibodies are administered at birth. The right schematic shows the rate of change between epidemiological groups when long-acting monoclonal antibodies are given other age group. The rate of loss of immunity is given by $\omega_{mab}$ and shown by the dashed line. Rate of loss of maternal protection occurs at rate $\xi$ and is shown by a solid line.

5.2.3 Intervention strategy 2: Infant, childhood and elderly vaccination

The second intervention strategy I consider is vaccination. To evaluate this intervention strategy, I assumed that a single dose of a vaccine conferred the same protection as that of a natural infection, such that 83.0% (95% CI 75.0–88.0%) of vaccinated individuals in the $i$th previous infection group who are susceptible ($S_i$) are moved to respective recovered group ($R_i$) after a delay reflect the build up of antibody immunity (Figure 5.3).125 I considered two vaccination programmes aimed at infants aged 2 months old; one administered seasonally (VAC-INF-S) and one year-round (VAC-INF-A), both achieving a coverage of 90%, consistent with the DTaP/IPV/Hib/HepB/PCV/Rota primary series vaccination coverage in England. I also considered two seasonal vaccination programmes aimed at elderly persons: one for those aged 75 years and older (VAC-75-S) and one for those aged 65 years and older (VAC-65-S), both achieving a coverage of 70%, consistent with vaccination coverage for the elderly influenza vaccine programme.129,130 Finally, I considered three seasonal programmes aimed at preschool children (aged 2–4 years, VAC-2-4-S) and school-age children (aged 5–9 years, VAC-5-9-S, and aged 5–14 years, VAC-5-14-S), that achieve
a coverage of 45% and 60% respectively, consistent with the live attenuated influenza vaccination programme in England.\textsuperscript{130} I assumed that all these vaccine programmes would be administered in addition to the existing Palivizumab programme in the UK. The infant, childhood, and elderly intervention programmes considered are given in Table 5.4.
<table>
<thead>
<tr>
<th>Intervention programme name</th>
<th>Prophylactic(s)</th>
<th>Eligible population</th>
<th>Window of administration</th>
<th>Coverage of eligible population</th>
<th>Annual number of courses</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAC-INF-S</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>Palivizumab</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>2-month-olds</td>
<td>September-January</td>
<td>90%</td>
<td>251,162</td>
<td></td>
</tr>
<tr>
<td>VAC-INF-A</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-INF-S</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>2-month-olds</td>
<td>Year-round</td>
<td>90%</td>
<td>617,724</td>
<td></td>
</tr>
<tr>
<td>VAC-2–4</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-INF-A</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>2–4 year olds</td>
<td>October-February</td>
<td>45%</td>
<td>917,008</td>
<td></td>
</tr>
<tr>
<td>VAC-5–9</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-2–4</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>5–9 year olds</td>
<td>October-February</td>
<td>60%</td>
<td>2,046,820</td>
<td></td>
</tr>
<tr>
<td>VAC-5–14</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-5–9</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>5–14 year olds</td>
<td>August-December</td>
<td>60%</td>
<td>4,093,640</td>
<td></td>
</tr>
<tr>
<td>VAC-75+</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-5–14</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>75+ year olds</td>
<td>November-March</td>
<td>70%</td>
<td>5,495,680</td>
<td></td>
</tr>
<tr>
<td>VAC-65+</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>VAC-75+</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>65+ year olds</td>
<td>November-March</td>
<td>70%</td>
<td>10,281,800</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4: Summary of the characteristics of the intervention programmes which use vaccines.
5.2.4 Intervention strategy 3: Maternal vaccine programmes

The third intervention strategy I consider is vaccination of pregnant women. To evaluate the indirect effects of maternal vaccination while maintaining computational tractability and epidemiological realism, I used a previously published method for evaluating the impact of parental vaccination. In brief, this method tracks the number of mothers of infants less than one year of age, and the number of these women who are participating in a maternal vaccination programme (Figure 5.4). The proportion of persons in age group $a$ who are mothers with an infant less than 1 years of age, $u^a$, was calculated by multiplying the total number of infants less than 1 by the age-specific proportion of births by parental age $u^a_p$ ($u^a_p$ is non-zero for $a = 19, 20$ and 21 only). This gives proportions of 0.0175, 0.0601, and 0.0233 for 15–24, 25–34, and 35–44 years respectively. The proportion of mothers who are in the programme is given by $\phi_c = 0.6$. I define, $u^{a,p} = u^a(1 - \phi_c)$, $u^{a,c} = u^a\phi_c$ and $u^{a,n} = (1 - u^a)$.

<table>
<thead>
<tr>
<th>Superscript</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>Infants less than 1 years of age and who are not participating in the maternal vaccination programmes and adults who are not mothers who have given birth in the last year</td>
</tr>
<tr>
<td>$p$</td>
<td>Mothers who have given birth in the last year who are not in the maternal vaccine programme</td>
</tr>
<tr>
<td>$c$</td>
<td>Mothers who have given birth in the last year and are in the maternal vaccine programme and the newly born infant.</td>
</tr>
</tbody>
</table>

Table 5.5: Summary of the maternal vaccine-related states.
of the POLYMOD study.\textsuperscript{113} Accordingly, the force of infection between mothers and their infants is updated to reflect the vaccination status of the mother. I assume that the vaccinated mothers are themselves temporarily protected from infection consistent with the protection afforded by the childhood/elderly vaccination assumptions above. To evaluate the direct effect on infants of vaccinating pregnant women, I used the results of the previously mentioned Novavax’s maternal vaccine Prepare Trial which found 41.4\% (95\% CI 4.1–64.2) of infants born to these mothers are protected against hospitalisation for the first 3 months of life.\textsuperscript{40} Consistent with the trial, I assume pregnant women are vaccinated at any point between 28 and 32 weeks gestation. I considered two maternal vaccination programmes (Table 5.6), which are given in combination with the existing Palivizumab programme: a seasonal programme (MAT-S), and one administered year-round, (MAT-A) with a coverage of 60\% as observed for prepartum Tdap vaccination in England.\textsuperscript{40,130} I chose to use the vaccination coverage for prepartum Tdap, instead of Influenza maternally vaccine which is lower (around 40\% coverage), as the primary motivation behind both the prepartum Tdap vaccination programme and the RSV vaccination programme is to protect the unborn child from severe disease.\textsuperscript{130} For Influenza, the perception of pregnant women is that the primary motivation for Influenza vaccine is to protect the health of the mother rather than the unborn child.\textsuperscript{133} It has been hypothesised that the differences in perception between the primary motivation for Influenza and Pertussis is one of the reasons for the observed differences in coverage levels.\textsuperscript{134}
<table>
<thead>
<tr>
<th>Intervention programme name</th>
<th>Prophylactic(s)</th>
<th>Eligible population</th>
<th>Window of administration</th>
<th>Coverage of eligible population</th>
<th>Annual number of courses</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAT-S</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>August-December</td>
<td>90%</td>
<td>2,128</td>
<td>Palivizumab</td>
</tr>
<tr>
<td></td>
<td>Maternal vaccine</td>
<td>Pregnant women 28-32 weeks gestational age</td>
<td>October-February</td>
<td>60%</td>
<td>165,257</td>
<td></td>
</tr>
<tr>
<td>MAT-A</td>
<td>Palivizumab</td>
<td>VHR infants</td>
<td>October-February</td>
<td>90%</td>
<td>2,128</td>
<td>MAT-S</td>
</tr>
<tr>
<td></td>
<td>Maternal vaccine</td>
<td>Pregnant women 28-32 weeks gestational age</td>
<td>Year-round</td>
<td>60%</td>
<td>406,442</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.6:** Summary of the characteristics of the intervention programmes which use maternal-vaccines
Maternal vaccination

0–11mo
(1 ≤ j ≤ 12)

1–14yrs
(12 ≤ j ≤ 18)

15–44yrs
(19 ≤ j ≤ 21)

45+yrs
(22 ≤ j ≤ 25)

Mothers
(p)

Not protected

or mothers
(n)

Protected
(c)

μ(1−ϕc)

μϕc

Nj,n

Nj

Nj,p

Nj,c

Figure 5.4: The relationship between maternal vaccine groups in the maternal vaccine intervention model. The parameters are the birth rate, μ, and the proportion of women who are newly mothers included in the programme ϕc. The model ensure that all infants born to vaccinated women are protection (all into group M), otherwise they are born according to the dynamic maternal immunity assumption.
5.2.5 Optimising seasonal administration

To allow an unbiased comparison of the seasonal programmes, our framework assumes the programmes are given continuously for five months. For programmes that administer Palivizumab and long-acting monoclonal antibodies, I assume administration occurs during the Palivizumab-recommended time period of October to February. To determine the period of administration for the remaining intervention programmes, I chose the five-month period that resulted in the largest QALY gain relative to status quo (see Chapter 6 for details on calculation of the QALY gain).

5.2.6 Clinical outcomes

For each intervention programme the impact will be quantified by the reduction in five different clinical outcomes; symptomatic infection, GP consultations, hospital bed days, symptomatic infections, hospitalisations and deaths. To achieve this, I estimate a age and clinical-risk group specific probability of each outcome occurring per infection, by dividing the estimated annual incidence for each RSV-related outcome by the estimated annual incidence of RSV infection. The number of symptomatic cases averted is estimated directly from the transmission model for Palivizumab (i.e. the posteriors for $p_a$). The annual incidence for each RSV-related outcome is estimated by synthesis of all existing epidemiological evidence on RSV burden in England and Wales.

5.3 Comparing the impact of different intervention programmes

5.3.1 Estimating annual incidence of outcomes

I estimated the annual incidence of five different RSV-related outcomes (symptomatic infection, GP consultations, hospital bed days, symptomatic infections, hospitalisations and deaths) under the existing Palivizumab programme by synthesising recent incidence estimates for RSV outcomes in England. The number of symptomatic cases averted is estimated directly from the transmission model for Palivizumab (i.e. the posteriors for $p_a$). The incidence of GP consultations and deaths are age-dependent and estimated from three sources for each age category: 0–4 years of age, 5–54 years and 55 years and over. For hospital admissions and number of bed days, the incidence was dependent on age and clinical risk status. Reeves et al. gives the estimated number of hospital bed days and hospital admissions for high-risk (HR) and not-at-risk (NR) infants up to
11 months of age. For the individuals aged 1-4 years and 5-14 years (which are NR), the number of hospital admissions is estimated from Reeves et al. 2017, and Taylor et al. and the number of bed days per hospitalisation is 2 days. For persons aged 15-64 years and 65+ years, I used Fleming et al. and data from PHE and assuming the average number of bed days per hospitalisations is 3 days. For all the studies highlighted above, the mean $\mu$ and 95% CI $(c_l, c_u)$ are given, therefore, I fit a probability distribution using

**Fitting procedure 2:**

**Fitting procedure 2** If CI are symmetric: $|(c_u - \mu)| = |(c_l - \mu)|$: The fitted distribution is $N(\mu, (c_u - \mu)/2)$. If CI are non-symmetric: $|(c_u - \mu)| \neq |(c_l - \mu)|$: By choosing the parametric distributions, $\mathcal{X} = \{Gamma(\alpha, \mu/\alpha), \mathcal{LN}(\log(u), \sigma), Weibull(a, \mu(1 + 1/a)^{-1})\}$, (chosen such that $\forall X \in \mathcal{X}$, $E[X] = \mu$), the fitted parameters are found by solving the non-linear equation $\forall \theta \in \Theta = \{\alpha, \mu, a\}$

$$\int_{c_l}^{c_u} p_\theta(x)dx - 0.95 = 0$$

(5.1)

to find the fitted values $\tilde{\theta}$. I choose the uncertainty according to the distribution whose fitted parameter, $\tilde{\theta}$ minimising the cost function

$$\lambda(\tilde{\theta}) = (P_\tilde{\theta}(c_l) - 0.025)^2 + (P_\tilde{\theta}(c_u) - 0.975)^2$$

(5.2)

A summary of age-specific annual incidence rates for GP consultations, hospital admissions, number of bed days and deaths is given in **Figure 5.5** and **Figure 5.6**.
CHAPTER 5. EVALUATING THE IMPACT OF POTENTIAL INTERVENTION PROGRAMMES

Figure 5.5: Estimated annual incidence of GP consultations (top left), deaths (top right), hospital admission (bottom left) and number of bed days (bottom right) per 100,000 persons in each age group (x-axis) and clinical risk group.

Figure 5.6: Estimate annual incidence for each of the outcomes by age group.

5.3.2 Per-infection probability of each outcome

The results of dividing the estimated annual incidence of each outcome by the estimated annual incidence of RSV is given in Figure 5.7. The average probability of consulting a GP due to RSV infection is highest in children less than 5 years of age (0.006–0.065) and adults 65 years and older (0.103–0.132). The average probability of death per-infection
is highest in adults over 75 years (0.002) and rare in children and other adults in the remaining age groups (less than 3 in every 100,000 infections). The average probability of hospitalisation is highest in infants below 1 year of age (0.010–0.097), with peak risk occurring at 1 month of age, and lowest risk in persons aged 5-45 years of age (less than one in every 10,000 infections). HR and VHR infants have an increased risk of hospitalisation of 0.0138–0.129– and 0.14–0.37 respectively, compared with other infants (0.010–0.097). Similarly, the average number of bed days experienced per hospitalisation is greatest in infants less than 1 year of age (1–5) with the longest stays occurring at 1 month of age, and HR and VHR infants seeing an increase in the number of bed days of 5–7 and 8–25 respectively.
5.3.3 Determining start date of administration for seasonal programmes

As the incidence of RSV is seasonal in England and Wales, and the protection afforded by the prophylactics is temporary, then the effectiveness of the intervention programmes depends on the timing of administration. For example, vaccination programmes which start in March will afford protection to individuals during a period when RSV is not circulating, and may lose their protection by time the peak incidence occurs in December. In contrast, vaccination programmes given in October will afford the protection to individuals when the incidence of RSV is highest, making them more effective. To quantify
impact of timing on the effectiveness of seasonal intervention programmes, I measured the impact, in terms of discounted QALY loss, of starting each the seasonal intervention programmes at various start dates. The results of this analysis, and the optimal timings for the seasonal programmes (i.e. the lowest QALY loss) are summarised in Figure 5.8.

Figure 5.8: The total discount QALY loss over ten years when a seasonal programme starts administration on the month given on the x-axis.

5.3.4 Impact of intervention programmes

Long-acting monoclonal antibodies

The seasonal programmes aimed at VHR infants or VHR and HR infants (MAB-VHR-S and MAB-HR-S, respectively) are the most efficient long-acting monoclonal antibodies
programmes at preventing RSV hospitalisations, preventing 51 (95% CrI 43–55) and 36 (95% CrI 30–39) hospital cases per 1,000 administered courses and also RSV-related bed days preventing 162 (95% CrI 133–162) and 225 (95% CrI 211–243) hospital bed days cases per 1,000 administered courses. For GP consultations, these programmes prevent 34 (95% CrI 30–37) and 47 (95% CrI 44–50) consultations per 1,000 courses given, a similar amount to hospitalised cases. These intervention programmes are not effective in raising the median age of primary infection or at preventing deaths (Figure 5.11).

Childhood/elderly vaccination

I found that to maximise the health benefit of the seasonal vaccination programmes, the optimal period of administration is between November and March for elderly programmes, October to February for the VAC-2-4-S and VAC-5-9-S programmes, and August to December for the VAC-5-14-S programme. Vaccinating individuals 65 years and over is the most effective programme at preventing the total number of GP consultations, hospitals, bed days and deaths (23%, 25%, 26% and 49% reductions respectively) (Figure 5.9). However, the large size of the target group means this programme is inefficient, preventing 19.03, 1.63, 4.34, and 0.25 cases of GP consultations, hospitals, bed days and deaths respectively per 1,000 vaccine courses. The most effective school-age programme is the 5–14 year old programme, preventing 4.5% (95% CrI 3.9–5.4) of hospitalised cases, 4.9% (95% CrI 4.2–5.7) of bed days and 9.2% (95% CrI 8.4—10.9) of GP consultations. School-age programmes confer considerable herd protection, with 91.5% of the 5-9 year old programme and 94.9% of 5-14 year old programme of averted hospitalised cases due to indirect protection.

Maternal vaccination

Our results suggest that, to maximise the health benefit for a seasonal third trimester maternal programme, the optimal period of administration is from August until December (Figure 5.8). Such a programme prevents 8.5 (95% CrI 7.4–10.3) hospitalised cases and 29 (95% CrI 22–37) bed days per 1,000 vaccine courses administered, with 22-30% of the hospitalised cases prevented in infants less than 1 year of age attributable to indirect protection from vaccinated mothers. Though the seasonal maternal programme is more efficient than its year-round counterpart, it is less efficient at preventing hospitalised cases than any of the long-acting monoclonal antibodies programmes (Figure 5.10). For GP consultations the seasonal maternal programmes prevents 37 (95% CrI 31–41) consulta-
tions per 1,000 courses given; more efficient than the year-round maternal programme (28 (95% CrI 26–31) per 1,000 courses given). Neither of the maternal vaccination programmes are effective at preventing deaths.

![Figure 5.9: Impact of the intervention programmes at preventing RSV-related outcomes. Crosses refer to the mean value and the line is the 95% credible interval.](image-url)
5.3.5 Indirect effects

The influence of indirect effects at preventing healthcare and cost-related outcomes of RSV vary in magnitude across all intervention programmes. In all the programmes, indirect protection is acquired mainly from protection of infants (<1 years age group) and the elderly.
The programme for which indirect protection accounts for the largest proportion of total protection is all school age children (5-14 years), with indirect protection of the elderly and infants accounting for 77.4% and 78.4% of the total protection for hospital cases and number of bed days averted (Figure 5.12).

For the remaining programmes which are aimed at preventing infections in infants by direct protection, the proportion total protection which is from indirect protection is small. For example, indirect protection of infants aged <1 years of age accounts for 12.9% and 2.4% of the total number of hospital cases averted in the all-year maternal programmes and the mABs programme respectively. Further, indirect protection of the elderly is accounts for only 10.3% of the total number of hospital cases averted in the elderly programmes (Figure 5.12).

**Figure 5.12:** Impact of direct and indirect protection for each of the programmes for RSV-related outcomes; hospital admissions (top left), deaths (top right), GP consultations (bottom left) and bed days (bottom right)
5.4 Discussion

This chapter outlines the first model to use a dynamic transmission model to evaluate how Palivizumab, monoclonal antibodies, and maternal vaccines impact the incidence of RSV-related healthcare outcomes within a single framework. Consequently, this chapter gives a comprehensive overview of the impact of all currently proposed RSV programmes in terms of RSV-related outcomes (symptomatic infections, hospitalised cases, deaths, GP consultations and hospital bed days) averted. The majority of the healthcare burden associated with RSV is concentrated in the infants (particularly for hospital admission and bed days) and the elderly (particularly for deaths). Further, only the number of bed days averted has a notable burden in the high-risk and very-high-risk infants, with the majority of burden seen in low-risk persons for all other outcomes. There are a number of potential healthcare outcomes which were not included in this analysis, including A and E attendances and (P)ICU admissions. Unfortunately, it was difficult to find age- and risk-specific costs and QALY losses for these outcomes in England and Wales. Further research into determining QALY loss and costs due to severe bronchiolitis and RSV-related pneumonia for patients in emergency care would make it easier to augment the model in the future.

The estimated impact of the prevention programmes suggest that the elderly and mABs programmes are the most effective at reducing RSV-related outcomes. The elderly programme aimed at persons aged 65 years and older and the year-round mABs programme aimed at infants prevent a similar magnitude of hospitalised cases and bed days, with the elderly programme additionally preventing a significant number of deaths. The maternal and infant vaccination programmes are also effective at reducing outcomes, preventing between 8–14% of the total number of hospital cases depending on the intervention programme. Further, indirect protection accounts for a small proportion of the total protection of the intervention programmes aimed at infants and elderly, which is consistent with the observation that infants and the elderly have a low number of daily contacts compared to the rest of the population.\textsuperscript{113,117}

There are some limitations in the parameter estimates in the Palivizumab model. For the efficacy, I assume a value of 33% (95% CI 0.0–66.6) as observed in infants with Chronic Lung Disease aged <12 months at the start of the RSV season.\textsuperscript{123} I chose this study as
it is most recent clinical trial performed; has a large cohort comparable with all previous studies; and gives efficacy values for specific underlying congenital conditions. Further, the uncertainty estimate for Chronic Lung Disease is large, and spans values from the previous studies, such as an efficacy of 55% from the IMPACT trial and 45% from another clinical trial. A larger confidence interval for the efficacy is preferred in the modelling as Palivizumab efficacy depends on many factors, including gestational age, birth day, and underlying health conditions. Efficacy estimates for conditions specifically associated with the eligibility criteria for Palivizumab in England and Wales would help improve the accuracy of future models. The proportion of infants per age group who are eligible for Palivizumab (in the VHR group) is calculated using the number of Palivizumab doses sold per year in England and Wales, and I assume that 90% of these receive a course. There are two problems with this assumption. First, assuming that 90% of Palivizumab courses bought are administered (coverage of purchased courses) is probably an over-estimation due the logistical difficulty in administering a monthly dosing schedule to very sick infants. Performing more clinical surveys to determine the coverage of purchased courses of Palivizumab would help modellers make better informed estimates for this parameter. Second, is it likely that there are infants in hospitals who are eligible for Palivizumab who do not get Palivizumab courses purchased for them (purchasing coverage). The only way to determine the purchasing coverage is to calculate the prevalence of infants who are eligible for Palivizumab (which is likely to be very difficult given the complexity in the eligibility criteria for Palivizumab in England and Wales). As this model assumes a 90% coverage of purchased courses and 100% purchasing coverage of Palivizumab, it is likely to overestimate the impact of the Palivizumab programme (due to high coverage of purchased courses), and under estimate the impact of the monoclonal antibodies programmes (due to high purchasing coverage).

The maternal vaccine in this model is based on Novavax’s RSV F-nanoparticle formulation. Recent stage III trial results for this product failed to meet its primary end point of 40% efficacy against RSV lower respiratory tract infections (LRTI) during the first three months of life across all trial sites. However, variations in efficacy were observed depending on region and gestation age at administration. Regional variation in efficacy saw South Africa with promising efficacy estimates of 57% (95% CI 33%–73%) against RSV LRTI, whereas the US site saw no evidence of efficacy. Although in this analysis I assume the efficacy of the maternal vaccine is as estimated across all sites, I acknowledge that care
CHAPTER 5. EVALUATING THE IMPACT OF POTENTIAL INTERVENTION PROGRAMMES

should be taken when these results are projected onto the UK, which experiences seasonal RSV similar to the US trial site. Efficacy was also found to vary with gestational age at administration, with vaccination at the start of the third trimester (28–32 weeks) experiencing an efficacy of 54% (95% CI 23%–72%) against RSV-associated hospitalisation and showing superior antibody transfer when compared to administration later in the third trimester (efficacy of 26% (95% CI -23–56). In this chapter, I have chosen the efficacy given at 28-32 weeks gestation as the health care delivery system in England is such that specific uptake periods are feasible in GP clinics if individuals are notified at the relevant time. However, uptake during this specific window may be less feasible in countries with differing healthcare policy and thus lower coverage rates may be observed than used in this study.

I assume that infants who are at high-risk of developing complications for Influenza are the same infants at high-risk of developing complications for RSV (3.8% of infants under 1 year old). It is unclear if this is true, as no single study has compared clinical risk-factors for both Influenza and RSV in infants in the UK. However, separate studies have both identified prematurity, immunodeficiency, chronic lung disease, congenital heart diseases as the risk factors due to Influenza and RSV independently. However, prematurity is a stronger risk factor in RSV than Influenza, so assuming that children who are at high-risk at developing complications for Influenza are the same as those for RSV is probably an underestimation of the number of high-risk infants for RSV and can be see as a lower bound (3.8%). It is worth noting that the number of high-risk infants cannot be equal to or greater than 5%, as 5% of hospitalised RSV cases in England are due to high-risk infants. The intervention programmes evaluated in this study are therefore a conservative estimate for the impact and affordability of the monoclonal antibodies programmes aimed at high-risk infants. Finally, some of the burden estimates for bed days may longer due to recruitment bias for more severe infections. This implies that cost of RSV burden in adults may be over-estimated, reducing the effectiveness of intervention programmes.

With the impact of the intervention programmes evaluated in terms of RSV-related outcomes averted, in the next chapter I present a cost-effectiveness analysis for these programmes, using the National Institute of Clinical Excellence (NICE) reference case. Combining impact with costs from an NHS perspective allows for the calculation of the Incremental Cost-Effectiveness Ratio (ICER) which can be used to inform policy makers.
of the efficiency and affordability of the potential intervention programmes.
Chapter 6

Cost-effectiveness analysis of intervention programmes

6.1 Introduction

In addition to evaluating the effectiveness of an intervention programme, public health bodies require estimates for the resource burden associated with implementing an intervention programme. The formal method which public health bodies use to evaluate if the health benefits acquired from implementing a programme outweigh the additional costs is cost-effectiveness analyses (CEA). CEAs use pre-defined metrics to measure the cost and health benefits of an intervention programme which then enables the calculation of the relative efficiency of such programmes to better allocate healthcare budgets. Using CEA helps public health bodies to identify ways to redirect resources to maximise the health of the population; a process which is increasingly important in healthcare systems as demand for healthcare increases from a finite pool of national resources.

The National Institute of Clinical Excellence (NICE) produces UK-specific guidance of best practice on the methods of CEA of potential intervention programmes. These guidelines include specific methodological advice on the perspective from which the cost and benefits of an intervention programme should be assessed; the methods and units used for measuring health effects and resource use costs; and the time horizon for analysis and discounting rates. The NICE guidelines on the perspective taken suggest that only the cost and health benefits of a health intervention programme which directly impact the NHS resource burden should be included (an NHS perspective). The suggested units used for measuring the health effects are QALYs, and for costs, GBP and the time hori-
The aims of this chapter are to estimate the costs and health burden (in terms of QALY loss) of each of the intervention programmes outlined in Chapter 5 and then calculate the cost-effectiveness by applying the NICE guidelines for best practice for cost-effectiveness analysis.
6.2 Calculating the costs and QALY loss

A summary of the parameters used in this chapter are given in Table 6.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (95% CI where applicable)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Time horizon</td>
<td>10 years</td>
</tr>
<tr>
<td>r</td>
<td>Discount rate</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

**Costs**

Per GP visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (95% CI where applicable)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_{GP}$</td>
<td>All ages</td>
<td>£36.00 (fixed)</td>
</tr>
</tbody>
</table>

Hospital bed day

<table>
<thead>
<tr>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_H$</td>
<td>Pediatric (&lt;5 years)</td>
<td>£725.29 (718.13–733.99)</td>
</tr>
<tr>
<td>$\Phi_H$</td>
<td>Adults (≥ 5 years)</td>
<td>£425.24 (415.16–435.70)</td>
</tr>
</tbody>
</table>

Administration of prophylactics (per course)

<table>
<thead>
<tr>
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<th>Mean value (95% CI where applicable)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta_{pal}$</td>
<td>Palivizumab</td>
<td>£57.50</td>
</tr>
<tr>
<td>$\Delta_{mab}$</td>
<td>La-mABs</td>
<td>£11.00</td>
</tr>
<tr>
<td>$\Delta_{mat}$</td>
<td>Maternal vaccine</td>
<td>£9.00</td>
</tr>
<tr>
<td>$\Delta_{vac}$</td>
<td>Vaccine</td>
<td>£9.00</td>
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Purchasing prices (per course)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (95% CI where applicable)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_{pal}$</td>
<td>Palivizumab</td>
<td>£4035.50 (Fixed)</td>
</tr>
<tr>
<td>$\rho_X$</td>
<td>La-mABs, Maternal vaccine and vaccine</td>
<td>Not known</td>
</tr>
</tbody>
</table>

**QALY loss**

Symptomatic infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (95% CI where applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_S^a$</td>
<td>Paediatric (&lt;5 years)</td>
</tr>
<tr>
<td>$Q_S^a$</td>
<td>Adults (≥ 5 years)</td>
</tr>
</tbody>
</table>

Hospital admissions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value (95% CI where applicable)</th>
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</thead>
<tbody>
<tr>
<td>$Q_H^a$</td>
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</tr>
<tr>
<td>$Q_H^a$</td>
<td>Adults (≥ 5 years)</td>
</tr>
</tbody>
</table>

Deaths

<table>
<thead>
<tr>
<th>Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>81.0 years</td>
</tr>
</tbody>
</table>

Table 6.1: Health and economic parameters used in the cost-effectiveness analysis.

Costs were calculated in 2018 GBP, from the perspective of the NHS. The cost per GP consultation was calculated by assuming an average GP consultation time of 9 minutes at a cost of £4.00 a minute (£36.00).\textsuperscript{139,140} The cost per hospital bed day for children less than five years of age was calculated using the non-elective costs for paediatric Bronchiolitis (Health Resource group (HRG) PD15A–D)—the main cause of RSV-associated hospitalisations.\textsuperscript{30,141} The cost per hospital bed day for children five years and older was determined using the non-elective costs for unspecified Acute Lower Respiratory Infection (HRG DZ22K–Q).\textsuperscript{141} I assumed maternal, infant and elderly vaccines take 15 minutes to administer in a GP clinic at a cost of £9 per course (assuming one dose per course).\textsuperscript{139} Similarly, I assumed long-acting monoclonal antibodies and Palivizumab, take 15 minutes to administer in hospital by a nurse at a cost of £11.50 per course for long-acting...
monoclonal antibodies and £57.50 per course (5 doses) for Palivizumab. A course of Palivizumab costs £4035 (5 doses at £807 each).

In line with our previously estimated quality-adjusted life year (QALY) loss estimates per RSV episode for England, I assume that each GP consultation or hospitalisation resulted in a QALY loss of $4.098 \times 10^{-3}$ (95% CI $0.624 \times 10^{-3} - 13.141 \times 10^{-3}$) and $2.990 \times 10^{-3}$ (95% CI $0.346 \times 10^{-3} - 11.387 \times 10^{-3}$) for under fives and over fives respectively, while other symptomatic non-healthcare seeking infections resulted in a QALY loss of $2.336 \times 10^{-3}$ (95% CI $0.269 \times 10^{-3} - 9.255 \times 10^{-3}$) and $1.448 \times 10^{-3}$ (95% CI $0.135 \times 10^{-3} - 5.928 \times 10^{-3}$). QALY loss due to death was commensurate with the remaining number of expected healthy years of life remaining in the individual.

QALY loss due to death was commensurate with the remaining number of expected healthy years of life remaining in the individual (Supplementary material S4.1). Assuming an average life expectancy per person of 81.0 years, then using SF-6D population norms with annual weighting of $x_a$ per year, the quality adjusted life expectancy is given by $\sum_{a=0}^{81} x_a = 65.94$. Given death occurs at year of life $a_i$, then the QALY loss, assuming a discounting rate of $r = 0.035$, is given by

$$E[Q^a_{D}] = \sum_{a=a_i}^{81} x_a \exp(-0.035(a - a_i))$$  \hspace{1cm} (6.1)

I assume that the standard deviation of the life expectancy at age $a_i$ is 10% of the current life expectancy ($Q^a_{D} \sim \mathcal{N}(E[Q^a_{D}], 0.1(E[Q^a_{D}]))$).

### 6.2.1 Outline of the economic model

I conducted three separate cost-effectiveness analyses. First, I calculated the incremental cost-effectiveness ratio (ICER) of replacing the Palivizumab with any of the long-acting monoclonal programmes (MAB-VHR-S, MAB-HR-S, MAB-HR-S+, MAB-ALL-S, and MAB-ALL-S+). Second, I calculated the ICERs of supplementing the Palivizumab programme with the childhood or elderly vaccine programmes (VAC-INF-S, VAC-INF-A, VAC-2-4-S, VAC-5-9-S, VAC-5-14-S, VAC-75-S, VAC-65-S). Third, I calculated the ICER of supplementing the Palivizumab programme with the maternal vaccine programmes (MAT-S, MAT-A). A strategy is said to be dominated if it is either a) strongly dominated (both less effective and more costly than the next most effective strategy) or b) weakly dominated (when it’s ICER is higher than that of next most effective strategy).
For each of these three cost-effective analyses, using the non-dominated programmes only (programmes which are not dominated by another programme), I calculated the maximum price per course that would make each strategy cost-effective, assuming a cost-effectiveness threshold of £20,000/QALY. All costs and effects were discounted at a rate of 3.5% over a 10-year time horizon. For each intervention strategy, I calculated the confidence intervals using 1,000 Monte Carlo samples. For each Monte Carlo sample, I first estimated the number of RSV cases averted over the time horizon per outcome for an intervention strategy by sampling from the joint posterior distribution and running the intervention model for 10 years (Chapter 4). Then, by sampling from the per-infection probability of each outcome occurring, I converted the number of RSV cases averted to the number of outcomes averted (Chapter 5). Finally, I combined sampled values from the cost distributions with the number of each clinical outcome averted to calculate the distribution of the maximum price per prophylactic course. The formula for the maximum price per dose to implement programme P in an existing programme C to remain cost-effective at an 20,000£/QALY threshold is given by:

$$\rho(P, C) = \frac{20000(Q^C - Q^P) - (\Theta^P - \Theta^C) - (\Delta^P - \Delta^C)}{\sum_{w=1}^{52} T \sum_{r=1}^{T} D_{P,t}^a r^w e^{-rw/52} - \sum_{w=1}^{52} T \sum_{r=1}^{T} D_{C,t}^a r^w e^{-rw/52}}$$ (6.2)

where, assuming that X is the prophylactic associated with intervention programme P, the cost of treatment ($\Theta^P$), cost of administration ($\Delta^P$) cost of purchasing ($B^P$) and the total QALY loss ($Q^P$) associated with each treatment over the time horizon is given by:

$$\Theta^P = \sum_{w=1}^{52} T Z_{P,t}^a r^w (r_a^G \Theta_{GP} + r_a^B \Theta_{H}) e^{-rw/52}$$ (6.3)

$$\Delta^P = \Delta X \sum_{w=1}^{52} T D_{P,t}^a r^w e^{-rw/52}$$ (6.4)

$$B^P = \rho X \sum_{w=1}^{52} T D_{P,t}^a r^w e^{-rw/52}$$ (6.5)

$$Q^P = \sum_{w=1}^{52} T Z_{P,t}^a r^w (r_a^G Q_{GP} + r_a^B Q_{H}) e^{-rw/52}$$ (6.6)
6.2.2 Affordability

As per NICE guidelines, an intervention strategy is considered affordable if it costs less than £20 million annually during the first three years of implementation.\textsuperscript{145} Using this definition, I calculated the affordable purchasing price per course for each non-dominated programme, by subtracting the total, undiscounted cost of administering the intervention strategy for the first three years from £60 million (3 years at £20 million each) and dividing by the total number of courses given during this period.\textsuperscript{145}
6.3 Cost-effectiveness analysis projections

This section first outlines the maximum purchasing price per course for each of the intervention strategies to remain cost-effective (calculated using Equation 6.2). Then the affordability of the intervention programmes is discussed.

6.3.1 Maximum purchasing price per dose

Long-acting monoclonal antibodies: The maximum purchasing price per course for the long-acting monoclonal antibodies programme to be cost-effective when administered seasonally to only the VHR infants is £4,342.97 (95% CrI £4,126.31–4,462.25) (Figure 6.1). For this seasonal programme to remain cost-effective after extending to HR neonates (MAB-HR-S), and then to all HR infants less than 6 months at the start of season (MAB-HR-S+), requires substantially lower maximum purchasing prices per course of £201.15 (95% CrI £149.61–243.42) and £87.03 (95% CrI £64.80–116.99) respectively (Figure 6.1).

Maternal vaccination: The year-round maternal vaccination programme was dominated by the seasonal strategy. The maximum purchasing price per course for the seasonal maternal vaccination to be cost-effective is £85.27 (95% CrI £77.79–93.80) (Figure 6.1).

Childhood/elderly vaccination: The year-round vaccine programme aimed at infants 2 months of age is dominated by its seasonal counterpart, while the 65 years and over programme is dominated by the 75 years and older programme. Further, the pre-school, and school-age programmes are subject to extended dominance by the 75 years and older programme. For the seasonal vaccine programme aimed at infants aged 2 months of age, the maximum purchasing price per course to remain cost-effective is £94.76 (95% CrI 89.09–99.24). Targeting those aged 75 years and older requires a lower purchasing price per course of £20.71 (95% CrI 10.32–34.64) (Figure 6.1).
If the duration of protection varies between 150 and 365 days, the maximum purchasing price for the MAT-HR-S programme would also vary between £185.79-215.02, respectively (Figure 6.2).

6.3.2 Affordability

The long-acting monoclonal antibodies programmes: MAB-VHR-S, MAB-HR-S, and MAB-HR-S+ and the seasonal maternal programme (MAT-S) are affordable if implemented for a cost-effective purchasing price per course (affordable thresholds are £9,395.75, £1,712.46,
£873.08, and £121.02 respectively. The seasonal infant programme aimed at 2-month-olds and the 75 years and older programme are affordable if implemented for £79.62 and £3.63 respectively—81% and 16% of the estimated mean maximum purchasing price per course.
6.4 Discussion

This chapter outlined the process of integrating the results of the intervention model into a cost-effectiveness framework and evaluated the likely maximum dose prices of the new generation of RSV preventive pharmaceuticals to make them cost-effective and affordable in England. The CEA analysis found that replacing the existing seasonally administered Palivizumab programme with long-acting monoclonal antibodies would be cost-effective and affordable at a maximum course price of £4403 (95% CrI 4338–4511). Extending the programme to heightened risk or all infants would remain cost-effective and affordable at approximately £200 and £90, respectively. A seasonal maternal vaccination programme would be cost-effective and affordable with a maximum purchasing price per course of £85 (95% CrI 79–91).

This work in this chapter is also the first to directly link the impact of potential programmes from a dynamic transmission model to a CEA according to the NICE reference case—the gold standard approach for CEA in England and Wales, and the first to use EQ-5D-based QALY estimates for RSV. The CEA accounts for both the direct and indirect effects of intervention strategies. This approach is of particular importance when comparing the health benefits of vaccinating school-age children where the majority of hospitalised cases averted occur through indirect protection.

The total cost of each intervention programmes is estimated using NHS Improvement Reference Costs 2018\textsuperscript{141} which quote the average unit cost to the NHS of providing a service to NHS patients in England during 2018. These costs are appropriate for use in CEs as they give a recent and comprehensive picture of the cost of delivering healthcare services directly from the perspective of the NHS. The Reference Costs state that the cost of purchasing Palivizumab was £807 per dose. However, the size of the dose of Palivizumab given (the 50mg dose or the more expensive 100mg dose) depends on body weight of the infant when Palivizumab is administered.\textsuperscript{36} Assuming the £807 quoted is the weighted mean of the two sizes of dose given, then using the value in the cost-effectiveness analysis is approximately correct. However, if this quoted price is the cost of purchasing the small or large dose only, then the cost-effectiveness analysis will under- or over-estimate (respectively) the cost-effective purchasing price per dose of replacing the Palivizumab programme with a long-acting monoclonal antibodies programmes.
As RSV-specific case codes are not included in the NHS Improvement Reference Costs, prices for unit costs of all-case respiratory disease-related outcome are used in lieu, and it is not clear if this is a accurate representation of the unit cost of RSV-specific disease. In estimating the total costs and QALY loss of each programme, some potentially important health care outcomes were excluded, such as ICU infection. ICU admission was omitted due to lack of information about the QALY loss due to RSV-specific (P)ICU admission in England and Wales. Excluding (P)ICU admissions, which have a high expense and QALY loss, means that the CEA presented in this chapter will give a conservative estimate for the effectiveness of the mABs programmes, and consequently, will underestimate the maximum purchasing price per dose. There are other outcomes omitted from the model which could be important in estimating resource burden from the perspective of the NHS (e.g. prescription rates, A+E rate, sequelae etc.) however the model is limited in the number of outcomes it can predict, as there must be enough epidemiological evidence to produce age- and clinical-risk group specific per-infection risks for each outcome considered.

Though the results of this analysis suggest that the long-acting monoclonal antibodies and maternal programmes are cost-effective, implementation of these programmes will present clinical and logistical challenges that this analysis has not considered. For example, I assume the same administration price per dose for all the monoclonal antibody programmes. However, administration of monoclonal antibodies to those under 6 months, rather than just new-borns, will likely be more expensive and achieve lower rates of uptakes, all else equal, as they will need to make a separate appointment at a GP or hospital setting for dose administration. Consequently our results may overestimate the impact and cost-effectiveness of these programmes. Further, in estimating the per-infection risk for RSV-related outcomes, there were no clinical-risk-specific estimates for death and for GP consultations available in the literature, meaning the probability of these outcomes occurring may be underestimated in VHR or HR infants, implying costs and QALY burden of some of the intervention strategies may be conservative. Further studies which help estimate the burden of specific outcomes in England would help reduce uncertainty and increase the accuracy of the model predictions.

From Chapters 4–6, I have outlined the dynamic transmission model, intervention model and cost-effectiveness analysis to determine which of the RSV intervention programmes are likely to be implemented assuming cost-effectiveness threshold of 20,000£/QALY.
In the final chapters I discuss the open-source code which reproduces the work in the previous chapters, the significance of this work, its implications on future immunisations strategies, and future developments of this work.
Chapter 7

Summary of thesis and looking forward

In this thesis I have achieved the five aims and objectives outlined in Chapter 1. First, I have performed a cross-section survey to measure the health burden, in terms of QALY loss, of mild and severe RSV infection for both infants and adults in England. This is the first study to estimate the QALY loss due to acute RSV infection using standardised instruments such as EQ-5D questionnaires. As these are the gold standard for evaluating QALY loss according to NICE, the estimates from this study will be useful for all future cost-effectiveness analysis of RSV infection both in England and in other countries. Second, I performed a review of existing mathematical models of RSV transmission. This is the first time a review of RSV-specific models has been performed and the results will be of interest to mathematical modellers who require an oversight of the current RSV modelling landscape. Third, I developed and parameterised a novel mathematical model of RSV transmission for England and Wales which takes into account the important aspects of RSV transmission not currently modelled, as identified in the review in the previous chapter. The model is calibrated to historic incidence data specific to England and Wales and reproduces the observed incidence of RSV. Fourth, I evaluated the impact of different intervention programmes using the calibrated mathematical model. Finally, I evaluated the cost-effectiveness of the different intervention programmes by combining the mathematical model with an economic analysis and the QALY estimates for RSV infection. The results in this thesis suggest that regardless of the intervention strategy, seasonal administration is the optimal intervention compared to year-round administration. Moreover, there is little evidence that strategies aimed at children 2 years and older and those targeted at
the elderly would be cost-effective or affordable, respectively. In contrast, long-acting monoclonal antibodies and maternal vaccines may be a cost-effective replacement or addition to the existing Palivizumab programme, respectively. The scope of the intervention programme however will depend on the purchasing price when these pharmaceuticals are made available.

There are limitations with the mathematical model regarding assumptions about immunity and the parametrisation of the Palivizumab programme. For the immunity, I assumed that individuals experience a temporary period of complete protection from reinfection. The rationale for this assumption is from the heightened neutralising antibody levels which follow post-infection. However, the presence of neutralising antibody alone does not ensure protection from RSV infection, therefore assuming complete immunity post-infection is probably an overestimation of the acquired post-infection protective effects. Expanding the modelling to include the possibility of non-complete immunity post-infection could help elucidate information about the immunopathology of RSV infection. Further, some of the parameter estimates for the Palivizumab programme could be improved. For example, the model assumes a 90% coverage of Palivizumab, as is observed for other infant vaccination programmes, but this is likely to be an overestimation due to the logistical difficulties associated with administration. In addition, the model assumption of a 100% purchasing coverage (all persons who need Paliviumab have it purchased for them) is certainly an overestimation, however there is no data available which could be used to easily estimate this parameter. The overestimation of these two parameters means the model is likely to underestimate the burden of RSV in very-high-risk groups, therefore the purchasing price per dose for programmes which replace the Palivizumab programme (i.e. long-acting monoclonal antibodies) are underestimated in the model. However, these inaccuracies in the parameterisation of the Palivizumab programme will not greatly impact the incremental cost-effectiveness analysis of programmes which are supplementary to the Palivizumab programme. More epidemiology evidence is needed on the clinical attitudes towards Palivizumab administration to gain clearer estimates for these values for use in mathematical models. An important aspect of this work is the care in ensuring the uncertainty associated with each stage of the modelling has been properly quantified. Uncertainty in decision-making is particularly important as it provides evidence on the probability of an intervention programme being cost-effective and identifies specific areas which influence this probability. Funding epidemiological studies which would allow for
better estimates for these parameters to be derived would provide more certainty in future
cost-effectiveness analysis and consequently give more confidence to decision makers about
future policy.

The mathematical modelling in Chapters 4–6 was performed using C++ in a code
written by the author and the figures were made using Mathematica version 11. The C++ code is available at the author’s Github account (https://github.com/dchodge/
rsv_trans_model). The main file of the code (main.cpp) has five main functions which
perform all the work needed to recreate the results in this thesis. The first function
calibrates the RSV model and the outputs are the posterior distributions for each of
the fitted parameters and intermediary results which elucidate information about the
calibration process including the temperature ladder, covariance matrix and acceptance
ratio. The second function gives the exemplar results from Chapter 4 using the posterior
distributions from the first function. The third function determines the optimal week
for each of the seasonal programme to begin administration by calculating the QALY
loss for each possible starting week (Figure 5.8). The fourth function determines the
impact of each of the possible intervention programmes with outputs including the number
of cases averted, the number of each outcome averted, the discounted QALY loss and
cost for each programme. The final function produces the same output as the fourth
function but varies parameters according to the sensitivity analysis. The transmission
model is built such that persons with adequate knowledge of C++ could evaluate their
own intervention programmes, provided a timetable for uptake across various age-groups
is provided. However, ongoing work is turning the intervention part of this model into
an R package, which would allow users with basic knowledge of R to evaluate the impact
of custom intervention programmes related to specific policy requests, including multi-
prophylactic approaches. This flexibility and transparency will be useful looking forward
when decisions need to be made about which programmes are to be tested and prophylactic
products have been approved for licensure. These decisions are often made by evaluating
a specific suite of programmes according to the manufacturers proposed use, meaning the
many different programmes may need to be evaluated in a short space of time. The model
and future R package could be used to evaluate these different programmes quickly, and
thus respond to the ever-changing landscape of viable products for RSV prevention.
The parallel tempering MCMC used in the model has been converted to a general-purpose R Package (see https://github.com/dchodge/ptmc).

The R package allows the user to define the fitted parameters, likelihood, prior distributions and initial values for any statistical model (not just infectious disease transmission models). Once set up, it will sample from the posterior distributions of the fitted parameters for a user-defined number of iterations. It has various customising options for the temperature ladder, thinning, and run length and it allows for the option of adaptive covariance matrices. Its use is very similar to the popular BayesianTools Package in R which allows the user to use a suite of MCMC samples to obtain posterior distributions for a user-defined model. Preliminary analysis comparing the efficiency of the BayesianTools package and the self-written parallel-tempering MCMC package at fitting SIR-type epidemic models suggests that the latter has the most convincing convergence in a shorter space of time.

Using purpose built R packages, such as one the described, will assuage concerns surrounding convergence of epidemic models, allowing more time for analysis of issues more relevant to policy makers (i.e. impact of intervention programmes or cost-effectiveness analysis).

As outlined in the impact statement, there are several specific aspects of the thesis which will have a beneficial use both inside and outside academia. This thesis is the first to estimate the health burden of RSV in terms of Quality Adjusted Life Years lost. As this metric is the standard metric used for cost-effectiveness analysis, these values will be used by both academic, public health research and policy decision makers in future RSV-related cost-effectiveness analyses. Hopefully this small cross-sectional study will encourage larger and more sophisticated cohort studies on RSV-specific burden to be carried out. The transmission model presented in this thesis has been numerically solved and presented as an open-source software and therefore provides a framework which can be build upon in the future to evaluate different intervention programmes across different settings. From an epidemiological prospective, this thesis also shows that maternal protection in infants born in England alters with seasonality, with low protection occurring before the start of the RSV season, and peak protection occurring just after the RSV season. This observation contradicts the assumption that maternal protection is constant throughout the year as previous mathematical models have assumed. This could be used as evidence to inspire future clinical trials which try to find further epidemiology evidence to support the claims regarding maternal protection from this study. Finally, the cost-effective purchasing price per course for these intervention programmes are the first to be estimated from a dynamic...
transmission model (which takes into account herd immunity) and also the first to be estimated using an economic analysis informed from the National Institute of Clinical Excellence guidelines. There is already some developments with expanding this project in the future, including the building of a website where all the details of the RSV model, the C++ code, and a platform for interface will be available to policy makers and other public health workers.

To conclude, this thesis presents a novel mathematical model for RSV transmissions used to give a comprehensive overview of the cost-effectiveness of all feasible RSV prevention strategies at the time of writing for England and Wales. It describes the first dynamic transmission model for RSV in England and Wales, and it is also the first model to link the impact of Palivuzumab, long-acting monoclonal antibodies and maternal vaccines to a cost-effectiveness analysis. In addition the model is easily adaptable to include other strategies and other settings. Consequently, this work will be an essential tool to policymakers when making decisions on the future of RSV intervention strategies in England and Wales.
Supplementary material
Supplementary material for Chapter 2: Estimating the health burden due to RSV

S1.1 Statistical Analysis

S1.1.1 Linear regression model for severe disease

From this linear regression I find that the single explanatory variable healthcare-seeking behaviour (stratified by 2 levels) most parsimoniously predicts the observational data for when the peak HR-QoL loss from the data is above 0.6 (Figure S1.1). The best-fit model is therefore given by \( E[Y_S] = 0.7824 + 0.2436x_1 \) (t-value = 4.111 and \( P = 0.0012 \), AIC = -18.6) where \( x_1 = 0 \) when no healthcare is sought and 1 otherwise. The model-estimated peak HR-QoL loss for severe disease, stratified by healthcare-seeking behaviour can then be calculated (Figure S1.1–S1.2). Log-transforming the response variable reduces the likelihood (AIC = -9.7, results not shown), therefore I used an untransformed linear regression model.
**Figure S1.1:** Backwards stepwise regression analysis results for the five explanatory variables for the linear regression model for severe disease episodes. The P-value for each explanatory variable for each step in the backwards regression is shown, with an X indicating the variable was removed from the regression because it was the highest P-value above the threshold value of 0.05 (indicated by the pink region). The AIC value is the model-fit at the end of the regression with the remaining explanatory variables.

### S1.1.2 Log-transformed linear regression model for mild disease

From this log-transformed linear regression I find that the single explanatory variable, VAS score loss, most parsimoniously predicts the observational data when the peak HR-QoL loss from the data is below 0.6. The best-fit model is therefore given by \( \log(E[Y_M]) = -1.7885 + 0.0102x_5 \) (t-value = 4.0674, \( P = 0.000231 \) and AIC = 17.29) where \( x_5 \) is the VAS score loss. The model-estimated peak HR-QoL loss for mild disease, for VAS score loss values between 0 and 100, can then be calculated (Figure S1.3–S1.4).
Healthcare-seeking behaviour

Figure S1.2: The distribution for the model-estimated peak HR-QoL loss for severe disease. The solid black line indicates the mean of the distribution, the dotted lines indicate lower and upper 95% CI.

S1.1.3 Logistic regression model for classification of disease severity

From this logistic regression model, I find that coughing severity (stratified by two levels) most parsimoniously predicts the observation data when the peak HR-QoL loss is transformed to a binary response variable; 0 when less than 0.6 and 1 when greater than 0.6. The best-fit model is therefore given by $\mathbb{E}[p] = \sigma(-1.9924 + 3.4965x_2)$ ($Z = 3.908$, $P = 9.31\times10^{-5}$, $AIC = 46.35$) where $x_2$ is 0 with no/mild coughing and 1 otherwise (Figure S1.5–S1.6).
S1.1.4 Summary of results

I have used the mixture-model approach to calculate the model-estimated peak HR-QoL loss for a symptomatic RSV infection. I parameterized the model using questionnaire responses from respondents over five years of age with suspected RSV infection for whom I could estimate the peak HR-QoL loss derived from the EQ-5D questionnaires. I therefore determined the model-estimated peak HR-QoL loss as a function of healthcare seeking behaviour, productivity loss, age, VAS score loss, coughing severity all of which I knew from the questionnaire respondents.

Our results suggest that the model-estimated peak HR-QoL loss due to an RSV disease episode can be predicted by clinical information independent of a validated HR-QoL questionnaire. Specifically, the model-estimated peak HR-QoL loss can be estimated using only the VAS score loss, whether healthcare was sought, and whether severe coughing was...
Figure S1.4: The distribution for the model-estimated peak HR-QoL loss for mild disease as VAS loss increases. The solid black line indicates the mean of the distribution, the dotted lines indicate lower and upper 95% CI bands.

Figure S1.7: The distribution of the model-estimated peak HR-QoL for coughing severity, healthcare-seeking behaviour and VAS loss. The solid red line indicates the mean of the distribution, the black lines indicate lower and upper 95% CI bands.
Figure S1.5: Backwards stepwise regression analysis results for the five explanatory variables for the logistic regression model. The P-value for each explanatory variable for each step in the backwards regression is shown, with an X indicating the variable was removed from the regression because it was the highest P-value above the threshold value of 0.05 (indicated by the pink region.) The AIC value is the model-fit at the end of the regression with the remaining explanatory variables.

S1.1.5 Additional Tables

HR-QoL weight for the explanatory variables

Model-estimated peak HR-QoL loss and QALY loss for the explanatory variables
Figure S1.6: The distribution for the probability of severe disease, $p$. The solid black line indicates the mean of the distributions, the dotted lines indicate lower and upper 95% CI.

<table>
<thead>
<tr>
<th>HR-QoL weight (Median and range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>5–14</td>
</tr>
<tr>
<td>15+</td>
</tr>
<tr>
<td><strong>Coughing severity</strong></td>
</tr>
<tr>
<td>None or mild</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td><strong>Healthcare-seeking behaviour</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Seek healthcare</td>
</tr>
<tr>
<td><strong>Productivity</strong></td>
</tr>
<tr>
<td>Time taken off</td>
</tr>
<tr>
<td>No time taken off</td>
</tr>
<tr>
<td><strong>VAS score loss</strong></td>
</tr>
<tr>
<td>Below median (40)</td>
</tr>
<tr>
<td>Above median (40)</td>
</tr>
</tbody>
</table>

Table S1.1: HR-QoL weight for each explanatory variable for suspected cases in persons aged five years and older.
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Model-estimated peak HR-QoL loss (Mean and 95% CI)</th>
<th>QALD loss (Mean and 95% CI)</th>
<th>QALY loss (Mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>0.798 (0.208–1.462)</td>
<td>1.356 (0.161–4.643)</td>
<td>3.731 $\times 10^{-3}$ (0.456–12.710)</td>
</tr>
<tr>
<td>6-11</td>
<td>0.840 (0.235–1.438)</td>
<td>1.429 (0.187–4.731)</td>
<td>3.935 $\times 10^{-3}$ (0.505–12.889)</td>
</tr>
<tr>
<td>12-23</td>
<td>0.861 (0.301–1.446)</td>
<td>1.464 (0.219–4.765)</td>
<td>4.043 $\times 10^{-3}$ (0.585–13.325)</td>
</tr>
<tr>
<td>24-59</td>
<td>0.836 (0.244–1.419)</td>
<td>1.421 (0.199–4.626)</td>
<td>3.871 $\times 10^{-3}$ (0.521–12.727)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coughing severity</th>
<th>Model-estimated peak HR-QoL loss (Mean and 95% CI)</th>
<th>QALD loss (Mean and 95% CI)</th>
<th>QALY loss (Mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or mild</td>
<td>0.499 (0.148–1.482)</td>
<td>0.845 (0.097–3.292)</td>
<td>2.336 $\times 10^{-3}$ (0.269–9.255)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.878 (0.344–1.443)</td>
<td>1.496 (0.227–4.841)</td>
<td>4.098 $\times 10^{-3}$ (0.624–13.141)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthcare-seeking behaviour</th>
<th>Model-estimated peak HR-QoL loss (Mean and 95% CI)</th>
<th>QALD loss (Mean and 95% CI)</th>
<th>QALY loss (Mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No response</td>
<td>No response</td>
<td>No response</td>
</tr>
<tr>
<td>Seek healthcare</td>
<td>0.820 (0.222–1.450)</td>
<td>1.391 (0.179–4.617)</td>
<td>3.823 $\times 10^{-3}$ (0.492–12.766)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VAS loss</th>
<th>Model-estimated peak HR-QoL loss (Mean and 95% CI)</th>
<th>QALD loss (Mean and 95% CI)</th>
<th>QALY loss (Mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below median (65)</td>
<td>0.784 (0.200–1.393)</td>
<td>1.339 (0.166–4.488)</td>
<td>3.676 $\times 10^{-3}$ (0.453–12.250)</td>
</tr>
<tr>
<td>Above median (65)</td>
<td>0.860 (0.259–1.498)</td>
<td>1.462 (0.202–4.865)</td>
<td>3.989 $\times 10^{-3}$ (0.525–13.212)</td>
</tr>
</tbody>
</table>

Table S1.2: HR-QoL, QALD and QALY loss for each explanatory variable for confirmed cases in children under the age of five. *Conditional on ascertaining a confirmed
<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (years)</th>
<th>Coughing severity</th>
<th>Healthcare-seeking behaviour</th>
<th>Productivity</th>
<th>VAS loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–14</td>
<td>0.462 (0.118–1.308)</td>
<td>QALD loss (Mean and 95% CI)</td>
<td>QALY loss (Mean and 95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15+</td>
<td>0.452 (0.117–1.222)</td>
<td>0.637 (0.054–2.609)</td>
<td>1.740 ×10−3 (0.144–7.277)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15+</td>
<td>0.625 (0.052–2.607)</td>
<td>1.717 ×10−3 (0.144–7.078)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None or mild</td>
<td>0.382 (0.111–1.113)</td>
<td>0.528 (0.050–2.167)</td>
<td>1.448 ×10−3 (0.135–5.928)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
<td>0.785 (0.280–1.368)</td>
<td>1.103 (0.126–4.149)</td>
<td>2.990 ×10−3 (0.346–11.387)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>0.405 (0.111–1.137)</td>
<td>0.565 (0.049–2.349)</td>
<td>1.543 ×10−3 (0.136–6.406)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seek healthcare</td>
<td>0.616 (0.155–1.371)</td>
<td>0.866 (0.071–3.508)</td>
<td>1.950 ×10−3 (0.185–9.578)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time taken off</td>
<td>0.404 (0.111–1.176)</td>
<td>0.558 (0.048–2.342)</td>
<td>1.539 ×10−3 (0.137–6.382)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No time taken off</td>
<td>0.579 (0.139–1.369)</td>
<td>0.788 (0.06–3.184)</td>
<td>2.170 ×10−3 (0.173–8.818)</td>
</tr>
<tr>
<td>Below median (40)</td>
<td></td>
<td></td>
<td>0.373 (0.107–1.081)</td>
<td>0.524 (0.047–2.190)</td>
<td>1.417 ×10−3 (0.131–5.749)</td>
</tr>
<tr>
<td>Above median (40)</td>
<td></td>
<td></td>
<td>0.562 (0.141–1.382)</td>
<td>0.790 (0.068–3.246)</td>
<td>2.163 ×10−3 (0.182–8.945)</td>
</tr>
</tbody>
</table>

Table S1.3: HR-QoL, QALD and QALY loss for each explanatory variable for suspected cases in persons aged five years and older.
S1.2 Questionnaires

WHITE — Your child’s recent RSV infection

This section should be filled in by the parent/guardian of the child in your household who has recently been infected by the respiratory disease, RSV.

1. How old is your child, who was recently infected with RSV?  
   *(If your child is less than 1 years of age, please give their age in months)*
   ____ years ____ months

2. What is the date today?  *(Day/Month/Year)*
   ____/____/_____

3. What symptoms did your child have because of their infection?
   
   Please tick if your child experienced the following during their infection.
   
   □ Runny or blocked nose   □ Fever
   □ Coughing   □ Sore throat

   If your child experienced difficulty breathing (e.g. shortness of breath, wheezing) during his/her infection: please tick the relevant box(es) which best describe its effect on your child’s day-to-day activities (e.g. feeding, playing, moving if appropriate) and the duration it was experienced.

   □ No noticeable effect on his/her day-to-day activities ____ days
   □ Mildly affected his/her day-to-day activities ____ days
   □ Significantly affected his/her day-to-day activities ____ days

4. On what date did your child first experience the symptoms described in Q3?  *(Day/Month/Year)*
   ____/____/_____

5. Did you seek medical care for your child during these symptoms? *(please tick all that apply and indicate the number of times)*
   
   □ a. Phone/email NHS 111 / NHS 24 / NHS Choices ____ times
   □ b. Phone/email GP — response from the receptionist ____ times
   □ c. Phone/email GP — response from the doctor or nurse ____ times
   □ d. Visit (face-to-face) a GP or nurse ____ times
   □ e. Visit A&E department (including out of hours service) ____ times
   □ f. Admitted to hospital (as an inpatient) ____ times
   □ g. Other medical services, please specify:

6. Below are two line scales numbered from 0 to 100. 100 means the best health state you can imagine and 0 means the worst health state you can imagine.

   - In box A, please draw a line from the box to a point on the scale which shows how good or bad your child’s health was on the WORST DAY of infection.
   - In box B, please draw a line from the box to a point on the scale which shows how good or bad your child’s health is TODAY.
There are no questions on this page.
BLUE - Infections in persons 5 – 14 years old

If another child who is aged 5–14 in your household fits the following criteria, then it is likely that he/she was infected with RSV. Please complete the rest of this questionnaire on their behalf about their illness. If no one aged 5–14 in your household fulfils the criteria below, please leave this section blank and move to the YELLOW section.

- He/she experienced symptoms of respiratory illness (as listed in Q3) between 5 days before the start of your other child’s RSV infection, and 5 days after the end of your other child’s RSV infection.

If there are multiple persons in your household who fit the criteria, then please complete this section on behalf of the oldest.

7. How old is he/she?
   □ 5 – 9 years old   □ 10 – 14 years old

8. What is their sex?
   □ Male   □ Female   □ Other

9. What symptoms did he/she have because of their infection?
   Please tick if he/she experienced the following at any point during their infection.
   □ Runny or blocked nose   □ Fever
   □ Coughing   □ Sore throat

   If your child experienced difficulty breathing (e.g. shortness of breath, wheezing) during his/her infection: please tick the relevant box(es) which best describe its effect on your child’s day-to-day activities (e.g. feeding, playing, walking) and the duration it was experienced.
   □ No noticeable effect on his/her day-to-day activities   □ Mildly affected his/her day-to-day activities   □ Significantly affected his/her day-to-day activities

   10. On what date did he/she first experience the symptoms described in Q3?  (Day/Month/Year)

   11. On what date did he/she stop experiencing the symptoms described in Q3?  (Day/Month/Year)

   12a. Did he/she have to take time off school due to their recent infection?
   □ Yes   □ No

   5b. If YES how many days?

   13. Did you seek medical care for your child during these symptoms? (please tick all that apply and indicate the number of times)

   □ a. Phone/email NHS 111 / NHS 24 / NHS Choices   □ times
   □ b. Phone/email GP — response from the receptionist   □ times
   □ c. Phone/email GP — response from the doctor or nurse   □ times
   □ d. Visit (face-to-face) a GP or nurse   □ times
   □ e. Visit A&E department (including out of hours service)   □ times
   □ f. Admitted to hospital (as an inpatient)   □ times

   (If you ticked 6f. please answer i.)

   i. How many nights did he/she spend in hospital all together?

   □ g. None
   □ h. Other medical services, please specify

   □
A — Your child’s health on the worst day (5–14 years old)

By placing a tick in one box in each group below, please indicate which statements best describes your child’s health state on the WORST DAY of their infection.

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 themselves
He/she had no problems washing or dressing themselves □
He/she had some problems washing or dressing themselves □
He/she had a lot of problems washing or dressing themselves □

Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)
He/she had no problems doing their usual activities □
He/she had some problems doing their usual activities □
He/she had a lot of problems doing their 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 were not worried, sad or unhappy □
He/she were a bit worried, sad or unhappy □
He/she were very worried, sad or unhappy □

To help people say how good or bad your child’s health state was on the WORST DAY, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your child’s health was on the WORST DAY of their infection, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your child’s health state was on their WORST DAY.

— Please turn over —

Best imaginable health state

Worst imaginable health state
B — Your child’s health today (5–14 years old)

By placing a tick in one box in each group below, please indicate which statements best describes your child’s health state TODAY.

**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 themselves**
- He/she has no problems washing or dressing themselves
- He/she has some problems washing or dressing themselves
- He/she has a lot of problems washing or dressing themselves

**Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)**
- He/she has no problems doing their usual activities
- He/she has some problems doing their usual activities
- He/she has a lot problems doing their 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

To help people say how good or bad your child’s health state is TODAY, we have drawn a scale (rather like a thermometer) on which the best state you can imagine marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your child’s health is TODAY of their infection, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your child’s health state is TODAY.
There are no questions on this page.
There are no questions on this page.
If a young person or adult who is aged 15 or over in your household fits the following criteria, then it is likely that they were infected with RSV. Please ask them to complete the rest of this questionnaire about their illness. If no one aged 15 or over in your household fulfils the criteria below, please leave this section blank and RETURN ALL the forms.

- You experienced symptoms of respiratory illness (as listed in Q3) between 5 days before the start of your child’s RSV infection, and 5 days after the end of this child’s RSV infection.

If there are multiple persons in your household who fit the criteria, then the oldest should complete this section.

14. How old are you?
   - □ 15 – 24 years old
   - □ 25 – 44 years old
   - □ 45 – 64 years old
   - □ 65 years old or older

15. What is your sex?
   - □ Male
   - □ Female
   - □ Other

16. What symptoms did you have because of your infection?

   Please tick if you experienced the following at any point during your infection.

   - □ Runny or blocked nose
   - □ Fever
   - □ Coughing
   - □ Sore throat

   If you experienced difficulty breathing (e.g. shortness of breath, wheezing) during your infection: please tick the relevant box(es) which best describe its effect on your day-to-day activities (e.g. walking, housework) and the duration it was experienced.

   - □ No noticeable effect on my day-to-day activities
   - □ Mildly affected my day-to-day activities
   - □ Significantly affected my day-to-day activities

   If you ticked 6f. please answer i.)
   - □ How many nights did he/she spend in hospital all together?

17. On what date did you first experience the symptoms described in Q3? (Day/Month/Year)

18. On what date did he/she stop experiencing the symptoms described in Q3? (Day/Month/Year)

19a. Did you have to take time off school or work due to your recent infection?
   - □ Yes
   - □ No

5b. If YES how many days?

   _______ days

20. Did you seek medical care during these symptoms? (please tick all that apply and indicate the number of times)

   - a. Phone/email NHS 111 / NHS 24 / NHS Choices _______ times
   - b. Phone/email GP — response from the receptionist _______ times
   - c. Phone/email GP — response from the doctor or nurse _______ times
   - d. Visit (face-to-face) a GP or nurse _______ times
   - e. Visit A&E department (including out of hours service) _______ times
   - f. Admitted to hospital (as an inpatient) _______ times
   (If you ticked 6f. please answer i.)
   - i. How many nights did he/she spend in hospital all together?

   _______ days

   - g. None
   - h. Other medical services, please specify

   __________________________________________

________________________________________________________________________________________
A — Your health on the worst day (15 years or older)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state on the WORST DAY of your infection.

Mobility
I had no problems in walking about □
I had some problems in 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 □

To help people say how good or bad a health state was on the WORST DAY, we have drawn a scale (rather like a thermometer) on which the best state you can imagine marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is on the WORST DAY of your infection, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is on your WORST DAY.
B — Your health today (15 years or older)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state TODAY.

Mobility
I have no problems in walking about
I have some problems in 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 am in extreme pain or discomfort

Anxiety / Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

To help people say how good or bad a health state is TODAY, we have drawn a scale (rather like a thermometer) on which the best state you can imagine marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is TODAY, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is TODAY.
There are no questions on this page.
Supplementary material for Chapter 4: Development of a model for RSV transmission in England and Wales

S2.1 Calibration

S2.1.1 Probability distributions

<table>
<thead>
<tr>
<th>Notation</th>
<th>Distribution, $X$</th>
<th>Parameters, $\theta$</th>
<th>PDF, $f_X(\theta)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U(a, b)$</td>
<td>Uniform</td>
<td>$a$, lower limit</td>
<td>$1/(b-a)$ for $a \leq x \leq b$, and 0 otherwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$b$, upper limit</td>
<td></td>
</tr>
<tr>
<td>$N(\mu, \sigma)$</td>
<td>Normal</td>
<td>$\mu$, mean</td>
<td>$\frac{1}{\sigma \sqrt{2\pi}} \exp \left( -\frac{(x-\mu)^2}{2\sigma^2} \right)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma$, standard deviation</td>
<td></td>
</tr>
<tr>
<td>$LN(\mu, \sigma)$</td>
<td>Log-normal</td>
<td>$\mu$, mean</td>
<td>$\frac{1}{x \sigma \sqrt{2\pi}} \exp \left( -\frac{\ln(x)-\mu^2}{2\sigma^2} \right)$, $x &gt; 0$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma$, standard deviation</td>
<td></td>
</tr>
<tr>
<td>$N(\mu, \Sigma)$</td>
<td>Multivariate normal (k-dim)</td>
<td>$\mu$, mean vector</td>
<td>$\frac{\exp (-\frac{1}{2}(x-\mu)^T \Sigma^{-1}(x-\mu))}{(2\pi)^{k/2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\Sigma$, covariance matrix</td>
<td></td>
</tr>
<tr>
<td>$TN(\mu, \Sigma, S)$</td>
<td>Multivariate-truncated-normal</td>
<td>$\mu$, mean vector</td>
<td>$\frac{\exp (-\frac{1}{2}(x-\mu)^T \Sigma^{-1}(x-\mu))}{\int_{S} \exp (-\frac{1}{2}(x-\mu)^T \Sigma^{-1}(x-\mu))}$, $x \in S$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\Sigma$, covariance matrix</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$S$, support</td>
<td></td>
</tr>
<tr>
<td>$\beta(a, b)$</td>
<td>Beta</td>
<td>$a$, shape</td>
<td>$\frac{1}{\Gamma(a) b^a} x^{a-1} (1-x)^{b-1}$, $0 &lt; x &lt; 1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$b$, shape</td>
<td></td>
</tr>
<tr>
<td>Gamma($\alpha, \beta$)</td>
<td>Gamma</td>
<td>$\alpha$, shape</td>
<td>$\frac{\exp(-x/\beta) \beta^{-\alpha} x^{\alpha-1}}{\Gamma(\alpha)}$, $x &gt; 0$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\beta$, rate</td>
<td></td>
</tr>
<tr>
<td>Weibull($\lambda, k$)</td>
<td>Weibull</td>
<td>$\lambda$, shape</td>
<td>$\frac{k}{\lambda} \left( \frac{x}{\lambda} \right)^{k-1} \exp \left( -\frac{(x/\lambda)^k}{\lambda} \right)$, $x &gt; 0$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$k$, scale</td>
<td></td>
</tr>
</tbody>
</table>

Table S2.1: Summary of the notation for the probability distributions used in this chapter, where $\Gamma$ is the gamma function and $B$ is the beta function.
### S2.1.2 MCMC parameters

The values for all the parameters used in the MCMC model is given in Table S2.2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_0^k$</td>
<td>Initial value of the parameters for chain $k$</td>
<td>Sample from $p(\theta)$</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Initial mean of the parameters for chain $k$</td>
<td>$\theta_0^k$</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Scaling factor for initial covariance matrix</td>
<td>0.00001</td>
</tr>
<tr>
<td>$I_s$</td>
<td>Initial covariance matrix based on support $S$</td>
<td>See text</td>
</tr>
<tr>
<td>$\Gamma_0$</td>
<td>Initial mean of the parameters for chain $k$</td>
<td>$I_s$</td>
</tr>
<tr>
<td>$\lambda_0^k$</td>
<td>Initial value of non-adaptive the scaling factor for chain number $k$.</td>
<td>0</td>
</tr>
<tr>
<td>$M_0^k$</td>
<td>Initial value of the adaptive scaling factor for chain number $k$.</td>
<td>0</td>
</tr>
<tr>
<td>$T_0^k$</td>
<td>The initial temperature ladder for chain $k$</td>
<td>$10^{7 \frac{t-1}{k-1}}$</td>
</tr>
<tr>
<td>$S_0^k$</td>
<td>The initial distance function for the temperature ladder for chain $k$</td>
<td>$\log(T^{k+1} - T^k)$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Fixed value parameters</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{init}}$</td>
</tr>
<tr>
<td>$T_{\text{burn}}$</td>
</tr>
<tr>
<td>$T_{\text{end}}$</td>
</tr>
<tr>
<td>$k_1$</td>
</tr>
<tr>
<td>$k_2$</td>
</tr>
<tr>
<td>$\beta$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gain factors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_1(t)$</td>
</tr>
<tr>
<td>$\gamma_2(t)$</td>
</tr>
<tr>
<td>$\gamma_3(t)$</td>
</tr>
<tr>
<td>$\gamma_4(t)$</td>
</tr>
<tr>
<td>$\gamma_5(t)$</td>
</tr>
</tbody>
</table>

Table S2.2: Summary of the parameters used to describe the algorithms of the MCMC model

Due to the non-linear nature of the likelihood and the intractable nature of the integrals that arise from the normalising factor, it is not possible to find a close analytic form for the posterior distribution. However, it is possible to sample points from the unnormalised posterior distribution.
\[ p(\theta|D) \propto \mathcal{L}(D|\theta)p(\theta) \]  

through a sampling algorithm called Monte Carlo Markov Chain (MCMC.) Here, \( p(\theta) \) are the prior distributions, \( p(\theta|D) \) is the posterior distribution, given data \( D \). \( \mathcal{L}(D|\theta) \) is the likelihood which tells us the probability of generating the particular sample of data if the parameters in the statistical model are \( \theta \).

### S2.1.3 Likelihood function

Given the data from RDMS, \( \mathcal{D} \), I wish to infer the parameters of the dynamical system, \( \theta = \{\mathcal{M}^m, \mathcal{E}^c\} \), for the five detection models \( c = \{1, 2, 3, 4, 5\} \) and two maternal models, \( m = \{1, 2\} \). Assuming that the number of positive samples for an age group \( j \), week \( w_t \) is a random variable from a binomial distribution with sample size \( Z_{w_t}^{M^m,j} \), and probability of success given by \( \mathcal{E}^c \), the likelihood function is given by:

\[
\mathcal{L}(D|\theta) = \mathcal{L}(D|\mathcal{M}^m, \mathcal{E}^c) = \prod_{j=1}^{52} \prod_{t=1}^{7} \left( \frac{Z_{w_t}^{M^m,j}}{d_{w_t}^{M^m,j}} \right) (\mathcal{E})^{d_{w_t}^{M^m,j}} (1 - \mathcal{E})^{Z_{w_t}^{M^m,j} - d_{w_t}^{M^m,j}} \]  

### S2.1.4 Adaptive Metropolis Hasting algorithm with parallel tempering

To generate samples from the posterior distribution, I use the random walk Metropolis algorithm. This algorithm produces a Markov chain, \( \theta \) which has a stationary distribution which converges to the desired posterior distribution. The algorithm works by sampling a value from a proposal distribution \( \theta^* \sim q(\theta) \), and then probabilistically accepting this value into the Markov chain according to the following probability given by

\[
a(\theta_t, \theta^*) = \min \left( 1, \frac{\mathcal{L}(\theta^*)p(\theta^*)q(\theta_t|\theta^*)}{\mathcal{L}(\theta_t)p(\theta_t)q(\theta^*|\theta_t)} \right) \]  

In our analysis, the proposal distribution distribution, \( q(\cdot|\theta) \), is a multivariate normal distribution, truncated at points relative to the support of the sample, \( \mathcal{S} \).

**Adaptive Metropolis Hasting**

I use an advanced random walk Metropolis Hasting method called adaptive parallel tempering with adaptive temperature ladder to optimise run times. The adaptive metropolis hasting algorithm provides systematic method for modifying the shape of the...
proposal distribution based on the accepted steps of the current Markov chain, allowing for more efficient mixing of chains. Consequently, in order to provide a reasonable estimate for the covariance matrix, the Markov chain runs for an initial number of steps ($T_{\text{init}}$) from a truncated normal proposal distribution with a covariance matrix, $I_s$ which is calculated using the upper and lower bounds of the support $[s_{k0}, s_{k1}] \in S$, through $i_{k,k} = (s_{k1} - s_{k0})/\zeta$ and $i_{i,j} = 0$ otherwise, where $\zeta$ is a scaling factor.

Problematically, the proposal distribution using the covariance matrix, $\Sigma$, is no longer memoryless, and therefore chain may no longer converge to the correct stationary distribution. To overcome this problem, the proposal distribution must also sample from a non-adaptive Gaussian distribution modified to ensure that changes to the covariance matrix diminish over time. Further, to improve chain mixing and to optimise convergence rates, I include adaptive scaling factors, $\lambda_t$ and $M_t$ for the initial non-adaptive and adaptive proposals respectively, who’s magnitude diminish with the number of steps in the chain. The adaptive scaling factor for the non-adaptive proposal distributions stops once the model starts sampling from the adaptive proposal distributions. Overall, the combined non-adaptive and adaptive proposal distributions for the adaptive Metropolis Hastings is given by

\[
q(\cdot | \theta_t) = \begin{cases} \mathcal{N}(\theta_t, \exp(\lambda_t) I_s; S) & t \leq T_{\text{init}} \\ \mathcal{N}(\theta_t, \exp(\lambda_{t_{\text{init}}}) I_s; S) & t > T_{\text{init}} \end{cases} \]

with probability $\beta$, \[\mathcal{N}(\theta_t, \exp(\lambda_{t_{\text{init}}}) I_s; S) \quad \text{with probability } 1 - \beta\]

where $\Sigma_t = \exp(M_t) \Gamma_t$ and $M_t$, $\lambda_t$ and $\Gamma_t$ are updated iteratively through the stochastic approximation algorithm:

\[
\begin{align*}
M_{t+1} &= M_t + \gamma_1(t)(a(\theta_t, \theta^*) - 0.234) \\
\mu_{t+1} &= \mu_t + \gamma_2(t)(\mu_t - \theta_t) \\
\Gamma_{t+1} &= \Gamma_t + \gamma_3(t)[(\theta_t - \mu_{t+1})(\theta_t - \mu_{t+1})]^T - \Gamma_t \\
\lambda_{t+1} &= \lambda_t + \gamma_4(t)(a(\theta_t, \theta^*) - 0.234)
\end{align*}
\]

where $\gamma(t)$ are gain factors. A pseudo code outlining the algorithm for this procedure is by Algorithm 1.
Initialise $\theta_0, M_0, \lambda_0, \mu_0, \Sigma_0$:

$t = 1$;

for $t < T_{\text{end}}$ do

$b \sim U(0, 1)$

if $t < T_{\text{init}}$ OR $b < \beta$ then

$\theta^* \sim \mathcal{TN}(\theta_t, \exp(\lambda_t)\Gamma_{\text{init}}; S)$

else

$\theta^* \sim \mathcal{TN}(\theta_t, \Sigma_{t+1}; S)$

end

$u \sim U(0, 1)$

if $a(\theta_t, \theta^*) > u$ then

$\theta_{t+1} = \theta_t$

else

$\theta_{t+1} = \theta^*_t$

end

$t = t + 1$

if $t < T_{\text{init}}$ then

Update $\lambda_{t+1}$

end

Update $M_{t+1}, \mu_{t+1}, \Gamma_{t+1}$

end

Algorithm 1: Pseudo-code for adaptive Metropolis Hastings algorithm

Parallel Tempering

In order to prevent local-trap problem and overcome multimodal likelihood spaces, I used a parallel tempering algorithm. In this algorithm I consider the augmented space $(\theta, T)$, where $T$ is a scalar (temperature) and define the posterior distribution as

$$p(\theta, T|D) \propto [\mathcal{L}(D|\theta)p(\theta)]^{1/T}$$

where, at higher temperatures (i.e. larger $T$ value), the Markov chain more likely to accept proposal values and thus more free to explore the parameter space. In the algorithm, I run $K$ chains simultaneously, $(\theta^k, T^k)$ with $T^K > \cdots > T^1 > T^0 = 1$, and at each time step, $t$, I allow two adjacent chains $(\theta^k_t, T^k_t)$ and $(\theta^{k+1}_t, T^{k+1}_t)$ to swap their current positions $\theta^k_t$ and $\theta^{k+1}_t$ according to the swap probability
\[ \alpha_s(\theta^k_t, T^k_t; \theta^{k+1}_t, T^{k+1}_t) = \min \left(1, \left[ \frac{\mathcal{L}(\mathcal{D}|\theta^{k+1}_t)p(\theta^{k+1}_t)}{\mathcal{L}(\mathcal{D}|\theta^k_t)p(\theta^k_t)} \right]^{\left(\frac{1}{T^k_t} - \frac{1}{T^{k+1}_t}\right)} \right) \]

By allowing adjacent chains to swap positions, if one of the hotter chains (chains with a large \( T \) value) finds a local maximum, the position will be passed down the temperature ladder to the coldest chain \( (T^1 = 1) \). Therefore, by only monitoring the coldest few chains, an overview of the explorations of all the chains can be assessed.

To optimise exploration of the parameter space, the chains must swap at an acceptance rate of 0.234. Therefore, \( I \) update the values of the temperature at each step through an stochastic approximation to ensure the acceptance rate is optimal through the iterative updates:

\[ S^{k+1}_t = S^k_t + \gamma_5(t)(\alpha_s(\theta^k_t, T^k_t; \theta^{k+1}_t, T^{k+1}_t) - 0.234) \]

\[ T^{k+1}_t = T^k_t + \exp(S^{k+1}_t) \]

The algorithm for parallel tempering with adaptive temperature update is given Algorithm 2.
Initialise \((\theta^k_0, T^k_0)\) for \(1 \leq k \leq K\);

t = 1;

for \(t < T_{\text{end}}\) do

\[\begin{align*}
\text{for } 1 \leq k \leq K \text{ do} \\
&\text{Update } \theta^k_t \rightarrow \theta^k_{t+1} \text{ as in Algorithm 1} \\
\text{end}
\]

\[\begin{align*}
\text{for } 1 \leq k \leq K \text{ do} \\
&k \sim U_d(1, K - 1); \\
b \sim U(0, 1); \\
\text{if } a(\theta^k_{t}, T^k_{t}; \theta^{k+1}_{t}, T^{k+1}_{t}) > u \text{ then} \\
&(\theta^k_{t}, T^k_{t}) \rightarrow (\theta^{k+1}_{t}, T^{k}_{t}); \\
&(\theta^{k+1}_{t}, T^{k+1}_{t}) \rightarrow (\theta^k_{t}, T^{k+1}_{t}) \\
\text{else} \\
\text{end}
\end{align*}\]

\[\begin{align*}
&\text{Update } S^k_{t+1} \\
\text{end}
\]

\[\begin{align*}
\text{for } 1 \leq k \leq K \text{ do} \\
&\text{Update } T^k_{t+1} \\
\text{end}
\end{align*}\]

end

Algorithm 2: Pseudo-code for parallel tempering algorithm
Supplementary material for Chapter 5: Evaluating the impact of potential intervention programmes

S3.1 Equations of the adapted models

S3.1.1 Status quo (Palivizumab)

The ODEs of the Palivizumab programme for age group \( a \) and clinical-risk group \( r \) are:
\[ M^{a,r} = \mu p \mu p^{a,r} I_1(a)(1 - \phi_{P,Pal}^{a,r}) - \xi M^{a,r} \]

Transmission terms

\[ S^{a,r}_1 = (1 - p)\mu p^{a,r} I_1(a)(1 - \phi_{P,Pal}^{a,r}) + \xi M^{a,r} - \lambda_0^{a,r}(t)S_0^{a,r} \]
\[ E_0^{a,r} = \lambda_0^{a,r}(t)S_0^{a,r} - \sigma E_0^{a,r} \]
\[ A_0^{a,r} = p^r \sigma E_0^{a,r} - \gamma_0 A_0^{a,r} \rho \]
\[ I_0^{a,r} = (1 - p^r)\sigma E_0^{a,r} - \gamma_0 I_0^{a,r} \]
\[ R_0^{a,r} = \rho_0 A_0^{a,r} + \gamma_0 I_0^{a,r} - \omega R_0^{a,r} \]
\[ S_1^{a,r} = \omega R_0^{a,r} - \lambda_1^{a,r}(t)S_1^{a,r} \]
\[ E_1^{a,r} = \lambda_1^{a,r}(t)S_1^{a,r} - \sigma E_1^{a,r} \]
\[ A_1^{a,r} = p^r \sigma E_1^{a,r} - \gamma_1 A_1^{a,r} \rho \]
\[ I_1^{a,r} = (1 - p^r)\sigma E_1^{a,r} - \gamma_1 I_1^{a,r} \]
\[ R_1^{a,r} = \rho_1 A_1^{a,r} + \gamma_1 I_1^{a,r} - \omega R_1^{a,r} \]
\[ S_2^{a,r} = \omega R_1^{a,r} - \lambda_2^{a,r}(t)S_2^{a,r} \]
\[ E_2^{a,r} = \lambda_2^{a,r}(t)S_2^{a,r} - \sigma E_2^{a,r} \]
\[ A_2^{a,r} = p^r \sigma E_2^{a,r} - \gamma_2 A_2^{a,r} \rho \]
\[ I_2^{a,r} = (1 - p^r)\sigma E_2^{a,r} - \gamma_2 I_2^{a,r} \]
\[ R_2^{a,r} = \rho_2 A_2^{a,r} + \gamma_2 I_2^{a,r} - \omega R_2^{a,r} \]
\[ S_3^{a,r} = \omega R_2^{a,r} + \omega R_3^{a,r} - \lambda_3^{a,r}(t)S_3^{a,r} \]
\[ E_3^{a,r} = \lambda_3^{a,r}(t)S_3^{a,r} - \sigma E_3^{a,r} \]
\[ A_3^{a,r} = p^r \sigma E_3^{a,r} - \gamma_3 A_3^{a,r} \rho \]
\[ I_3^{a,r} = (1 - p^r)\sigma E_3^{a,r} - \gamma_3 I_3^{a,r} \]
\[ R_3^{a,r} = \rho_3 A_3^{a,r} + \gamma_3 I_3^{a,r} - \omega R_3^{a,r} \]
\[ V_p^{a,r} = \mu p^{a,r} I_1(a)\phi_{P,Pal}^{a,r} + (N^{a,r} - V_p^{a,r})\phi_{P,Pal}^{a,r} \]
\[ Z^{a,r} = \sigma(E_3^{a,r} + E_3^{a,r} + E_3^{a,r} + E_3^{a,r}) \]

Aging terms

\[ -\eta M^{a,r} + \eta^{a-1} M^{a-1} p^{a,r} (1 - \phi_{P,Pal}^{a,r}) \]

Palivizumab terms

\[ + V_p^{a,r} \omega_{Pal} \]

(S3.1)
where an overdot refers to differentiation with respect to $t$, $\mathbb{1}_1(a)$ is the indicator function (non-zero at $a = 1$), and the equation for the force of infection is:

$$
\lambda^{a,r}_i(t) = q_p f_i(t) \sum_{b=1}^{25} \frac{(p^{a,b} + q_c c^{a,b})}{N_b} \left( \sum_{r, i} A^{b,r}_{i} \alpha + I^{b,r}_i \right)
$$

where $\sum_{r, i}$ is the sum over all the Palivizumab eligible and non-Palivizumab eligible clinical-risk groups, and exposure groups $i = \{0, 1, 2, 3\}$ and $f_i(t) = q_p (1 + b_1 \exp((t - \phi)^2/(2\psi^2))) \prod_{i=0}^{i} \delta_{i'}$. Further, $\phi_{\text{Pal}}^{a,r}$ is the number of persons who are protected by Palivizumab in age group $a$ and clinical-risk group $r$. The initial conditions for this set of ODEs are given in Chapter 4 with $N = N^{a,r}$ and $V_p^{a,r} = 0$.

### S3.1.2 Long-acting monoclonal-antibodies

The ODEs of the RSV intervention model for the long-acting monoclonal antibodies programmes, for age group $a$ and clinical-risk group $r$ are:
\[
\begin{align*}
M_{a,r} &= \mu a \mu^a r \mathbb{I}_1(a) (1 - \phi_{P,mab}^a r) - \xi M_{a,r}^m

S_{a,r} &= (1 - p_a) \mu a \mu^a r \mathbb{I}_1(a) (1 - \phi_{P,mab}^a r) + \xi M_{a,s}^m - \lambda_{a,r}^a (t) s_{a,r}^m

E_{0,a} &= \lambda_{a,r}^a (t) s_{0,a}^m - \sigma E_{0,a}^m

A_{0,a} &= \gamma_{a,r}^a a_{0,a}^r - \gamma_{a,r}^a a_{0,a}^r \rho

I_{0,a} &= (1 - p_a) \sigma E_{0,a}^m - \gamma_{0,a}^m

R_{0,a} &= \gamma_{0,a}^m a_{0,a}^r + \gamma_{0,a}^m a_{0,a}^r - \omega R_{0,a}^m

S_{1,a} &= \omega R_{0,a}^m - \lambda_{1,a}^a (t) s_{1,a}^m

E_{1,a} &= \lambda_{1,a}^a (t) s_{1,a}^m - \sigma E_{1,a}^m

A_{1,a} &= \gamma_{1,a}^a a_{1,a}^r + \gamma_{1,a}^a a_{1,a}^r - \omega R_{1,a}^m

I_{1,a} &= (1 - p_a) \sigma E_{1,a}^m - \gamma_{1,a}^m

R_{1,a} &= \gamma_{1,a}^m a_{1,a}^r + \gamma_{1,a}^m a_{1,a}^r - \omega R_{1,a}^m

S_{2,a} &= \omega R_{1,a}^m - \lambda_{2,a}^a (t) s_{2,a}^m

E_{2,a} &= \lambda_{2,a}^a (t) s_{2,a}^m - \sigma E_{2,a}^m

A_{2,a} &= \gamma_{2,a}^a a_{2,a}^r + \gamma_{2,a}^a a_{2,a}^r - \omega R_{2,a}^m

I_{2,a} &= (1 - p_a) \sigma E_{2,a}^m - \gamma_{2,a}^m

R_{2,a} &= \gamma_{2,a}^m a_{2,a}^r + \gamma_{2,a}^m a_{2,a}^r - \omega R_{2,a}^m

S_{3,a} &= \omega R_{2,a}^m + \omega R_{3,a}^m - \lambda_{3,a}^a (t) s_{3,a}^m

E_{3,a} &= \lambda_{3,a}^a (t) s_{3,a}^m - \sigma E_{3,a}^m

A_{3,a} &= \gamma_{3,a}^a a_{3,a}^r + \gamma_{3,a}^a a_{3,a}^r - \omega R_{3,a}^m

I_{3,a} &= (1 - p_a) \sigma E_{3,a}^m - \gamma_{3,a}^m

R_{3,a} &= \gamma_{3,a}^m a_{3,a}^r + \gamma_{3,a}^m a_{3,a}^r - \omega R_{3,a}^m

V_{0,a} &= \mu a \mu^a r \mathbb{I}_1(a) (1 - \phi_{P,mab}^a r) + (\lambda_{a,r}^a - V_{P,a}^m) \phi_{P,mab}^a r

Z_{a,r} &= \sigma (E_{0,a}^m + E_{1,a}^m + E_{2,a}^m + E_{3,a}^m)
\end{align*}
\]
where an overdot refers to differentiation with respect to $t$, $1_1(a)$ is the indicator function (non-zero at $a = 1$), and the equations for the force of infection is:

$$
\lambda_{i}^{a,r}(t) = q_{p}f_{i}(t) \sum_{b=1}^{25} \left( \frac{p_{a,b} + q_{c}c_{a,b}}{N_{b}} \right) \left( N_{b} \right) \left( \sum_{r,i} A_{r,i}^{a,b} \alpha + I_{i}^{a,b} \right)
$$

where $\sum_{r,i}$ is the sum over all risk groups $R = \{NR, HR, VHR\}$ and exposure groups $i = \{0, 1, 2, 3\}$ and $f_{i}(t) = q_{p}(1 + b_{1}\exp((t - \phi)^{2}/(2\psi^{2}))) \prod_{i'=0}^{i} \delta_{i'}$. Further, $\phi_{P,mab}^{a,r}$ is the number of persons who are protected by monoclonal antibodies in age group $a$ and clinical risk group $r$. The initial conditions for this set of ODEs are given in Chapter 4 with $N = N^{a,r}$ and $V_{M}^{a,r} = 0$.

### S3.1.3 Childhood/elderly vaccination programmes

The ODEs of the RSV intervention model for the above childhood and elderly programmes, for age group $a$ and clinical-risk group $r$ are:
\[ M^{a,r} = \left( \frac{\rho R}{I_a} \right)^{\bar{r}_a} \left( 1 - \phi_{p,pal}^{a,r} \right) - \xi M^{a,r} \]

\[ S_0^{a,r} = (1 - \rho R) m^{a,r} + 1 \left( 1 - \phi_{p,pal}^{a,r} \right) + \xi M^{a,s} - \lambda_0^{a,r}(t) S_0^{a,r} \]

\[ P_0^{a,r} = \lambda_0^{a,r}(t) S_0^{a,r} - \sigma E_0^{a,r} \]

\[ A_0^{a,r} = p^a \sigma E_0^{a,r} - \gamma_0 A_0^{a,r} \rho \]

\[ I_0^{a,r} = (1 - \rho^a) \sigma E_0^{a,r} - \gamma_1 I_0^{a,r} \]

\[ R_0^{a,r} = \rho \gamma_0 A_0^{a,r} + \gamma_0 I_0^{a,r} - \omega R_0^{a,r} \]

\[ S_1^{a,r} = \omega R_0^{a,r} - \lambda_1^{a,r}(t) S_1^{a,r} \]

\[ E_1^{a,r} = \lambda_1^{a,r}(t) S_1^{a,r} - \sigma E_1^{a,r} \]

\[ A_1^{a,r} = p^a \sigma E_1^{a,r} - \gamma_1 A_1^{a,r} \rho \]

\[ I_1^{a,r} = (1 - \rho^a) \sigma E_1^{a,r} - \gamma_1 I_1^{a,r} \]

\[ R_1^{a,r} = \rho \gamma_1 A_1^{a,r} + \gamma_1 I_1^{a,r} - \omega R_1^{a,r} \]

\[ S_2^{a,r} = \omega R_1^{a,r} - \lambda_2^{a,r}(t) S_2^{a,r} \]

\[ E_2^{a,r} = \lambda_2^{a,r}(t) S_2^{a,r} - \sigma E_2^{a,r} \]

\[ A_2^{a,r} = p^a \sigma E_2^{a,r} - \gamma_2 A_2^{a,r} \rho \]

\[ I_2^{a,r} = (1 - \rho^a) \sigma E_2^{a,r} - \gamma_2 I_2^{a,r} \]

\[ R_2^{a,r} = \rho \gamma_2 A_2^{a,r} + \gamma_2 I_2^{a,r} - \omega R_2^{a,r} \]

\[ S_3^{a,r} = \omega R_2^{a,r} + \omega R_3^{a,r} - \lambda_3^{a,r}(t) S_3^{a,r} \]

\[ E_3^{a,r} = \lambda_3^{a,r}(t) S_3^{a,r} - \sigma E_3^{a,r} \]

\[ A_3^{a,r} = p^a \sigma E_3^{a,r} - \gamma_3 A_3^{a,r} \rho \]

\[ I_3^{a,r} = (1 - \rho^a) \sigma E_3^{a,r} - \gamma_3 I_3^{a,r} \]

\[ R_3^{a,r} = \rho \gamma_3 A_3^{a,r} + \gamma_3 I_3^{a,r} - \omega R_3^{a,r} \]

\[ V_p^{a,r} = \mu p^{a,r} \chi_1(n) \phi_{p,pal}^{a,r} + (N^{a,r} - V_p^{a,r}) \phi_{p,pal}^{a,r} \]

\[ Z^{a,r} = \sigma (E_0^{a,r} + E_1^{a,r} + E_2^{a,r} + E_3^{a,r}) \]
where an overdot refers to differentiation with respect to \( t \), \( \mathbb{I}_1(a) \) is the indicator function (non-zero at \( a = 1 \)), and the equation for the force of infection is:

\[
\lambda_{i}^{a,r}(t) = q_{p} f_{i}(t) \sum_{b=1}^{25} \left( \frac{p^{a,b} + q_{c} c^{a,b}}{N_{b}} \right) \left( \sum_{r,i} A_{r}^{b,r} \alpha + I_{i}^{b,r} \right)
\]

where \( \sum_{r,i} \) is the sum over all risk groups \( \mathcal{R} = \{ NR, HR, VHR \} \) and exposure groups \( i = \{ 0, 1, 2, 3 \} \) and \( f_{i}(t) = q_{p}(1 + b_{i} \exp((t - \phi)^2/(2\psi^2)) \prod_{i' = 0}^{i} \delta_{i'} \). Further, \( \phi^{a,r}_{p,pal} \) is the number of persons who are protected by Palivizumab in age group \( a \) and clinical risk group \( r \), and \( \phi^{a,r}_{p,vac} \) is the number of persons protected by vaccination in age group \( a \) and clinical risk group \( a \) at time \( t \). The initial conditions for this set of ODEs are given in Chapter 4 with \( N = N^{a,r} \) and \( V_{p}^{a,r} = 0 \).

**Uptake rate for Influenza \( (q_{I}) \)**

The rate at which the coverage is reached for some of the programmes is estimated using data on seasonal influenza uptake. The cumulative uptake of LAV over the seasonal, given by \( q_{I} \) is summarised in Figure S3.1 for various age groups.
**Figure S3.1**: Uptake rate for various age groups for the 2018/19 Influenza season.
S3.1.4 Maternal vaccination

Transmission terms

\[
M^{a,r,s} = p \rho_0 p^{a,r,s} u^{a,s} 1(a)(1 - \phi_{P,pal}^{a,r,s})(1 - \phi_{P,mat}^{a,r,s}) + \phi_{P,mat}^{a,r,s} p^{a,r,s} u^{a,s} 1(a) - \xi M^{a,r,s}
\]

\[
S_0^{a,r,s} = (1 - p) \rho_0 p^{a,r,s} u^{a,s} 1(a)(1 - \phi_{P,pal}^{a,r,s}) + \xi M^{a,r,s} - \lambda_0^{a,r,s}(t) S_0^{a,r,s}
\]

\[
E_0^{a,r,s} = \lambda_0^{a,r,s}(t) S_0^{a,r,s} - \sigma E_0^{a,r,s}
\]

\[
A_0^{a,r,s} = p^s \sigma E_0^{a,r,s} - \gamma_0 A_0^{a,r,s}
\]

\[
I_0^{a,r,s} = (1 - p^s) \sigma E_0^{a,r,s} - \gamma_1 I_0^{a,r,s}
\]

\[
R_0^{a,r,s} = \rho_0 A_0^{a,r,s} + \gamma_0 I_0^{a,r,s} - \omega R_0^{a,r,s}
\]

\[
S_1^{a,r,s} = \omega R_0^{a,r,s} - \lambda_1^{a,r,s}(t) S_1^{a,r,s}
\]

\[
E_1^{a,r,s} = \lambda_1^{a,r,s}(t) S_1^{a,r,s} - \sigma E_1^{a,r,s}
\]

\[
A_1^{a,r,s} = p^s \sigma E_1^{a,r,s} - \gamma_1 A_1^{a,r,s}
\]

\[
I_1^{a,r,s} = (1 - p^s) \sigma E_1^{a,r,s} - \gamma_1 I_1^{a,r,s}
\]

\[
R_1^{a,r,s} = \rho_1 A_1^{a,r,s} + \gamma_1 I_1^{a,r,s} - \omega R_1^{a,r,s}
\]

\[
S_2^{a,r,s} = \omega R_1^{a,r,s} - \lambda_2^{a,r,s}(t) S_2^{a,r,s}
\]

\[
E_2^{a,r,s} = \lambda_2^{a,r,s}(t) S_2^{a,r,s} - \sigma E_2^{a,r,s}
\]

\[
A_2^{a,r,s} = p^s \sigma E_2^{a,r,s} - \gamma_2 A_2^{a,r,s}
\]

\[
I_2^{a,r,s} = (1 - p^s) \sigma E_2^{a,r,s} - \gamma_2 I_2^{a,r,s}
\]

\[
R_2^{a,r,s} = \rho_2 A_2^{a,r,s} + \gamma_2 I_2^{a,r,s} - \omega R_2^{a,r,s}
\]

\[
S_3^{a,r,s} = \omega R_2^{a,r,s} + \omega R_3^{a,r,s} - \lambda_3^{a,r,s}(t) S_3^{a,r,s}
\]

\[
E_3^{a,r,s} = \lambda_3^{a,r,s}(t) S_3^{a,r,s} - \sigma E_3^{a,r,s}
\]

\[
A_3^{a,r,s} = p^s \sigma E_3^{a,r,s} - \gamma_3 A_3^{a,r,s}
\]

\[
I_3^{a,r,s} = (1 - p^s) \sigma E_3^{a,r,s} - \gamma_3 I_3^{a,r,s}
\]

\[
R_3^{a,r,s} = \rho_3 A_3^{a,r,s} + \gamma_3 I_3^{a,r,s} - \omega R_3^{a,r,s}
\]

\[
V_{P,pal}^{a,r,s} = \mu_0 p^{a,r,s} u^{a,s} 1(a) \phi_{P,pal}^{p,a,s} + (N^{a,r,s} - V_{P,pal}^{a,r,s}) \phi_{P,pal}^{a,r,s}
\]

\[
Z^{a,r,s} = \sigma(E_0^{a,r,s} + E_1^{a,r,s} + E_2^{a,r,s} + E_3^{a,r,s})
\]

Aging terms

\[
-\eta^a M^{a,r,s} + \eta^a -1 M^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a S_0^{a,r,s} + \eta^a -1 S_0^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a E_0^{a,r,s} + \eta^a -1 E_0^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a A_0^{a,r,s} + \eta^a -1 A_0^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a I_0^{a,r,s} + \eta^a -1 I_0^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a R_0^{a,r,s} + \eta^a -1 R_0^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a S_1^{a,r,s} + \eta^a -1 S_1^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a E_1^{a,r,s} + \eta^a -1 E_1^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a A_1^{a,r,s} + \eta^a -1 A_1^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a I_1^{a,r,s} + \eta^a -1 I_1^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a R_1^{a,r,s} + \eta^a -1 R_1^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a S_2^{a,r,s} + \eta^a -1 S_2^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a E_2^{a,r,s} + \eta^a -1 E_2^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a A_2^{a,r,s} + \eta^a -1 A_2^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a I_2^{a,r,s} + \eta^a -1 I_2^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a R_2^{a,r,s} + \eta^a -1 R_2^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a S_3^{a,r,s} + \eta^a -1 S_3^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a E_3^{a,r,s} + \eta^a -1 E_3^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a A_3^{a,r,s} + \eta^a -1 A_3^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a I_3^{a,r,s} + \eta^a -1 I_3^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a R_3^{a,r,s} + \eta^a -1 R_3^{a-1} p^{a,r,s} u^{a,s} \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
-\eta^a V_{P,pal}^{a,r,s} + \eta^a -1 V_{P,pal}^{a,r,s} p^{a,r,s} u^{a,s}
\]

\[
-\eta^a \phi_0(1 - \phi_{P,pal}^{a,r,s})
\]

\[
+ V_{P,pal}^{a,r,s} \omega_{pal}
\]

Palliative terms

\[
+ S_0^{a,r,s} \phi_{P,mat}
\]

Vaccination terms

\[
- S_0^{a,r,s} \phi_{P,mat}
\]
where the force of infection is given by defining $I_{b,s} = \sum_{i,r} A_{i}^{b,r,s} \alpha + I_{b,r,s}^{i}$ for maternal vaccine groups, $s = \{n, p, c\}$, then the equations for the force of infection for the three maternal vaccine states are:

$$
\lambda_{a,r,n}^{i}(t) = q_{p} f_{i}(t) \sum_{b=1}^{25} \left[ \left( p_{a(n),b(n)} + q_{c} c_{a(n),b(n)} \right) I_{b,n}^{n} \right] + \left( p_{a(n),b(p)} + q_{c} c_{a(n),b(p)} \right) I_{b,p}^{n} + \left( p_{a(n),b(c)} + q_{c} c_{a(n),b(c)} \right) I_{b,c}^{n} \right]$$

(S3.5)

$$
\lambda_{a,r,p}^{i}(t) = q_{p} f_{i}(t) \sum_{b=1}^{25} \left[ \left( p_{a(p),b(n)} + q_{c} c_{a(p),b(n)} \right) I_{b,n}^{p} \right] + \left( p_{a(p),b(p)} + q_{c} c_{a(p),b(p)} \right) I_{b,p}^{p} + \left( p_{a(p),b(c)} + q_{c} c_{a(p),b(c)} \right) I_{b,c}^{p} \right]$$

(S3.6)

$$
\lambda_{a,r,c}^{i}(t) = q_{p} f_{i}(t) \sum_{b=1}^{25} \left[ \left( p_{a(c),b(n)} + q_{c} c_{a(c),b(n)} \right) I_{b,n}^{c} \right] + \left( p_{a(c),b(p)} + q_{c} c_{a(c),b(p)} \right) I_{b,p}^{c} + \left( p_{a(c),b(c)} + q_{c} c_{a(c),b(c)} \right) I_{b,c}^{c} \right]$$

(S3.7)

where the contact matrices are defined in Table S3.1. These contact matrices are modified versions of the matrices outlined in the mathematical model used to evaluate the impact of maternal Pertussis vaccines.149
<table>
<thead>
<tr>
<th>Participant</th>
<th>Contact, Age group (a), Maternal-vaccine group (s_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (a) (yrs)</td>
<td>Maternal-vaccine group (s_1)</td>
</tr>
<tr>
<td>&lt;1yrs</td>
<td>n</td>
</tr>
<tr>
<td>15–44yrs</td>
<td>n</td>
</tr>
<tr>
<td>1–14, 45+</td>
<td>n</td>
</tr>
</tbody>
</table>

**Table S3.1:** Formulae for synthesing the contact matrices with maternal-vaccine stratification.

- **Symbol**
  - \( p^{a,b}_H \): Number of daily household physical contacts only made by age group \( a \) with age group \( b \)
  - \( p^{a,(s_1),b,(s_2)} \): Total number of daily household physical contacts made by age group \( a \) and maternal vaccine group \( s_1 \) with age group \( b \) and maternal vaccine group \( s_2 \). \( s_i = \{n, p, c\} \)
  - \( c^{a,b}_H \): Number of daily household conversational contacts only made by age group \( a \) with age group \( b \)
  - \( c^{a,(s_1),b,(s_2)} \): Total number of daily conversational contacts made by age group \( a \) and maternal vaccine group \( s_1 \) with age group \( b \) and maternal vaccine group \( s_2 \). \( s_i = \{n, p, c\} \)

**Source**
- 113, 117
- Generated by Table S3.1

Further, \( \phi^{a,r}_{P,pal} \) is the number of persons who are protected by monoclonal antibodies in age group \( a \) and clinical risk group \( r \) and \( \phi^{a,r}_{P,vac} \) is...
the number of persons protected by vaccination in age group $a$ and clinical risk group $r,s$ at time $t$. The initial conditions for this set of ODEs are given in Chapter 4 with $N = N^{a,r,s}$ and $V_P^{a,r,s} = 0$. 
Supplementary material for Chapter 6: Cost-effectiveness analysis of intervention programmes

S4.1 QALY loss for death per age

<table>
<thead>
<tr>
<th>Age</th>
<th>Life expectancy</th>
<th>Mean QALY loss for death (at 3.5% discounting rate)</th>
<th>Uncertainty for QALY loss for death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1mo</td>
<td>81.240</td>
<td>26.0456</td>
<td>Weibull(37.631, 26.224)</td>
</tr>
<tr>
<td>1</td>
<td>81.183</td>
<td>26.0425</td>
<td>Weibull(38.327, 26.235)</td>
</tr>
<tr>
<td>2</td>
<td>81.127</td>
<td>26.0395</td>
<td>Weibull(37.224, 26.211)</td>
</tr>
<tr>
<td>3</td>
<td>81.070</td>
<td>26.0334</td>
<td>Weibull(37.086, 26.208)</td>
</tr>
<tr>
<td>4</td>
<td>81.013</td>
<td>26.0302</td>
<td>Weibull(37.232, 26.219)</td>
</tr>
<tr>
<td>5</td>
<td>80.957</td>
<td>26.0271</td>
<td>Weibull(37.479, 26.211)</td>
</tr>
<tr>
<td>6</td>
<td>80.900</td>
<td>26.0239</td>
<td>Weibull(37.347, 26.211)</td>
</tr>
<tr>
<td>7</td>
<td>80.843</td>
<td>26.0208</td>
<td>Weibull(37.817, 26.210)</td>
</tr>
<tr>
<td>8</td>
<td>80.787</td>
<td>26.0176</td>
<td>Weibull(37.195, 26.198)</td>
</tr>
<tr>
<td>9</td>
<td>80.730</td>
<td>26.0144</td>
<td>Weibull(37.348, 26.195)</td>
</tr>
<tr>
<td>10</td>
<td>80.673</td>
<td>26.0113</td>
<td>Weibull(36.975, 26.120)</td>
</tr>
<tr>
<td>11</td>
<td>80.617</td>
<td>26.0081</td>
<td>Weibull(37.435, 26.187)</td>
</tr>
<tr>
<td>1yr</td>
<td>80.560</td>
<td>25.9526</td>
<td>Weibull(36.955, 26.193)</td>
</tr>
<tr>
<td>2</td>
<td>79.500</td>
<td>25.8944</td>
<td>Weibull(36.282, 26.136)</td>
</tr>
<tr>
<td>3</td>
<td>78.500</td>
<td>25.8342</td>
<td>Weibull(35.037, 26.080)</td>
</tr>
<tr>
<td>4</td>
<td>77.600</td>
<td>25.6393</td>
<td>Weibull(34.188, 26.036)</td>
</tr>
<tr>
<td>5–9</td>
<td>74.615</td>
<td>25.5943</td>
<td>Weibull(31.925, 25.872)</td>
</tr>
<tr>
<td>10–14</td>
<td>69.643</td>
<td>25.2649</td>
<td>Weibull(28.079, 25.532)</td>
</tr>
<tr>
<td>25–34</td>
<td>52.445</td>
<td>23.3148</td>
<td>Weibull(18.632, 23.757)</td>
</tr>
<tr>
<td>35–44</td>
<td>42.795</td>
<td>21.5683</td>
<td>Weibull(14.880, 22.085)</td>
</tr>
<tr>
<td>44–54</td>
<td>33.415</td>
<td>19.1862</td>
<td>Weibull(11.927, 19.818)</td>
</tr>
<tr>
<td>55–64</td>
<td>24.493</td>
<td>16.0485</td>
<td>Weibull(9.8262, 16.698)</td>
</tr>
<tr>
<td>75+</td>
<td>8.0987</td>
<td>6.90928</td>
<td>Weibull(7.113, 7.344)</td>
</tr>
</tbody>
</table>

Table S4.1: Summary of the life expectancy (ONS 2018 estimate\textsuperscript{143}) and QALY loss for each age group assuming a 3.5% discount rate.
Bibliography


Roy LMC. Deriving health utility weights for infants with Respiratory Syncytial Virus (RSV) [Masters Thesis]. The University of British Columbia; 2013.


Kravetz HM, Knight V, Chanock RM. Respiratory Syncytial Virus III: Production of illness and clinical observations in adult volunteers. JAMA. 1961;176:657.


71 White LJ, Waris M, Cane PA, Nokes DJ, Medley GF. The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Fin-


95 Okiro EA, White LJ, Ngama M, Cane PA, Medley GF, Nokes DJ. Duration of shedding of respiratory syncytial virus in a community study of Kenyan children. BMC Infectious Diseases. 2010;10:15.


119 La BB, Miasojedow Z, And EM, Vihola M. Adaptive Parallel Tempering Algorithm; 2012.


144 Bernard B. SF-6D Population Norms. 2012;.


