THE EPIDEMIOLOGY OF RESPIRATORY SYNCYTIAL VIRUS INFECTION IN AUCKLAND, NEW ZEALAND

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Abstract

Respiratory syncytial virus (RSV) is a leading cause of acute respiratory infection (ARI) in young children and older adults worldwide. Preventative strategies for RSV remain limited, however, several RSV immunoprophylaxis and vaccine candidates are in development.

This thesis provides evidence to inform the implementation of new RSV preventative strategies.

It is divided into two broad aims:

1. To estimate the health and economic burden of RSV in Auckland, New Zealand (NZ) by socio-demographic and health factors.

2. To assess the health impact of a potential RSV vaccine/immunoprophylaxis.

For the first aim, administrative data were linked to a population-based ARI surveillance project. The work showed that among children aged <5 years, RSV accounted for 40% of ARI hospitalisations, equating to a hospitalisation rate of 6/1,000 and costing on average NZ$5,040 per episode. Among adults aged ≥18 years, RSV accounted for 8% of ARI hospitalisations resulting in a hospitalisation rate of 0.2/1,000 and costing NZ$4,758 per hospitalisation. Among children and adults, RSV rates varied by age, ethnicity, and socioeconomic status.

When investigating risks posed by specific chronic comorbidities (CMCs); adults with CMCs experienced a significantly increased risk of RSV hospitalisation compared to adults without the respective CMC. The risk posed by CMCs were particularly high in younger adults.

In a sub-study of infants presenting to the hospital emergency department, rates of RSV-associated visits to the emergency department only were 1.5 times higher than RSV-associated hospitalisations.

For the second aim, a mathematical model parametrised to RSV data from Auckland was used to assess the impact of an RSV maternal vaccine or a seasonal infant immunoprophylaxis. The model found that an RSV maternal vaccination and a seasonal immunoprophylaxis could reduce RSV hospitalisation burden by approximately 20-50% and 40-60% in children aged <2 years, respectively. Overall, a seasonal immunoprophylaxis showed a greater impact as it provided protection to a wider age range. However, a maternal vaccine offering six months of protection also reduced RSV hospitalisations among children aged 6-23 months, indicating some indirect effects, potentially making it more cost-effective than previously estimated.

This thesis utilises various data sources and methods to understand the epidemiology of RSV. Findings will be useful in informing RSV disease prevention in NZ.

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Table of contents

List of tables

List of figures

List of abbreviations

RSV	Respiratory syncytial virus
NZ	New Zealand
ARI	Acute respiratory infection
ALRI	Acute lower respiratory tract infection
LRTI	Lower respiratory tract infection
OR	Odds ratio
CI	Confidence Interval
RT-PCR	Real-time polymerase chain reaction
US	United States of America
mAb	Monoclonal antibody
SIR	Susceptible-Infected-Recovered
SEIR	Susceptible-Exposed-Infected-Recovered
SHIVERS	Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance
US-CDC	United States Centers for Disease Control and Prevention
NHI	National Health Index number
DHB	District Health Board
WHO	World Health Organization
SARI	Severe acute respiratory infections
ED	Emergency department
RV	Rhinovirus
ADV	Adenovirus
hMPV	Human metapneumovirus
ICD-10	International Classification of Diseases (ICD), 10th edition
DRG	Diagnosis Related Group
SES	Socioeconomic status
PPV	Positive predictive value
IR	Incidence rate
IRR	Incidence rate ratio
NZ$	New Zealand Dollars
US$	United States of America Dollars
ICU	Intensive Care Unit
LOS	Hospital length of stay
IQR	Inter-quartile range
MICE	Multivariate imputation by chained equations
CMCs	Chronic medical conditions
COPD	Chronic obstructive pulmonary disease
CHF	Congestive heart failure
CAD	Coronary artery disease
CVA	Cerebrovascular accident
DM	Diabetes mellitus
ESRD	End-stage renal disease
PLS	Predictive partial least squares

1 Introduction and background

1.1 Preface

Since its discovery from a laboratory chimpanzee in 1956 [1] and subsequent isolation from children with respiratory disease [2], respiratory syncytial virus (RSV) is now known as the global leading cause of acute respiratory infections (ARI) among young children [3, 4]. It is also increasingly being recognized as a common cause of respiratory illness in older adults [5].

There has been unprecedented progress in RSV vaccine and immunoprophylaxis development in the last decade, with a candidate likely to be commercially available within the next five to ten years. However, there are vital information gaps in RSV disease burden and epidemiology that need to be addressed before such preventative strategies can be effectively introduced. This thesis aims to fill some of these gaps.

In the following chapter, I describe the thesis aims and structure. I also provide an overview of the literature on RSV and the methods used in this thesis. This overview is divided into two parts. Firstly, I discuss the key virological, clinical, and epidemiological characteristics of RSV. Secondly, I provide a brief summary of the mathematics of infectious disease modelling and discuss some previously published mathematical models of RSV, including those that have assessed the impact of theoretical RSV preventative strategies.

1.2 Thesis aims and structure

The overall aim of the thesis is to estimate the health and economic burden of RSV in young children and adults by key socio-demographic and health factors using an active, population-based respiratory surveillance project linked with individual-level, administrative data.

Additionally, the thesis aims to use this data to model the impact of a potential RSV preventative strategy.

The overall aim can be broken down into the five following objectives:

1. To estimate the health and economic burden of RSV-associated hospitalisations among children.
2. To estimate the burden of RSV and other respiratory virus-related visits among infants seen only in hospital emergency departments and compare this to RSV and other respiratory-virus related hospital admissions.
3. To estimate the health and economic burden of RSV-associated hospitalisations among adults aged 18 years or more.
4. To investigate risks posed by specific chronic comorbidities among adults on RSV-associated hospitalisations.
5. To assess the health impact of a potential RSV maternal vaccine or a seasonal infant immunoprophylaxis candidate using mathematical modelling.

These five objectives have been presented in the thesis as a series of publications, as such some details are repeated throughout the body of work. However, it is the intention that each chapter provides a unique perspective and in-depth understanding of areas relevant to RSV epidemiology.

1.3 An introduction to RSV

1.3.1 The virus

Respiratory syncytial virus is an enveloped virus belonging to the *Orthopneumovirus* genus within the *Pneumoviridae* family. Its genome is carried on a non-segmented, negative sense, single strand RNA [6]. RSV is contracted through direct contact with large droplets secreted from infected people or through contaminated fomites. The virus has been shown to remain viable for several hours on hard surfaces and hands [7].

The RSV genome contains 10 viral genes encoding 11 proteins (see Figure 1.1). Two of these proteins, the G glycoprotein and F fusion proteins are considered important as they associate with the lipid bilayer to form the viral envelope. Following cell attachment by the G protein, the F protein undergoes structural changes into a post-fusion form that allows cell entry by fusing viral and host cell membranes [8]. The F and G proteins of RSV are the antigens targeted by neutralizing antibodies induced by infection, hence are also important target sites for RSV vaccine and immunoprophylaxis candidates [8]. The RSV G protein exhibits sequence variation while the RSV F protein is highly conserved between groups and can be recognized by cross-neutralizing antibodies. Consequently, there are more vaccine candidates targeting the RSV-F protein [9]. Moreover, the pre-fusion form of the F protein has been shown to be more effective than the post-fusion form in stimulating an immune response [10].

RSV has been classified into two distinct subtypes (A and B), based on antigenic differences [11]. Within these subtypes, nucleotide sequence analysis has led to the identification of 13 RSV-A and 20 RSV-B genotypes [12]. Molecular studies have shown RSV-A and RSV-B and the several genotypes within these two groups to co-circulate during an RSV epidemic season [13-15].

It remains unclear whether different RSV subtypes and genotypes affects virulence or severity of disease [15-17] and typing at the genotype level will not be discussed further in this thesis.

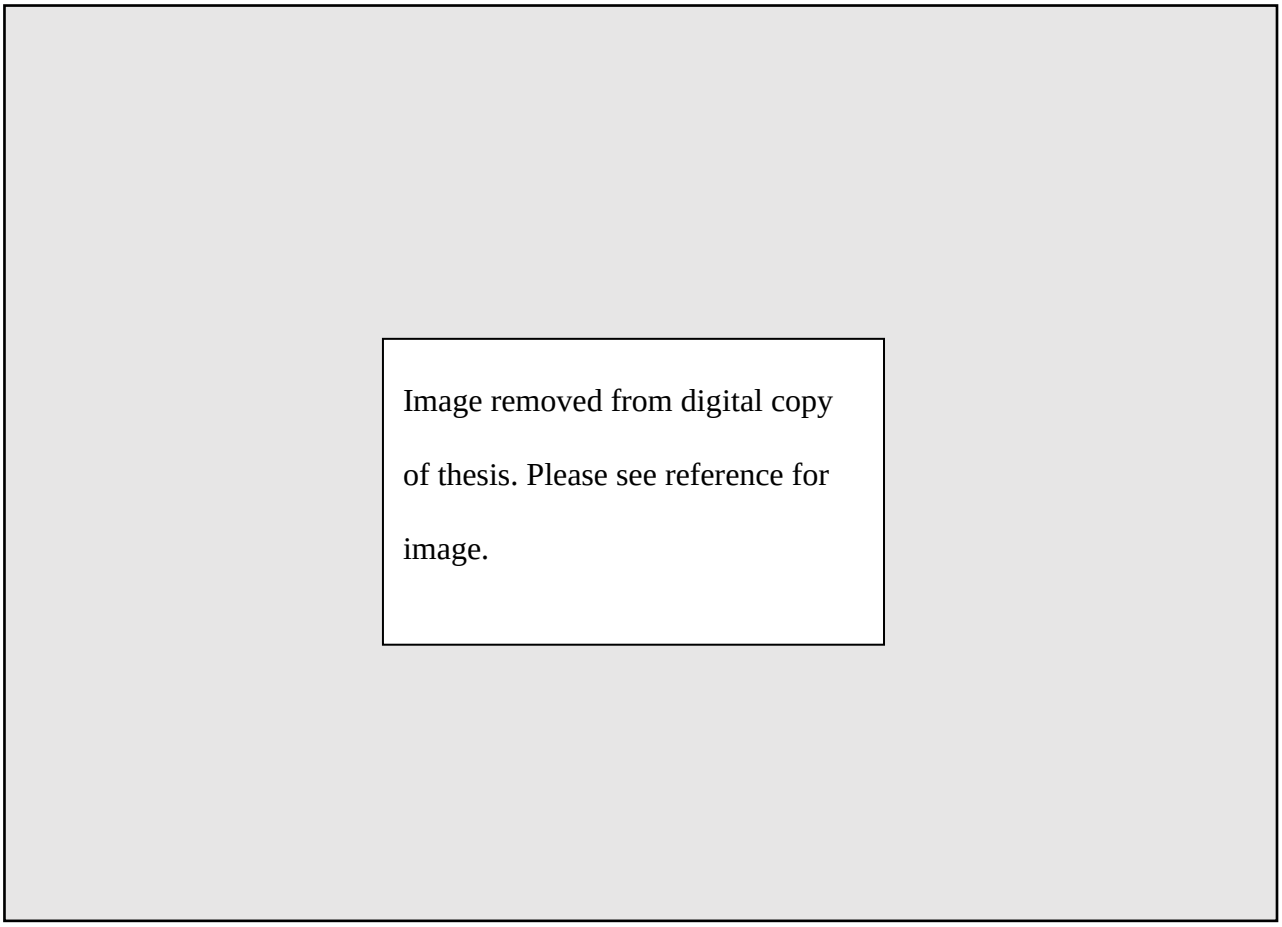


Figure 1.1 Structure of human respiratory syncytial virus (RSV) [18]

1.3.2 Clinical features

Primary infection from RSV often occurs during infancy. It is estimated that almost all children have had at least one RSV infection by two years of age [19]. While there is some protection from infection in the first few months of life, due to trans-placental transfer of RSV neutralizing antibody from mother to child [20, 21], infection is still reported among neonates and very young infants [22]. The greatest burden of severe disease requiring hospitalisation is reported in infants, with peak rates reported in infants aged six weeks to six months [23, 24].

Following exposure, viral replication and onset of symptoms occurs in the nasopharynx after an estimated incubation period of four to five days [25]. The latent period, which is defined as the time from exposure to becoming infectious, is similar to the incubation period as infectiousness of RSV generally corresponds with onset of symptoms [7]. The duration of acute illness and infectiousness is estimated to last between four to ten days [26, 27].

The clinical presentation of RSV infection ranges from asymptomatic carriage, through to cold-like symptoms and severe acute lower respiratory tract infection (ALRI). In general, RSV positive cases present with signs of upper respiratory tract infection including nasal congestion, rhinorrhoea, cough, and wheezing, and less frequently develop fever when compared to cases infected with influenza [28-30].

Among children with RSV, the most common clinical manifestation is upper respiratory tract infection [31]. Acute otitis media is also common [32, 33]. Apnoea is reported in 1.2–23.8% of hospitalised infants with RSV and may precede other respiratory symptoms [34]. Approximately one third of children with RSV are reported to develop ALRI, most commonly seen as bronchiolitis, but pneumonia and croup are also observed [31, 35]. Wheeze, increased work of breathing, dyspnoea, retractions of the chest wall, and poor feeding are some common characteristics of ALRI due to RSV in children [31, 35]. Concurrent bacterial infections among infants and children hospitalised for RSV-associated illness also occurs. While there is a large variation in the reported proportions, most studies report less than 11% of RSV cases to have bacterial co-infection [36-38].

In addition to the acute disease cause by RSV infection, evidence suggests that severe RSV disease in young children may cause lung damage and impair lung development, resulting in recurrent wheeze and asthma later in life [39, 40]. In a systematic review and meta-analysis of studies assessing the association between RSV-confirmed hospitalisation in children aged less

than three years with asthma/wheeze later in life, it was found that RSV disease early in life was associated with a higher incidence of subsequent wheezing and asthma (Odds Ratio [OR] 3.8, 95% Confidence Interval [CI] 3.2–4.6) and that this association decreased with age of follow-up [41]. Nevertheless, it remains unclear whether these long-term sequelae are caused by RSV infection or reflect underlying predispositions that existed before infection and instead also contributed to severe RSV disease. One study showed that prevention of severe-RSV disease through the use of RSV-neutralizing antibody significantly reduced the risk of recurrent wheeze in children who lacked a predisposition to asthma, suggesting RSV does have a causal role [42], however, other studies have showed the converse relationship [43], making the link controversial.

Details on RSV-related immune responses remain poorly understood. As mentioned earlier, there is trans-placental transfer of RSV neutralizing antibody from mother to child. Sero-prevalence surveys show 100% of infants aged 0–1 month have RSV antibodies, which then declines rapidly within three months, and then peaks to 100% again by three years of age [44, 45]. The level of protection conferred by antibodies, however, remains unclear as infection is still possible in age groups with high antibody levels.

Immunity from RSV infections also appears temporary, as reinfections are reported throughout life [46]. In a prospective study of children in day care, the attack rates for the first, second, and third RSV infection was reported to be 98%, 75%, and 65%, respectively [47]. Moreover, in a study by Hall et al., 15 healthy young adults were challenged with RSV 2, 4, 8, 14, 20, and 26 months after natural infection. By two months around 50%, and by eight months 66% of subjects had a reinfection. Over the course of the two-year study, 73% of the subjects had two or more infections and 47% had three or more [48]. The nature of RSV immunity acquisition following infection and reinfection, and the degree of protection such immunity offers against infectiousness and disease severity remains unclear.

The clinical presentation of RSV in most adults is mild consisting of non-specific upper respiratory tract infection symptoms including nasal congestion, rhinorrhoea, sore throat, and cough [18]. However, in older adults (often defined as adults aged 50 years and above), RSV infection can involve the lower respiratory tract, similar to young children. RSV has also been reported to cause exacerbation of pre-existing cardiopulmonary conditions [49-51].

1.3.3 Diagnosis

The diagnosis of RSV infection can be made through: the isolation of the virus using cell culture; detection of RSV antigens using direct or indirect immunofluorescent staining; enzyme-linked immunosorbent assays; or through detection of RSV specific nucleic acid sequences using amplification assays, mainly by reverse transcription polymerase chain reaction (RT-PCR) [52].

Cell culture was previously considered the gold standard for identification of RSV, however, it is not as commonly used now due to length of time to diagnosis, a need for high technical expertise in specimen handling, and a lower sensitivity compared to antigen detection tests or RT-PCR [52, 53]. Antigen based tests are more commonly used as they are easy to perform and provide results in a short time, however, this method has significantly lower sensitivity in older children and adults, likely due to lower viral loads [54]. As such, RT-PCR or antigen detection tests are considered effective for diagnosing RSV in infants and younger children, while for older children and adults RT-PCR is now considered the gold standard [55].

1.3.4 Epidemiology

RSV infection and disease in children

RSV causes significant morbidity and mortality across the globe. Pneumonia is the leading cause of death among children younger than five years, with RSV shown to be the most common aetiological agent, accounting for almost a third of all pneumonia cases [3].

In a meta-analysis of 55 published studies from 32 countries reporting RSV-associated ARI hospitalisations; the global RSV-ARI hospitalisation rate was estimated to be 4.4 per 1,000 children aged less than five years and 19.2 per 1,000 among infants [56]. Similarly, a systematic review and meta-analysis of published and unpublished data focusing on RSV-associated ALRI, estimated that globally in 2015 there were 33.1 million episodes of RSV-ALRI and 3.2 million hospital admissions (approximately 3 per 1,000) in children under five years of age [4].

Such studies and reviews have been informative in highlighting the global importance of RSV as a cause of paediatric morbidity; however, they also show substantial heterogeneity in RSV-associated disease burden estimates by regions and countries. Possible explanations for this variation include methodological differences in case ascertainment, differences in diagnostic tests used to detect RSV, surveillance bias due to differences in healthcare seeking behaviour, hospital resources and healthcare access, as well as true geographical and epidemiological variation. Such discrepancies emphasize the need for comprehensive, country-specific data to inform local RSV prevention and treatment strategies.

In terms of country-specific data, one study from the United States of America (US), that carried out active, population-based surveillance for laboratory-confirmed RSV-associated ARI hospitalisations found that 20% of ARI hospitalisations among children under five years of age were associated with RSV infection, giving an annual hospitalisation rate of 3.0 per 1,000

children [57]. Another study from Australia utilising linked administrative datasets and RSV specific hospital discharge codes, estimated an annual RSV-associated ARI hospitalisation rate of 4.9 per 1,000 children under five years [58].

There is limited data on the incidence of RSV infection in outpatient or emergency care settings [57, 59]. Available data suggests that the burden of RSV in these settings remains under-recognised. For example, in one study from the US only 3% of outpatients with laboratory-confirmed RSV received a diagnosis of RSV [57]. Additionally, in another study carried out in emergency departments in the US, it was estimated that RSV resulted in twice as many visits among children aged seven years or younger than influenza (21.5 per 1,000 vs 10.2 per 1,000) [59].

Some studies have tried to investigate the burden and transmission of RSV in the community. In one study of 36 families during an RSV season in the US, 44% of families and 22% of family members were infected with RSV. Moreover, the likely index case in 50% of families was found to be an older sibling [60]. Likewise, in a study that enrolled all family members of children hospitalised with RSV in Finland, 77% of families and 47% of family members were also positive for RSV. An older sibling or parent was the probable index case in 58% of families [61]. Finally, in a prospective study of 44 households during an RSV season in rural Kenya, RSV was detected in 84% of households. In this study, among infants that were infected with RSV from within their household, 66% were likely to be infected by an older school-aged sibling [62]. Such findings suggest that school-aged siblings play an important role in transmission of RSV regardless of geographical and social setting.

Mortality due to RSV infection in high-income countries is low. It is estimated that 99% of RSV-associated mortality occurs in low-and-middle-income countries [4], however, such RSV-associated mortality rates are likely to be underestimates, as almost half of respiratory tract

infection deaths occur outside of the hospital in developing countries where data are sparse [63, 64].

The majority of children affected with RSV-ARI do not have other comorbidities, but conditions such as premature birth, low birth weight, and congenital heart disease have been identified as risk factors for severe RSV disease [56, 65]. A number of environmental factors have also been implicated in RSV disease severity, including low socioeconomic status, crowded living conditions, second-hand tobacco smoke exposure, air pollution, and an absence of breastfeeding [66, 67]. Furthermore, studies have reported Aboriginal children in Australia [68], and Native American and African-American children in North America [69, 70], to have higher RSV-associated hospitalisation rates compared to the general population.

Acute lower respiratory infection and RSV disease burden among children in New Zealand

In New Zealand (NZ), lower respiratory tract infection is the most common cause of acute infectious overnight hospital admissions, accounting for roughly 30% of all infectious hospital admissions from 2004 to 2008 [71]. Additionally, ALRI hospitalisation rates increased in NZ, from around 3.4 per 1,000 admissions in 1989–1993 to 5.6 per 1,000 admissions in 2004–2008, with the most pronounced increase seen in children under five years, especially those of Māori or Pacific ethnicity [71]. When compared to other high-income countries, children aged less than two years are more than twice as likely to be hospitalised with bronchiolitis in NZ (2006–2010: 45/1,000) [72] than in England (2007–2010: 20/1,000) [73] or the US (2000–2009: 16/1,000) [74]. Additionally, hospitalisation rates for pneumonia in children less than two years of age in NZ (2006–2010: 14/1,000) [72] are twice those in the US (2007–2009: 7/1,000) [75].

Despite these unfavourable comparisons, only a few studies have measured the proportion of acute respiratory infections caused by RSV infection among children in NZ [76-79].

Some of these studies have been limited by small sample sizes. Additionally, none have provided population-based incidence rates or estimates of the economic burden caused by RSV among young children in NZ.

In one NZ study that investigated 75 ARI hospitalisations among children (age group not specified), RSV was found to be the aetiological agent in 48% of cases [78]. Likewise in another study that recruited 230 children under two years of age hospitalised with bronchiolitis, 61% of infants were RSV positive [77]. Moreover, in a larger study that recruited 1,371 children less than two years of age hospitalised with a lower respiratory tract infection (LRTI), RSV was identified in 39% of cases [76]. Finally, in a recent study from NZ that aimed to investigate the viral aetiology of ARIs among children aged 1–8 years in the community; 3.8% of 400 cases of ARI in the community were positive for RSV [79].

RSV infection and disease in adults

While it is rare for RSV to cause hospitalisation among healthy young adults, the virus is increasingly being recognised as an important cause of morbidity and mortality among older adults [80, 81].

A systematic review and meta-analysis in 2015 of 36 articles and 8 unpublished studies with relevant data on RSV-ARI burden among adults aged 65 years or older, estimated that there were approximately 1.5 million episodes of RSV ARI in high-income countries, of which 214,000 required hospital admission [5]. Similar to RSV disease burden among children, estimates varied considerably by location, likely due to methodological differences in case ascertainment, diagnostics, healthcare seeking behaviour as well as true epidemiological variation.

Studies have reported adults with cardiopulmonary conditions to be more likely to be hospitalised with RSV and have severe disease [51, 81, 82]. In one US study using active surveillance, cell

culture and RT-PCR confirmed RSV infection occurred annually in 3–7% of healthy patients aged 65 years or older, 4–10% of high-risk adults (aged 21 years or older with chronic cardiopulmonary conditions), and 8–13% of adults aged 65 years or older hospitalised with an ARI. In another study from Hong Kong comparing adults aged 18 years or older hospitalised with RSV to those hospitalised with influenza; underlying chronic lung diseases were more common in RSV positive patients (35.6% vs 24.1%, p-value <0.001) [82]. Evidence of the role of other comorbidities such as diabetes, asthma, and renal conditions on RSV disease risk among adults remains limited.

RSV hospitalisation rates in adults relative to influenza appear to change depending on circulating influenza strains. In the study from US using active surveillance, RSV infection was reported to result in more hospitalisations than influenza A H1N1 but not influenza A H3N2 [81]. In another US study that used statistical modelling of weekly RSV and influenza surveillance data; influenza hospitalisation rates (predominantly influenza A H3N2) were higher than RSV hospitalisation rates (309 per 100,000 vs 86 per 100,000) [83]. To date, no study has investigated RSV-associated disease burden among adults in NZ.

1.3.5 Economic impact

Given the high burden of disease and healthcare utilization associated with RSV, it is not surprising that it has a large impact on cost and resource-use within healthcare systems worldwide. Nevertheless, published studies estimating RSV healthcare associated costs are few in number. One study from Australia, which estimated the economic burden of RSV among children aged less than five years using passive surveillance data, found the total RSV-associated direct annual healthcare cost to range between $24 and $50 million Australian dollars (2005 value) [84]. This cost was considerably higher than healthcare costs due to influenza virus or rotavirus among children aged less than five years during the same period [84].

In a US study that estimated healthcare costs due to RSV among all age groups and compared it to cases without RSV; healthcare resource use in terms of hospital stay, emergency department, ambulatory, and outpatient visits were significantly higher in RSV positive patients than non-RSV matched controls for all age groups. The adjusted costs in US dollars (2014 value) among RSV patients ranged from $7535 (0–1 year age group) to $40,405 (75–85 year age group) per episode while in the match controls ranged from $5015 (0–1 year age group) to $19,037 (75–85 year age group) [85].

1.3.6 Seasonality

In temperate climates, RSV shows a distinct seasonal pattern, causing cases in late autumn through to late spring, (i.e., March to October in the Southern hemisphere and November to April in the Northern hemisphere), with very low levels of infection during the summer [86]. Within temperate climates, some areas report consistent annual seasonality [87, 88], while others exhibit a biennial or two year seasonal pattern, where a year of high RSV incidence alternates with a year of low RSV activity [89, 90]. Additionally, some regions show years with low incidence RSV epidemics to start later in the year compared to high incidence epidemics, which is described as a ‘delayed biennial’ pattern [91]. In contrast, RSV in tropical countries shows a wide range of variability in terms of timing and duration of seasonal epidemics [87, 88].

Similar to other seasonal respiratory pathogens, possible drivers of RSV seasonality include: increased indoor crowding during winter or rainy periods; school holidays; reduced host immunity due to declines in nutritional wellbeing; reduced sunlight exposure; increased pathogen survival due to variations in temperature, humidity, and sunlight [92].

1.3.7 Management and treatment

The management of RSV consists predominantly of supportive care. Infection of the respiratory tract with RSV is self-limiting and the inflammatory response is considered to have a greater effect on severity of disease than viral replication [24, 93]. Among hospitalised infants and adults, depending on the severity of disease, treatment may include supplemental oxygen, ventilation support, fluid status management, and feeding support. Despite the low reported incidence of bacterial co-infection in RSV infected patients, antibiotics are still often prescribed for respiratory illnesses caused by RSV [36, 38, 94].

Ribavirin is a broad-spectrum antiviral agent licensed for use as a treatment in infants but not adults. Additionally, its use in children remains controversial. A 2007 Cochrane review suggested that the available evidence was not sufficient to confidently state that Ribavirin is clinically effective at treating infant RSV bronchiolitis [95]. Consequently, Ribavirin is not commonly used for the management of bronchiolitis in children [96]. In NZ it is recommended for very restricted use among severely immunocompromised patients with a very high risk of RSV ALRI [97].

Another treatment that has been considered for RSV is the use of immunoglobulins. However, a 2019 Cochrane review found insufficient evidence of a difference between immunoglobulins and placebo when used to treat RSV ALRI in infants and young children [98]. There are no formal guidelines regarding the use of RSV antivirals or immunoglobulins for treatment of RSV in adults [18].

1.3.8 Prevention

Currently, the only preventive RSV medication licensed for use is Palivizumab, an immunoprophylaxis through monoclonal antibody (mAb) targeted against the RSV F protein. Palivizumab has been shown to be safe and effective in infants [99]. However, due to its

requirement of monthly dosing and high acquisition costs, its use remains limited. Studies have found Palivizumab to only be cost-effective when used among subgroups of high-risk infants [100]. In a 2002 cost-effectiveness study from NZ, in no group of infants was the use of Palivizumab found to result in net cost savings [101]. Palivizumab is not funded and rarely used in NZ [102].

There is currently no licensed vaccine for RSV. In the 1960s a formalin inactivated RSV vaccine clinical trial found enhanced respiratory disease in vaccinated children once infected with RSV [103]. This concern in disease enhancement as well as an inadequate understanding of RSV immune responses has posed challenges to RSV vaccine development.

Nonetheless, there has been major progress in RSV vaccine and mAb development in the last decade with a range of vaccine types; particle-based, vector-based, subunit, live-attenuated or chimeric vaccines, and mAbs now in clinical development [104]. Target populations for vaccines include RSV naive young infants and children (usually aged under six months), children aged over six months, pregnant women (with candidates offering protection to newborns through transplacental transfer of RSV-specific antibodies), and older adults. Additionally, new RSV specific mAbs are being developed to be given to newborns at birth.

As immunity following an RSV infection is temporary, it is likely that protection from an RSV vaccine or mAb will also be of short duration. The main objective of an RSV maternal or newborn preventative strategy is to delay the onset of an infant's first RSV infection in the first six months of life, when the child is most likely to develop severe disease [20, 57]. Strategies in older children and adults will likely require boosters or multiple vaccinations for enduring protection.

The most advanced candidates for RSV prevention include the RSV F nanoparticle maternal vaccine and a single dose mAb, called MEDI8897. The RSV F maternal vaccine did not meet its primary endpoint in Phase 3 clinical trials despite showing favourable safety and an efficacy of 39.4% (95% CI, 5.3–61.2) against medically significant RSV LRTI and 44.4% (95% CI: 19.6–61.5) efficacy against RSV LRTI hospitalisations after 90 days. It did, however, meet secondary objectives of reducing RSV LRTI hospitalisations and severe hypoxemia, with benefits through to 180 days after vaccination. In addition to preventing RSV illness, the vaccine was also shown to reduce 'all cause' (i.e. without a requirement for RSV) LRTI events [105]. Given these promising results, the vaccine has been approved to undergo an additional Phase 3 trial [104].

The extended half-life monoclonal antibody MEDI8897 showed a 70.1% (95% CI 52.3–81.2) efficacy against medically significant RSV LRTI and 78.4% (95% CI: 51.9–90.3) efficacy against RSV LRTI hospitalisations after 150 days in healthy pre-term infants [106] and is currently being trialled for use in all infants [104]. Producers of MEDI8897 expect the product to have vaccine-like pricing [107], this in combination with high efficacy and extended half-life could make this preventative strategy a more viable and cost-effective approach than Palivizumab. It is expected that an RSV preventive strategy will be available for use within the next five to ten years.

1.4 Mathematical modelling of RSV

Mathematical models of infectious diseases can be used to extrapolate current information about a disease to study the mechanisms by which the disease spreads. They can also help to predict the future course of an outbreak and to evaluate strategies to control epidemics. The following section provides a brief background on mathematical modelling of infectious diseases. It also reviews the literature on published RSV mathematical models, including models that have been used to assess the impact of theoretical RSV preventative strategies.

1.4.1 Background to infectious disease modelling

There are several different approaches to mathematical modelling of infectious diseases. These approaches can be characterised as static, deterministic, stochastic, time series, or a combination of these forms. Such models can be further divided into individual based models, network models, household models, compartmental models, and Bayesian models. This review focuses primarily on deterministic, compartmental models, based on ordinary differential equations (ODE) using the "Susceptible-Infectious-Recovered" (SIR) concept, as this is the type of model employed in this thesis. A more comprehensive explanation of the other types of infectious disease models can be found in books by Anderson and May [108] and Keeling and Rohani [109].

Work by Kermack and McKendrick in 1927 established the majority of the theory behind mathematical models of infectious diseases [110]. The SIR model is a special case of the Kermack-McKendrick model and is now widely used in epidemiological modelling. The SIR concept operates on the principle that individuals can be classified by their epidemiological state, which in its simplest form is; susceptible to infection (S), infected and infectious (I), and recovered therefore no longer infectious and immune (R). These epidemiological states are treated

as separate compartments in the model with rates of transition between these compartments determined using differential equations.

In a simple SIR model of a single, brief outbreak in a naïve population, births and deaths can be ignored as the outbreak occurs in such a short period that demographic processes are not influential. Consequently, the only transitions that need to be determined are movement of S individuals to I (transmission rate/force of infection) and the movement of I individuals to R (recovery rate). The transmission rate is dependent on the prevalence of infections in the population, the underlying contact structure, and the probability of infection given contact with an infectious individual. The recovery rate depends on the length of time individuals have an infection; which, for simplicity, is often based on the average infectious period and results in a constant rate.

A simple SIR model predicts an outbreak following intuitive patterns. It shows the number of infected cases to increase exponentially until there are not enough susceptible individuals left in the population to infect. This process continues until all infected individuals recover, becoming immune and the number of infected cases drops until the pathogen becomes extinct (Figure 1.2).

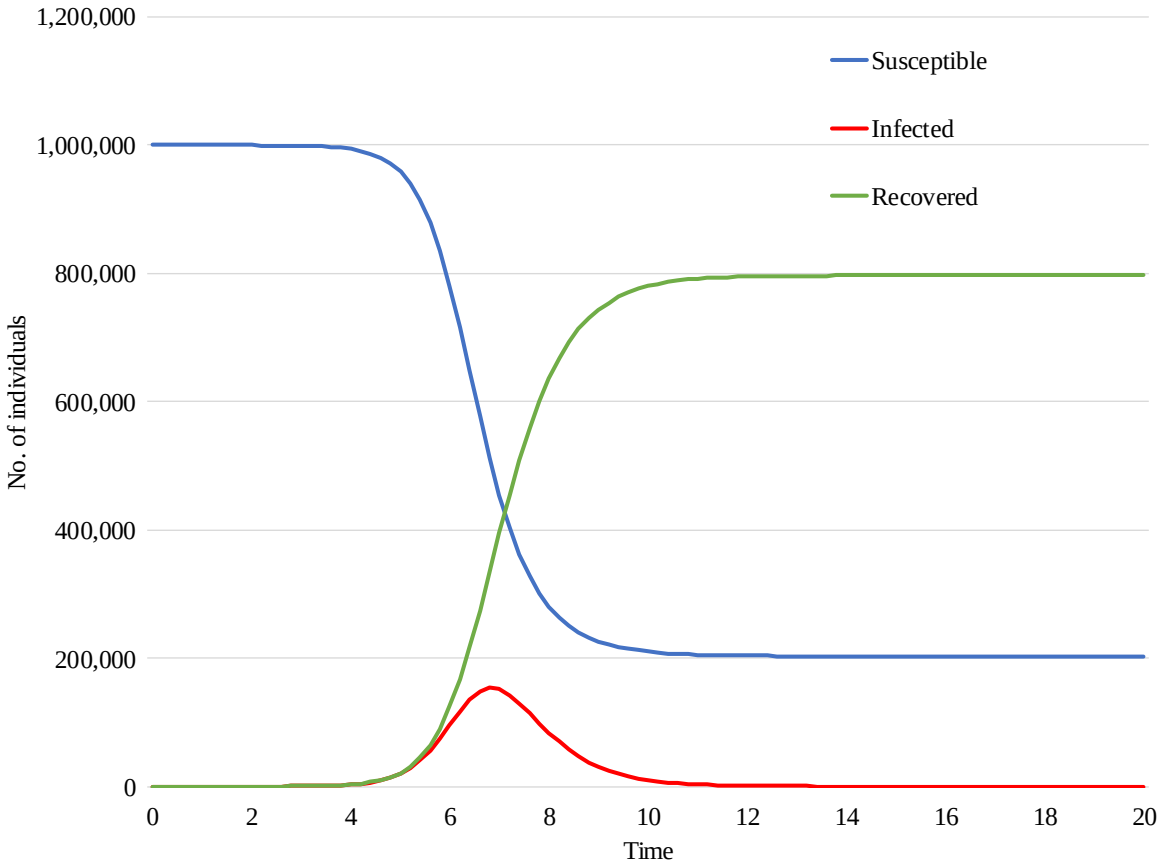


Figure 1.2 Illustration of the movement of individuals between states in the Susceptible-Infectious-Recovered model (self-drawn)

The differential equations representing this process are:

$\frac{dS}{dt}$ = -λSI Equation no. (1.1)

$\frac{dI}{dt}$ = λSI - γI (1.2)

$\frac{dR}{dt}$ = γI (1.3)

N = S+I+R (1.4)

S; Susceptible, I; Infectious, R; Recovered, N; Total population

In these equations, the parameter λ represents the transmission rate or force of infection (as a product of the contact rates and infection probability given contact) while γ is the proportionality constant for the recovery rate.

Within the SIR ODE model framework, several extensions and modifications are possible which enable the model to better represent reality and to investigate control strategies. Below is a brief overview of some commonly used modifications and extensions to the SIR model.

Latent period: The SEIR model

For some infections there is delay between initial inoculation and transmissibility to other susceptible hosts. This delay is known as the latent period. To account for this period in the SIR model, a new compartment, exposed (E), is added, resulting in a SEIR model. The rate of transition from E individuals to I individuals is estimated by the average duration of a latent period for a particular infection, given by $1/\sigma$, which represents a loss of latency rate σ.

Demography

In the simplest compartmental model framework, it is assumed that an infection spreads and becomes extinct sufficiently fast so as to not be influenced by births and deaths. However, when modelling endemic diseases or infections with long-term persistence, such demographic processes become important, particularly in terms of the influx of new susceptible individuals through birth. The most common way to introducing demography into the SIR model is through inclusion of a birth rate μ into the S class. The birth rate μ corresponds to a host "lifespan" $1/\mu$. In some models, it is assumed μ also equals the population death rate, resulting in a constant total population size N. Such assumptions are valid for infectious diseases with a short infectious period compared to an average lifespan and when death due to infection is rare.

Age structure and contact rates

In standard SIR compartmental models, populations are classified based on epidemiological status only. However, in reality, populations are heterogeneous and have other characteristics that differentiate their risk of contracting or transmitting an infection. One of the most common host heterogeneities is age as it greatly influences a host's susceptibility to infection as well as their contact rates. The most common approach to incorporating age into a model is to further divide a model's epidemiological compartments by discrete age groups (i.e. S_1, I_1, R_1, and S_2, I_2, R_2 for age group 1 and 2, respectively) and to incorporate continuous ageing into the equations.

Contact rates between individuals are a critical component in determining the transmission rate of an infectious disease, and as mentioned above, are expected to vary significantly by age. To this day, many infectious disease models are parameterised using contact data obtained from the POLYMOD study; a large, prospective, population-based study carried out in eight European countries [111]. In this seminal study, 7,290 participants were prospectively followed and asked to record characteristics of their contacts. The study found mixing patterns and contact characteristics to be very similar across different countries. Moreover, contact patterns were highly assortative with age, showing that children and young adults mix the most with each other [111]. Recently, a study projected data from the POLYMOD study to 152 other countries using a Bayesian hierarchical model and demographic data from these countries, providing contact rates for locations that were not previously available [112]. This study also noted highly assortative mixing with age in all countries. However, it did find some regional differences, with inter-generation contact rates higher in Asian countries compared to other locations [112].

Seasonal forcing

Similar to other respiratory infections, RSV displays distinct seasonality with peaks in winter and rainy seasons. This implies that the transmission rate is greater at some time points compared to others. In a standard SIR/SEIR model, the transmission rate λ is constant and therefore cannot replicate the seasonal nature of such infections. Consequently a well-established method of incorporating seasonal dynamics into a model is by replacing λ with a time-varying sinusoidal forcing function [113], such as:

$$\lambda_i = \beta_0(1 + \beta_1 \cos(\frac{2\pi t}{52} + \varphi)) \qquad (1.5)$$

In this equation β_0 is the mean transmission coefficient, β_1 is the amplitude of seasonal forcing, and φ represents the phase shift which can be used to fit peak disease incidence in the model to data.

Vaccination or other preventative strategies

Compartmental ODE models can also be used to predict dynamics of infection after the introduction of a vaccination or other infection reduction strategy programs. For example, in a simple SIR model with births and deaths the impact of a newborn/maternal vaccination programme can be investigated through the addition of a vaccinated (V) compartment. This creates a class of children who are born with some form of protection to infection due to a preventative strategy.

The differential equations representing this process are:

$$\frac{dS}{dt} = (1\text{-}p)\ \mu N - \lambda SI - \mu S \qquad (1.6)$$

$$\frac{dV}{dt} = (p)\ \mu N - (1\text{-}e)\lambda V I - \mu V \qquad (1.7)$$

$$\frac{dI}{dt} = \lambda SI + (1\text{-}e)\lambda V I - \gamma I - \mu I \qquad (1.8)$$

$$\frac{dR}{dt} = \gamma I - \mu R \qquad (1.9)$$

S; Susceptible, I; Infectious, R; Recovered, V; Vaccinated, N; Total population

In these equations, as mentioned earlier, μ represents birth and death rates, which are equal, resulting in a stable total population *N*. The fraction of the newborn population that is vaccinated is represented by *p* while *e* equals vaccination effectiveness i.e. the level of protection afforded by a vaccine to a vaccinated population.

In equations (1.6) – (1.9); it is assumed that protection from vaccination is life-long. However, if the impact of a vaccine was temporary, the term -ωV could be added to equation (1.7) where ω would represent the rate of loss of vaccine-induced immunity. This term would then also be added to equation (1.6) to indicate addition of individuals back to the susceptible state.

Strengths and weakness of compartmental ODE models

The deterministic, compartmental ODE model approach does have some limitations. Firstly, by employing a deterministic model, stochastic events inherent in populations are not accounted for. However, deterministic models are more computationally efficient and are considered suitable for

modelling large population dynamics such as those used in this thesis. Secondly, the simplest form of a compartmental ODE model assumes a spatially and socially homogenous population. While some heterogeneities (such as age structure and contact patterns) can be accounted for in such models, a compartmental ODE model is unable to describe any spatial aspects of the spread of the disease.

Parameterisation of models

For a model to be useful as a predictive tool, parameters in a model such as the transmission and recovery rate, need to be assumed or inferred (i.e. fitted to) from epidemiological data, and highlight the interplay between mathematical models and statistics. A common approach used to infer model parameters from epidemiological data is through the use of maximum likelihood estimation, which is the method used in this thesis.

In brief, maximum likelihood estimation is a method that will identify a model with a specific set of parameters that is in closest agreement with the data i.e. maximises the likelihood that the model resulted in the data. The likelihood function can be defined as:

$$L(\theta; x) = f(x|\theta)$$

Where θ is a distribution parameter and x are a set of observations and we are interested in finding the value of θ that maximises the likelihood.

If we assume that the observations x are multiple independent samples (x_1, x_2, x_3), the likelihood of the full dataset is the product of the likelihoods from each sample.

$$L(\theta; x) = f_0(x_1, x_2, x_{3\ldots x_n} | \theta) = f_0(x_1|\theta).\ f_0(x_2|\theta).\ f_0(x_3|\theta) \ldots\ldots f_0(x_n|\theta)$$

The derivative is taken of this function to find the maxima. It is mathematically simpler to take the log of the likelihood function and minimise the negative log likelihood function. Resulting in the function:

$$LL(\theta; x) = \log(f_0(x_1|\theta)) + \log(f_0(x_2|\theta)) + \log(f_0(x_3|\theta)) \ldots\ldots \log(f_0(x_n|\theta))$$

Further detail on maximum likelihood estimation can be found in books by Miller [114] and Eliason [115].

1.4.2 Previous mathematical models of RSV

Despite the significant health and economic burden of RSV, there are few mathematical models investigating its transmission compared to models investigating other infectious diseases such as influenza, rotavirus, and pertussis. The following section reviews several mathematical RSV models reported in the peer reviewed literature. Also reviewed are models that have been used to assess the impact of theoretical RSV preventative strategies. Other approaches have also been used to model RSV transmission and preventative strategies, such as individual based models [116], time series models [117], and static models [118, 119], though these will not be discussed in detail in this review.

A seminal paper on mathematical models for RSV was published in 2001 by Weber et al. [120]. The paper initially considered a deterministic, compartmental Susceptible-Infectious-Recovered-Susceptible (SIRS) model with homogenous mixing and seasonal forcing using a cosine function. The model was then extended to incorporate more of the characteristic features of RSV including a latency period and protection due to maternally derived antibodies. It also incorporated a stepwise reduction in susceptibility following reinfections, where the risk of reinfection was 50% after one infection, 35% after two infections and 25% after three infections. Both the simple and extended model were fit to hospital case data from the Gambia, Florida, Finland, and Singapore,

with an assumption that the ratio of number of hospitalisations to number of infectious individuals in the population was constant. The paper found both the simple and extended model were able to represent seasonal patterns of RSV in different locations almost equally well.

A paper by White et al. from 2005 presented a deterministic, compartmental model that explicitly accounted for differences in transmission and immunity by RSV subtypes (RSV-A and RSV-B) [121]. The model was fitted to data from the United Kingdom and Finland and was found to successfully display differences in both infection dynamics, and the ratio of RSV A/B predominance by location. The published manuscript reporting these data highlights the value of RSV models that account for RSV-subtype diversity, especially for assessing the impact of future RSV vaccines, however, such models require RSV subtype specific data, which can be challenging to obtain.

A 2007 paper by White et al., aimed to investigate the role of reinfection and immunity in the transmission dynamics of RSV [122]. Using a family of nested deterministic models, eight models with varying infection, reinfection, and immunity scenarios were examined. Models were fitted to RSV incidence data from eight countries. The models assuming no immunity or complete, lifelong immunity following infection were unable to reproduce RSV transmission dynamics. The model assuming partial lifelong immunity following infection provided the best and most parsimonious fit to the data.

Leecaster et al. developed a Susceptible-Exposed-Infected-Detected (infected)-Recovered (SEIDR) model with the aim of investigating variations of RSV across epidemic years [123]. The model was fitted to RSV hospitalisation data from Salt Lake County, Utah, US and included two age classes: children less than two years old and those older than two years. Three parameters associated with epidemic year variation were examined: the transmission parameter (β), the detection fraction, and the temporal offset of the epidemic cycle. Different models were specified

where these three parameters were either held constant or allowed to vary across seasons. Overall, it was found that the goodness of fit for the models where the estimated transmission parameter or detection fraction were held constant did not differ from those where these parameters were allowed to vary by epidemic year.

Finally, Hogan et al., and Moore et al., from Australia published a number of related studies on seasonally forced, deterministic, compartmental models for RSV infection. In work published in 2013 [124], a simple SEIRS model with seasonal forcing was constructed and then expanded to capture two age classes (<2 years and ≥2 years). The age classes had different transmission rate parameters to better reflect the age-specific transmission dynamics known to be present for RSV. The paper found both the single-age class and the two-age class model accurately demonstrated biennial or annual RSV seasonality, depending on values selected for β_0 and β_1 in a seasonal forcing equation.

In a paper from 2014 [89], Moore et al. used a two-age class SEIRS model with seasonal forcing and fitted it to Western Australian RSV data from 2000 to 2005. The data used in the study was state-wide, routinely collected laboratory data from children aged 0–9 years with ALRI and showed RSV detections to display a distinct biennial seasonal pattern. The SEIRS model used in the study accurately represented this biennial seasonality. When variations in parameters related to the latency period, infectious period, and duration of immunity were explored, the best fit to the data was a model with latency and infectious periods consistent with what is reported in the literature (4 days and 10 days respectively) and a slightly lower estimate for the immunity period (160 days).

Hogan et al., in 2016 [86], used a two-age class SEIRS model with seasonal forcing and carried out parameter space and bifurcation analyses to document how parameter ranges resulted in different RSV seasonal patterns. The study found differences in birth rates, transmission rate, and

seasonality parameters to affect RSV seasonal patterns. Findings from this study emphasised the importance of fitting RSV transmission models to local data when using it as a predictive tool.

1.4.3 Modelling theoretical RSV vaccination strategies

The literature shows there is a clear need for mathematical modelling to examine the potential impact of different interventions strategies on RSV disease [62, 125]. To date, a number of models exploring RSV vaccination and immunoprophylaxis strategies have been published.

One study from 2015 by Kinyanjui et al.[126], used a deterministic, age structured, compartmental model fitted to RSV ALRI hospitalisation data from Kilifi, Kenya to assess the impact of an RSV vaccination. The vaccine was assumed to result in an immune response and protection equivalent to that gained from primary infection. There were 99 age classes in the model: 24 monthly age classes for the first two years of life and yearly age classes thereafter. The model assumed all individuals were born into a maternal antibody class. It also assumed that repeated RSV infections (up to the third infection) build immunity, resulting in reduced risk of infection, disease, and reduced infectivity. This model was referred to as the Sequential Immunity Acquisition (SIA) model. The model was assessed using two different contact matrices and fitted to hospitalisation data from rural Kenya and found vaccination of infants aged 5–10 months to be the optimal method for protecting infants aged less than six months, and that most of this benefit was from indirect protection.

In a related 2017 study by Pan-Ngum et al.[127], the outputs from the SIA model mentioned above were compared to another structurally different model. In this new model, referred to as the BWI model, partial immunity to RSV could only be maintained by repeated/boosted infection. The models were fitted to hospitalisation data from rural Kenya and were used to assess which RSV vaccine features had the greatest impact on disease. Both the SIA and BWI models predicted

significant and similar impacts of vaccination, with up to a 70% reduction in hospitalisations in children aged less than five years of age. In both models, vaccines that reduced infectiousness and duration of infection were found to have the greatest impact on RSV disease burden. In a 2020 study by Kinyanjui et al.[128], the SIA and BWI models were fitted to RSV data from the United Kingdom, where, again a vaccine that reduced infectiousness and duration of infection was shown to have the greatest impact.

Yamin et al., developed a compartmental model stratified by eight age groups: 0–5 months, 6–11 months, 1 year, 2–4 years, 5–24 years, 25–49 years, 50–64 years, and ≥65 years [129]. The model assumed that individuals were born with temporary protection through maternal antibodies and the immunity following first infection lead to lower viral load and severity in subsequent infections. The model also assumed that following infection, individuals had full protection for approximately 7 months. The model was fitted to RSV data obtained through passive surveillance from four states in the US. RSV vaccination strategies targeting specific age groups (6 months–4 years, 5–24 years, 25–49 years, and ≥50 years) and the entire population for a range of efficacy values (40%–80%) were assessed in the model. The paper found that vaccinating children aged less than five years would be the most effective strategy to prevent RSV infection in both children and adults.

Hogan et al., used a deterministic, compartmental model with 75 age classes (60 one-month age classes among children less than five years or age, and 5-year age groups thereafter) to assess the impact of an RSV maternal vaccine [130]. The model assumed that infants aged less than three months had some protection due to maternal antibodies and that individuals aged 10 years or more were less infectious than young children. The model was fitted to RSV-ALRI hospitalisation data obtained from passive surveillance of children in Western Australia. The study found that an RSV maternal vaccine with a similar uptake to that for pertussis and influenza vaccines in Western

Australia (50%), and effectiveness ranging from 60% to 90%, could reduce hospitalisation by around 6–37% in children aged 0–2 months, and by 30–46% in those aged 3–5 months. In the study, a maternal vaccine was found to have negligible impact on children older than six months of age i.e. had limited indirect effects.

1.4.4 Future direction for modelling the impact of potential RSV preventative strategies

Given the high burden of disease attributable to RSV, and the progress in RSV vaccine and immunoprophylaxis development, there is a need for more mathematical modelling to assess optimal strategies and impact. To date, the modelling of RSV transmission and vaccination using compartmental models have employed a wide variety of structural models and assumptions. This likely reflects the high degree of uncertainty regarding RSV immunity and its acquisition. While more epidemiological evidence to inform such parameters are crucial, in the interim, quantitatively similar outputs from mathematical models employing different structures and assumptions are likely to be the best form of evidence.

Additionally, while studies to date have been informative, they are specific to particular settings and locations. Furthermore, many of these studies were carried out before clinical trial results for RSV preventative strategies were available and have therefore assumed varying effectiveness and duration of protection values. Finally, as RSV is not a notifiable disease, testing and surveillance methods vary by location and are often limited to children. There is a need to develop and fit RSV models to specific areas, especially using comprehensive RSV surveillance data among all age groups.

2 Data sources and linkage

2.1 Preface

The data used in this thesis derive from the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) study, which was a large, prospective, population-based ARI surveillance project in Auckland, NZ. I completed the majority of the data cleaning and coding for the SHIVERS dataset with guidance and assistance from members in the SHIVERS study team.

In order to provide population-based incidence rates and estimates of the economic burden caused by RSV, the SHIVERS study data were linked with individual-level administrative data from the NZ Ministry of Health National Collections. I assisted in this data linkage which was also carried out by the SHIVERS study team. This chapter provides a description of the SHIVERS study, the NZ Ministry of Health National Collections datasets, the data linkage process, and the key variables used for analysis. It also discusses the strengths and weaknesses of these data.

2.2 The Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) study

The 2009 influenza A(H1N1) pdm09 pandemic highlighted gaps in global pandemic preparedness, particularly related to disease surveillance and scientific knowledge of respiratory diseases in the Southern Hemisphere. This led to a request for proposals from the US Centers for Disease Control and Prevention (US-CDC) for a Southern Hemisphere temperate country to establish research on the disease burden, epidemiology, and prevention of influenza and other respiratory infections.

The US-CDC awarded funding to the NZ proposal. NZ was chosen as the study site for a number of reasons: first, it has a predominantly public funded healthcare system with all non-elective healthcare services provided at public hospitals; second, all New Zealanders are assigned a unique National Health Index (NHI) identifier allowing record linkage to other administrative datasets and tracking of healthcare use over time; finally, most New Zealanders are registered with a primary healthcare provider who maintains updated record of demographics and residential details. Consequently, the SHIVERS study was established for a five-year period (2012–2016) within the Auckland region (the most populous and ethnically diverse region of NZ).

SHIVERS included two active, prospective, population-based surveillance systems, one among hospitalised patients with ARI and another among patients seeking healthcare for influenza-like-illness at sentinel primary healthcare facilities. In 2015, a sero-epidemiological study for influenza was also carried out among a sample of patients enrolled at sentinel primary healthcare facilities. In this thesis, only data from the hospital surveillance component of the SHIVERS study was utilised, therefore details on other aspects of the study will not be provided. Detailed information on the SHIVERS study has been published in the peer-reviewed literature [131, 132]. Ethical approval for the SHIVERS project was granted by the NZ Health and Disabilities Ethics Committee (NTX/11/11/102).

2.2.1 Study setting

SHIVERS ARI hospital surveillance was conducted in four public hospitals, two adult and two paediatric hospitals, which provide all public healthcare to the NZ population living in two adjacent district health board (DHB) regions: Auckland and Counties-Manukau DHB. The Auckland DHB provides healthcare to residents in central Auckland and the Counties-Manukau DHB provides healthcare to residents in east and south Auckland (see Figure 2.1).

ADHB and CMDHB are predominantly urban and based on Statistics NZ population estimates included approximately 1 million people in 2015 [133], with a demographic distribution broadly similar to the NZ population [131]. The adult and paediatric public hospitals in Auckland DHB are Auckland City Hospital and Starship Children's Hospital. The adult and paediatric hospitals in Counties-Manukau DHB are Middlemore Hospital and Kidz First Children's Hospital. These hospitals provide all inpatient services for the population residing in the area. All patients are triaged in the emergency department. The two surveillance hospitals in ADHB are located on the same site and have separate adult and paediatric Emergency Departments (ED). The two surveillance hospitals in CMDHB are located on the same site and have a shared adult and paediatric ED.

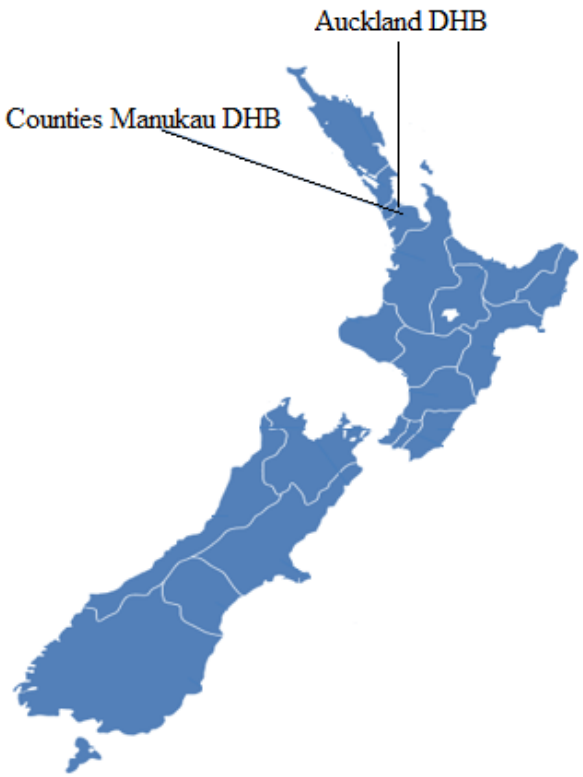


Figure 2.1 Map of New Zealand with SHIVERS study sites (Auckland District Health Board [ADHB] and Counties Manukau District Health Board (CMDHB)

2.2.2 Hospital surveillance

From 30th April 2012 to 31st December 2015, research nurses reviewed daily admission records to identify all overnight admissions with a suspected ARI. Suspected ARI cases were identified through a combination of reviewing admission diagnoses and interviewing patients about their presenting signs and symptoms. Among suspected ARI patients, those meeting the World Health Organization (WHO) severe acute respiratory infection (SARI) case definition, defined as cough and measured or reported fever within the last 7 days (in 2012) and the last 10 days (from 2013 onwards) were enrolled [134]. Study nurses obtained consent, collected nasopharyngeal aspirates/swabs from cases and filled in detailed case report forms inquiring on a range of factors including comorbidities, influenza vaccination status, antibiotic treatment, and clinical outcomes.

To provide an understanding of RSV and other respiratory virus hospitalisation burden among ARI patients not meeting the SARI definition, between 2013–2015, study nurses enrolled samples of non-SARI respiratory patients, i.e. patients with cough and/or measured or reported fever but not both within 10 days. Sampling of non-SARI respiratory patients in 2013 was during the peak winter period (12th August to 6th October) and included weekly random selection of two paediatric and two adult inpatients at each hospital. In 2014 and 2015, this surveillance was extended to randomly enrol approximately six paediatric and six adult non-SARI respiratory patients weekly from each hospital from weeks 18 to 39 (end of April to end of September).

In addition to respiratory virus test results generated by the SHIVERS study, hospital laboratories also provided results from clinician-ordered tests performed on hospitalised SARI and non-SARI respiratory patients during the study period. This additional testing data was especially valuable in expanding the number of laboratory tested non-SARI patients in our dataset, since fewer non-SARI patients were systematically enrolled in the SHIVERS study. Clinician ordered results were included after validation of the hospital assay performance.

2.2.3 Laboratory methods

Collected specimens were tested for RSV, influenza, rhinovirus, adenovirus, and human metapneumovirus using the US-CDC real-time RT-PCR protocol [135, 136] at the Institute of Environmental Science and Research, or using the AusDiagnostic PCR protocol and real-time PCR assays at hospital laboratories [137]. A sample of positive specimens were further sub-typed. Further information on the performance of the hospital assays compared to the US-CDC real-time RT-PCR as a gold standard are provided in Appendix 1.1.

2.2.4 Emergency department (ED) surveillance

From 2014 through to 2016, SHIVERS conducted a sub-study among infants presenting to the ED at Kidz First Children's Hospitals in CMDHB. During the study period, a study nurse was present in the ED every day from 1pm to 9 pm to identify infants with suspected ARI who were discharged home from the ED (i.e. not admitted to hospital). Study nurses obtained consent from caregivers and collected nasopharyngeal aspirates. In 2014, ED surveillance lasted for a 10-week period that coincided with the peak NZ influenza season (start of July to mid-September), and in 2015–2016, was extended to a 21-week winter period (week 18-39, end of April to end of September).

Data on ED visits from the 2014 winter weeks not under surveillance and those occurring outside 1pm to 9 pm were extracted from the hospital patient management system database. These data included date and time of visit, date of birth, sex, ethnicity, socioeconomic status based upon residential address, respiratory viral testing results, and presenting signs and symptoms. ED visits were classified as ARI-associated visits if infants presented with at least one of the following signs or symptoms: apnoea, cyanosis, shortness of breath, cough, wheeze, increased work of breathing, stridor, or fever. Cases with fever and gastrointestinal symptoms without any other

ARI-associated symptoms were excluded. Specimens collected from infants in the ED were tested in the same manner as the SHIVERS inpatient surveillance protocol.

2.2.5 Duplicate events

For incidence calculations carried out in this thesis, if a case with confirmed RSV was transferred to another hospital or had two or more RSV positive events within 14 days, they were considered a singular RSV event. Additionally, to ensure correction of non-testing for incidence rates was only done for singular RSV illness episodes, cases with two or more untested ARI events within 14 days were considered as one ARI episode. Such 'non-unique' events were, however, included in direct healthcare-associated cost calculations as they were considered valid indicators of healthcare utilisation and cost.

2.3 New Zealand administrative health data

As mentioned earlier, individual-level data included in the NZ Ministry of Health National Collections were linked with SHIVERS study data using NHI identifiers, which were available in both datasets.

The NHI number is a three-letter, four-digit unique identifier in the format ABC1234. It is assigned to an individual at their first healthcare related contact, which can be at birth, if the child is born in a NZ hospital, or later on attendance at a primary care facility or hospital emergency department. An NHI number is meant to be unique, however, it is possible for an individual to be assigned more than one NHI number if different demographics are provided on different health visits or if a patient's identity cannot be established. In such situations, incorrect NHI numbers are linked back to primary NHIs during the hospital stay or by the NZ Ministry of Health at an administrative level.

The SHIVERS study team obtained access to several datasets with NHIs from the NZ Ministry of Health National Collections. These datasets were made available to researchers following ethical approval and compliance with strict confidentiality policies. Details of these datasets are provided below.

2.3.1 Primary Health Organisation Enrolment Collection

The Primary Health Organisation Enrolment Collection contains demographic (date of birth, sex, socioeconomic status, and ethnicity) and residential information on individuals enrolled with a primary healthcare facility [138]. The database is updated monthly and provides enrolment data on a quarterly basis. Individuals who had residential data from SHIVERS study areas and were enrolled in a primary healthcare service for at least three months during a year were classified as residents for that year. According to Stats NZ population projections, 91% of Auckland DHB and 99% of Counties Manukau DHB residents were enrolled with a primary healthcare organisation in October 2015 [139].

2.3.2 National Minimum Dataset

The National Minimum Dataset (NMDS) contains information on public and private hospital discharges, for both inpatients and day patients [140]. Data includes patient demographics (date of birth, sex, and ethnicity), residential information, clinical information such as International Classification of Diseases 10th edition (ICD-10) hospital discharge codes, dates of hospital admission and discharge, intensive care unit (ICU) admission, and cost weight of each hospitalisation event. The NMDS enabled capture of individuals who, based upon their residential data in the NMDS, resided in the SHIVERS study region but were not enrolled with a primary healthcare facility.

2.3.3 National Maternity Collection

The National Maternity Collection provides demographic and clinical information on publicly funded maternity services up to nine months before and three months after a birth [141]. It enabled capture of women who were SHIVERS study area residents, were not enrolled with a primary healthcare facility, but had a maternity event. It also enabled capture of newborns in the SHIVERS study area.

2.3.4 National Non-Admitted Patient Collection

The National Non-Admitted Patients Collection provides demographic and clinical information on non-admitted patient (outpatient and emergency department) visits [142]. It enabled capture of individuals who were study area residents, were not enrolled with a primary healthcare facility, but had a non-admitted patient visit.

2.3.5 National Mortality Collection

The Mortality Collection classifies the underlying cause of death for all deaths registered in NZ, and all registerable stillbirths (foetal deaths) [143]. It enabled identification of any deaths among SHIVERS study area residents.

2.4 Data linkage, key variables and population estimates

Each national collection dataset was limited to individuals who resided in SHIVERS study areas each year between 2012 and 2015. If residential and demographic data were inconsistent across datasets for a particular year, the mode for each variable was used. When the mode was unavailable, data from the most recent dataset were used. These datasets were then aggregated to create annual, population-based cohorts of Central, East and South Auckland residents i.e. line entry records of residents in the SHIVERS study area for each year. As the SHIVERS study

dataset is a line entry record of ARI hospitalisations, where an individual could have multiple rows if they had more than one hospitalisation, the SHIVERS data had to first be ‘collapsed’ to number of hospitalisations per individual in order to be linked. A diagram illustrating the data linkage process is shown in Figure 2.1. Details on key variables, their sources, definitions and use are provided in Table 2.1.

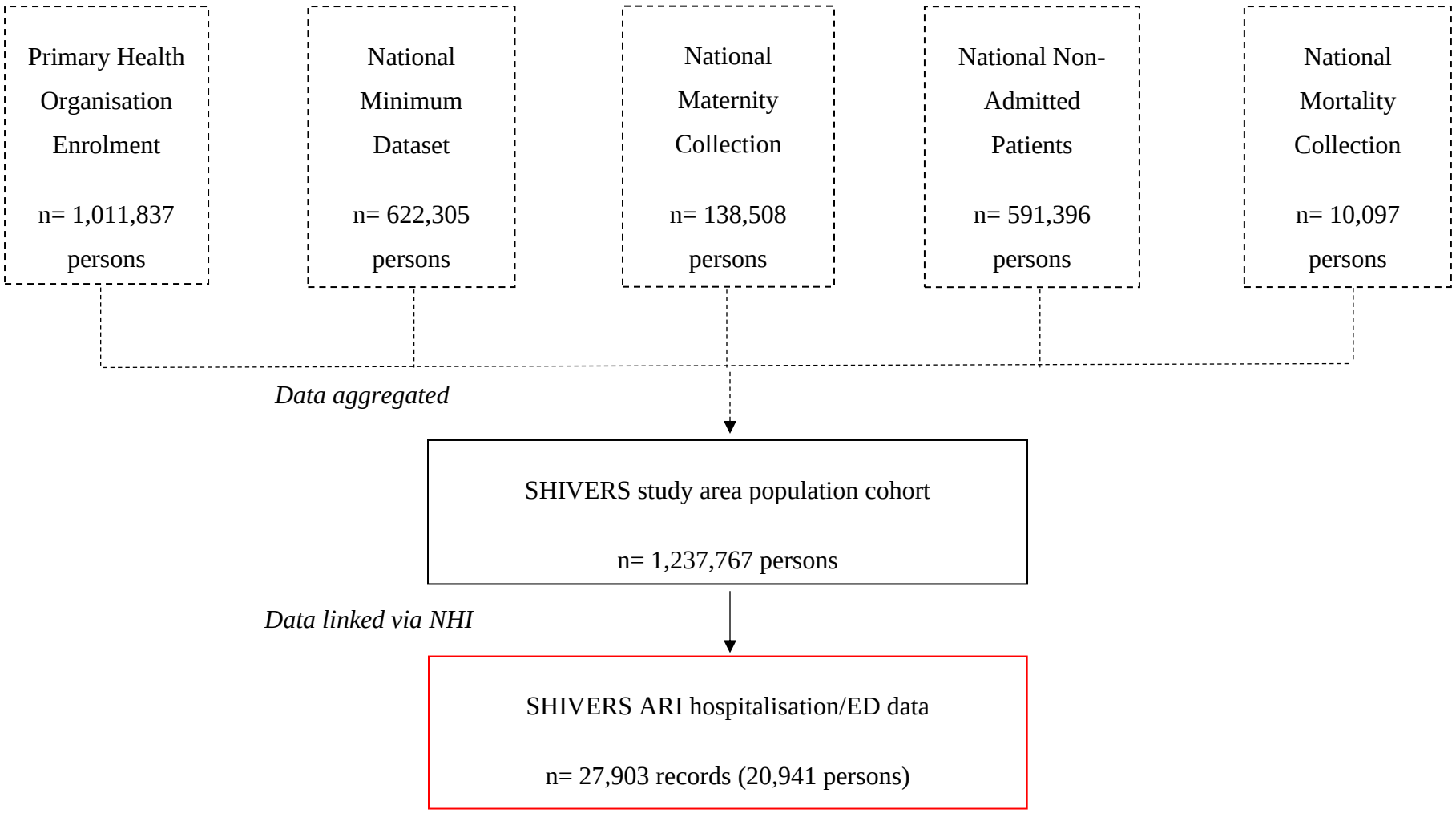


Figure 2.2 Illustration of data linkage process using NZ Ministry of Health National Collections and SHIVERS study data, available from 2012 and 2015

Table 2.1 Key variables used in thesis, data source(s), definitions and use

Variable	Data Source(s)	Variable definition and use
NHI	All NZ Ministry of Health National Collection datasets SHIVERS dataset	The National Health Index number is a three-letter, four-digit alphanumeric code and is used as a unique identifier for an individual who experiences a health event in NZ.
Date of birth	All NZ Ministry of Health National Collection datasets SHIVERS dataset	Date field used to calculate age at acute respiratory infection associated event.
DHB	All NZ Ministry of Health National Collection datasets SHIVERS dataset	Three-digit code to identify which District Health Board a patient sought care at i.e. Auckland or Counties Manukau District Health Board.
Domicile	All NZ Ministry of Health National Collection datasets	Four-digit code to identify residential location of patient. Used to identify residents of SHIVERS study area (central, east and south Auckland).
Prioritised ethnicity	All NZ Ministry of Health National Collection datasets	A standardised form of recording ethnicity in NZ, where each person is allocated to a single ethnic group based on the ethnicities that have identified with. Reported ethnicity is prioritised in the order shown below. Further detail provided in reference [144]. 1. Māori 2. Pacific 3. Asian 4. European/Other
Neighbourhood socioeconomic status (NZ Deprivation score 2013)	Primary Health Organisation Enrolment Collection	NZ Deprivation score 2013 - combines census data relating to income, home ownership, employment, qualifications, family structure, housing, access to transport and communications to create a deprivation score for each meshblock in NZ. Meshblocks are the smallest geographical area defined by Statistics NZ, with a population of around 60–110 people. NZDep2013 groups' deprivation scores into deciles, where 1 represents the areas with the least deprived scores and 10 the areas with the most deprived scores. A value of 10 therefore indicates that a meshblock is in the most deprived 10% of areas in NZ. Deciles (1–10) are converted to an NZDep2013 quintiles (1–5) which were used for the current analysis. Further detail provided in reference [145].
Date of admission	National Minimum Dataset SHIVERS dataset	Date field showing when a patient was admitted to hospital.
Date of discharge	National Minimum Dataset SHIVERS dataset	Date field showing when a patient was discharged from hospital.
LOS	National Minimum Dataset SHIVERS dataset	Hospital length of stay.
ICU	National Minimum Dataset SHIVERS dataset	Date field of admission to an intensive care unit. Blank if not admitted.
Clinical code(s)	National Minimum Dataset	String field providing ICD-10 primary and secondary discharge codes for each hospitalisation event.

Variable	Data Source(s)	Variable definition and use
DRG code	National Minimum Dataset	Diagnosis Related Group (DRG) code. A coding system which categorises hospitalisations into clinically similar events with comparable resource.
Cost weight	National Minimum Dataset	DRG codes, together with information on hospital length of stay and additional interventions such as mechanical ventilation are used to calculate a cost weight for each hospitalisation event. Hospitalisation costs were calculated by multiplying each cost weight with the NZ fixed cost multiplier applicable for the 2017/18 financial year. Further information provided in reference [146].
Auckland resident	SHIVERS dataset	Flag field (0/1) identifying if inpatient was a SHIVERS study resident or not.
SARI	SHIVERS dataset	Flag field (0/1) identifying if inpatient fit the SARI case definition or not.
Test order	SHIVERS dataset	Variable classifying if patient was tested for respiratory viruses using SHIVERS study protocol (1) or through clinician ordered testing (2).
RSV	SHIVERS dataset	Variable classifying if patient tested positive (1) or negative (0) for respiratory syncytial virus. Variable was coded (.) if not tested.
RSV subtype	SHIVERS dataset	Variable classifying if respiratory syncytial virus positive case was subtype A (1), or B (2). Variable was coded (.) if not subtyped/not respiratory syncytial virus positive.
Influenza	SHIVERS dataset	Variable classifying if patient tested positive (1) or negative (0) for influenza. Variable was coded (.) if not tested.
RV	SHIVERS dataset	Variable classifying if patient tested positive (1) or negative (0) for Rhinovirus. Variable was coded (.) if not tested.
hMPV	SHIVERS dataset	Variable classifying if patient tested positive (1) or negative (0) for human metapneumovirus. Variable was coded (.) if not tested.
ADV	SHIVERS dataset	Variable classifying if patient tested positive (1) or negative (0) for adenovirus. Variable was coded (.) if not tested.

Table 2.2 compares annual population estimates (in broad age groups) obtained from Statistics NZ with estimates obtained from linkage of SHIVERS study area resident data. Overall, population estimates were found to be broadly similar.

Table 2.2 Annual population estimates in central, east and south Auckland from Statistics NZ compared to population estimates obtained from data linkage process, overall and by age groups, 2012–2015**Error! Not a valid link.**

2.5 Strengths and weaknesses of data used in this thesis

The SHIVERS study provided a rich dataset with valuable information on RSV. Major strengths of this dataset include: active surveillance for all ARI-associated hospitalisations at facilities providing inpatient care to the study area; testing of a large proportion of cases for RSV and other respiratory viruses using RT-PCR; detailed information on a range of factors among consented patients; and inclusion of NHI numbers, which enabled linkage and validation of data with administrative datasets at an individual level.

One weakness of the SHIVERS study with regards to the work carried out in this thesis was its prioritisation of testing among cases fitting the WHO SARI case definition. This was because the SHIVERS study was funded to primarily inform influenza disease burden and epidemiology. As mentioned earlier, RSV positive cases less frequently develop fever compared to influenza positive cases; therefore relying exclusively on the SARI case definition would result in a number RSV positive cases being missed [28-30]. To counteract this limitation, the SHIVERS study tested a weekly random sample of paediatric and adult patients with ARI not fitting the SARI case definition (non-SARI respiratory) and included test results from clinician-ordered tests.

Another weakness of the SHIVERS study dataset was its limitation to ARI hospitalisations and ED visits among infants. While SHIVERS did carry out surveillance at sentinel primary healthcare facilities, this surveillance was only among patients presenting with influenza-like-illness, which like the SARI case definition requires fever [134] and therefore had low sensitivity for detecting RSV. Consequently, analysis in this thesis was limited to hospital and ED level data and did not provide information of RSV disease burden in other health care settings. Moreover, the SHIVERS study did not obtain data on non-respiratory healthcare events. Thus, any healthcare

events due to RSV that did not present as an ARI were not included, potentially leading to underestimation of RSV disease burden.

A final limitation of the SHIVERS study was that ARI surveillance was only carried out in the central, southern, and eastern regions of Auckland, limiting generalisability of study findings to other regions of NZ. However, the SHIVERS study area is the most populous regions of NZ, and includes a diverse range of socioeconomic, cultural, ethnic and demographic groups that are considered broadly similar to the NZ population.

In terms of the strengths and weaknesses of administrative data used in this thesis; the most important strength of these data is that they provide up-to-date, individual-level data for the entire study population. Population-level data are key for reducing selection bias generated by analysing case/numerator data only. Moreover, individual-level population data enables incidence rates to be calculated by relevant strata and with adjustments, reducing bias generated from effect modification and confounding, respectively.

One of the key weakness of using administrative data to form a population-based cohort, as has been done so in this thesis, is that it does not guarantee that all individuals classified as residents of the study area sought healthcare at surveillance sites. However, as the administrative data sources used in this thesis are continually updated and validated and the SHIVERS surveillance sites are the only hospitals providing acute inpatient paediatric care in the area, this approach was considered the most robust method in estimating incidence rates.

3 The health and economic burden of RSV-associated hospitalisations among children aged less than five years

3.1 Preface

This chapter addresses objective one of this thesis: to estimate the health and economic burden of RSV-associated hospitalisations among children aged less than five years. The research presented in this chapter has been published in *Epidemiology and Infection:*

Prasad N, Newbern EC, Trenholme AA, Wood T, Thompson MG, Aminisani N, Huang QS, Grant CC. Respiratory syncytial virus hospitalisations among young children: a data linkage study. Epidemiology and Infection 2019; 147: e246. https://doi.org/10.1017/S0950268819001377

I designed the study with guidance from my supervisors and co-authors. I carried out data management and analysis and drafted the initial manuscript. All co-authors reviewed and approved the final manuscript.

3.2 Introduction

Respiratory syncytial virus (RSV) is a common aetiological agent in childhood acute respiratory infections (ARI) [4], however, uncertainties in RSV burden estimates among children remain. Reported RSV incidence rates vary, with annual hospitalisation rates for RSV-associated ARI among children aged less than one year in high-income countries ranging from 17/1,000 to 40/1,000 per year [23].

The methods used to quantify RSV disease burden have also varied considerably. Some studies are based on hospital discharge records [58, 147], which rely on passive surveillance for case ascertainment and may lack laboratory confirmation, while others have used indirect statistical

methods to quantify RSV attributable burdens [148, 149]. Finally, RSV laboratory methods have evolved, with real-time polymerase chain reaction (PCR) having a higher sensitivity than previously used immunofluorescence and virus isolation techniques [150]. It is unclear whether varied estimates of RSV disease burden are due to hospital coding, testing, other methodological differences or reflect true geographic and seasonal variation; regardless, they highlight the value of active surveillance of RSV with PCR laboratory confirmation.

Only one RSV-specific immunoprophylaxis treatment is currently available, but is not considered cost-effective in NZ [151]. Several RSV vaccine and immunoprophylaxis candidates are currently in development [152] with a candidate likely to be available for clinical use within the next five to ten years. Comprehensive, country specific RSV burden estimates are essential to guide the introduction of such interventions.

This study linked active, population-based surveillance and individual-level administrative datasets to estimate the incidence of laboratory-confirmed, RSV-associated hospitalisations and their direct healthcare costs among children aged less than five years in Auckland, NZ. Additionally, we compared RSV disease estimates determined through active surveillance to those derived from hospital discharge codes.

3.3 Methods

In this study we retrospectively reviewed a cohort of children aged less than five years residing in central, east and south Auckland in 2012 to 2015 for ARI and RSV-confirmed hospitalisations. This was done using linked administrative datasets and active ARI hospital surveillance as part of the Southern Hemisphere Influenza Vaccine Effectiveness and Research (SHIVERS) project [132]. The SHIVERS study areas are predominantly urban and based on Statistics NZ population estimates included approximately 71,770 children aged less than five years in 2015, of whom

14% were Māori (NZ's indigenous population), 22% Asian, 27% Pacific (including ethnic groups from Samoa, Cook Islands, Tonga, Niue, Fiji, Tokelau, Tuvalu, and Kiribati), and 35% were of European or other ethnicities [133]. Ethical approval for the SHIVERS project was obtained from the NZ Health and Disabilities Ethics Committee (NTX/11/11/102).

Note: Details in sections 3.3.1–3.3.2 have been previously mentioned in section 2.2.

3.3.1 Hospital surveillance

The SHIVERS project was an active ARI surveillance project conducted in two adult and two paediatric public hospitals serving the central, east and south Auckland region. These hospitals provide all inpatient services for the population residing in the area. From 30th April 2012 to 31st December 2015, research nurses reviewed daily records to identify all overnight admissions with suspected ARI. All patients meeting the WHO severe acute respiratory infection (SARI) case definition, defined as cough and measured or reported fever within the last 7 days (in 2012) and 10 days (from 2013 onwards) were enrolled [134]. Study nurses obtained consent, collected nasopharyngeal swabs, and completed detailed case report forms.

To provide an understanding of the respiratory virus hospitalisation burden among ARI patients not meeting the SARI definition, between 2013–2015 study nurses enrolled samples of non-SARI respiratory patients, i.e. patients with cough and/or measured or reported fever but not both within 10 days. Sampling in 2013 was during the peak winter period (12th August to 6th October) and included weekly random selection of two paediatric inpatients who fitted the non-SARI respiratory definition at all participating facilities. In 2014 and 2015, this surveillance was extended to randomly enrol approximately six paediatric non-SARI respiratory patients weekly in all facilities from week 18 to 39 (end of April – September).

In addition to respiratory virus test results generated by SHIVERS surveillance, hospital laboratories also provided results from clinician-ordered tests performed on SARI and non-SARI respiratory patients during the study period. These results were included after validation of the hospital assay performance (Appendix 1.1).

3.3.2 Laboratory methods

Specimens were tested for RSV, influenza, rhinovirus (RV), adenovirus (ADV), and human metapneumovirus (hMPV) using the United States Centers for Disease Control and Prevention real-time reverse-transcription (RT)-PCR protocol [135, 136] at the Institute of Environmental Science and Research or the AusDiagnostic PCR protocol and real time RT-PCR assay at hospital laboratories [137]. A sample of positive specimens were further subtyped.

3.3.3 Incidence rate denominator

We used national administrative datasets including hospital discharges from the National Minimum Dataset, primary healthcare enrolments from Primary Health Organisation Enrolment Collection, births from the National Maternity Collection, deaths from the National Mortality Collection, and specialist visits from the National Non-Admitted Patient Collection [153] to identify children aged less than five years residing in the SHIVERS study area during our surveillance period. Individuals in these datasets had a unique National Health Index (NHI) number, enabling dataset linking.

The Primary Health Organisation Enrolment Collection dataset identified approximately 98% of our study population with other datasets identifying an additional 2%. Each identified child was followed from birth or their first year of residence in Auckland until the end of the study period, or until they reached five years of age, moved out of Auckland, or died. Each child's time at risk during a defined winter seasons was calculated. A child could contribute time at risk in multiple

age groups (0–2 months, 3–5 months, 6–11 months, 12–23 months, and 2–4 years) depending on their birth date, residence, and timing of winter seasons. This population data was linked to the SHIVERS dataset using NHI numbers to identify those with ARI and RSV-associated hospitalisations.

3.3.4 Comparison to hospital discharge codes

All ARI hospitalisations identified via SHIVERS also had an International Classification of Diseases (ICD), 10th edition (ICD-10) diagnostic code, enabling comparison of hospitalisation incidence obtained through active surveillance with laboratory confirmation to incidence based upon hospital discharge codes. We classified a child as having an RSV event based on hospital discharge codes if they had at least one primary or secondary RSV specific ICD-10 code (Table 3.1). A flowchart illustrating the different components of the study is provided in Figure 3.1.

Table 3.1 International Classification of Diseases, 10th edition (ICD–10) diagnostic codes used to identify respiratory syncytial virus (RSV) associated hospitalisations among children aged less than five years in Auckland, NZ, 2012–2015

Diagnostic Category	**ICD-10 Code [a]**	**Number identified in study**	**Percentage of all acute respiratory hospitalisations N=5309**
Primary ICD-10 codes			
RSV as the cause of disease classified to other chapters	B974	88	(1.7)
RSV pneumonia	J121	235	(4.4)
Acute bronchiolitis due to respiratory syncytial virus	J210	862	(16.2)
Acute bronchitis due to respiratory syncytial virus	J205	4	(0.1)
Secondary ICD-10 codes only			
RSV pneumonia	J121	22	(0.4)
Acute bronchiolitis due to respiratory syncytial virus	J210	36	(0.7)
Acute bronchitis due to respiratory syncytial virus	J205	0	-
Total	**-**	**1247**	**(23.5)**

* ICD-10 diagnostic code for hospital inpatient cases are reported in the National Minimum Dataset.

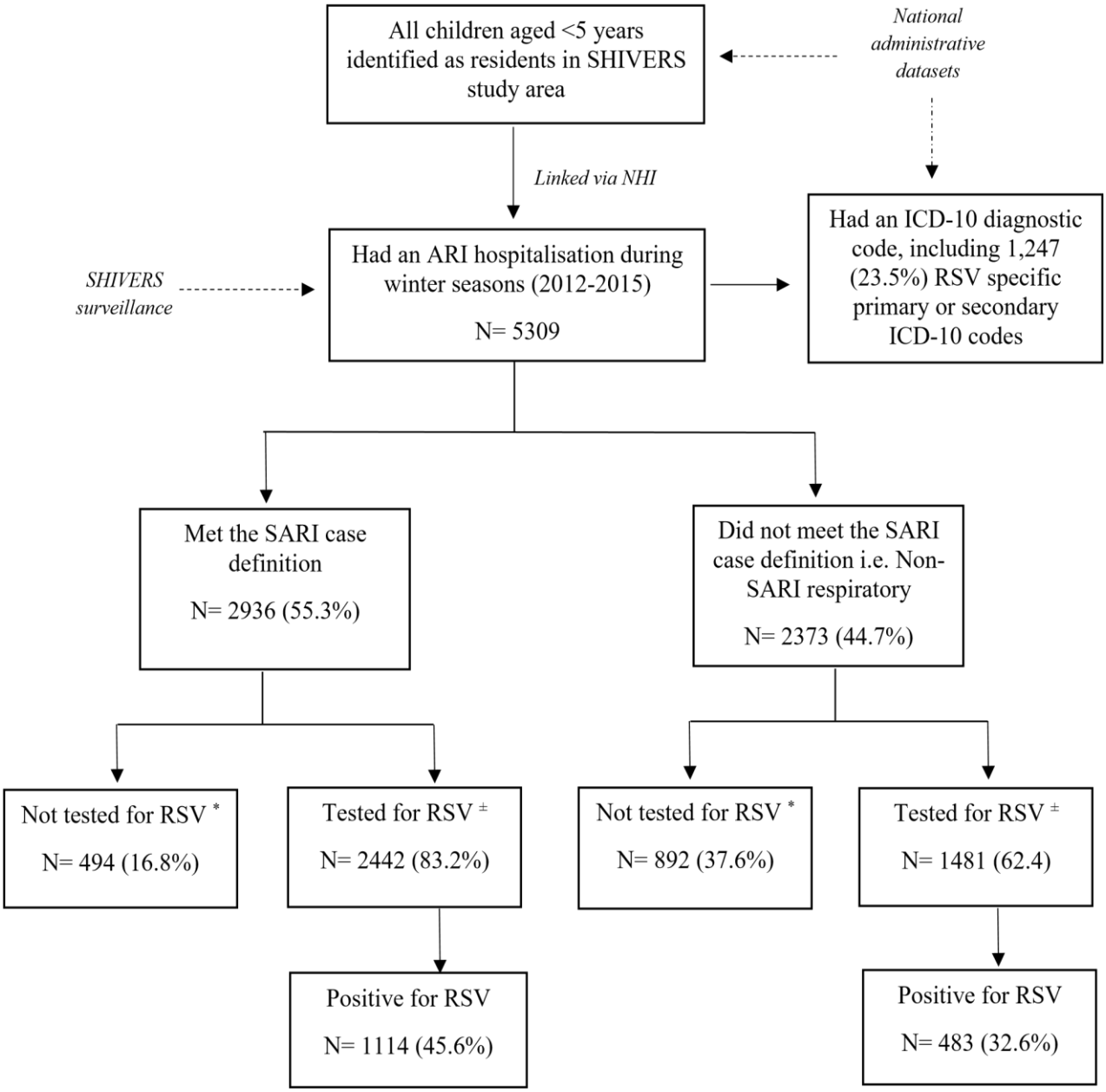


Figure 3.1 Flowchart detailing retrospective cohort of children aged less than five years in Auckland, New Zealand in 2012–2015 and number of RSV laboratory confirmed and/or an RSV International Classification of Diseases (ICD), 10th edition (ICD-10) diagnostic codes

* For incidence rate calculations, correction of non-testing among ARI patients was done using multivariate imputation by chained equations (MICE) method of imputation.
± Includes both SHIVERS systematic testing results and any results from samples tested for clinical purposes.

3.3.5 Cost estimation

Inpatient events and related clinical codes in the National Minimum Dataset are also allocated a Diagnosis Related Group (DRG) code. The DRG coding system categorises hospitalisations into clinically similar events with comparable resource. These codes, together with information on hospital length of stay and additional interventions such as mechanical ventilation are used to calculate a cost weight and therefore a cost for each inpatient hospital admission. We calculated hospitalisation costs by multiplying each cost weight with the NZ fixed cost multiplier applicable for the 2017/18 financial year [146].

3.3.6 Statistical analysis

Year-round surveillance data showed that RSV follows a well-established seasonal pattern with 91.8% of RSV-confirmed cases detected between end of April and September (winter season in NZ) from 2012 to 2015 (Figure 3.2). Moreover, since SHIVERS non-SARI respiratory case testing was only conducted during the winter seasons, the current analysis was limited to week 18–39 (end of April to end of September) of each year.

For incidence calculations, if a child with confirmed RSV was transferred to another hospital or had two or more RSV positive hospitalisations within 14 days, they were considered a singular RSV event. We calculated seasonal incidence rates in two ways: 1) calculating the number of singular RSV-associated ARI hospitalisations (events) divided by the number of children residing in the study area during a season; and 2) dividing the number of events by time at risk during each winter season measured as child-years. The first definition was used to enable comparison to other RSV hospitalisation rates while the second definition was used to have a more precise denominator of time at risk during the surveillance period.

Incidence was stratified by age, ethnicity, and socioeconomic status (SES) as they are considered key modifiers of RSV infection risk [4, 70, 154]. SES was quantified using a small area-measure of neighbourhood deprivation derived from the national census (NZDep2013) [145] and was used to separate the cohort into SES quintiles. Confidence intervals for incidence and rate ratios were based on the Poisson distribution. Māori and Pacific peoples are over-represented in lower SES groups in NZ [155]. This overrepresentation may confound the relationship of ethnicity and SES with RSV hospitalisation risk, therefore rates and rate ratios relating to these exposures were adjusted for each other to evaluate independence of their effects.

Chi-square tests were used to test associations between categorical variables and Student's t-tests for continuous variables. The sensitivity, specificity, and positive predictive value of RSV hospital discharge codes for identifying RSV laboratory-confirmed hospitalisations were also calculated. All analyses were performed using Stata 14 (College Station, TX: StataCorp LP).

Correction for non-testing for incidence rates

We verified that non-tested patients were missing at random using a Missing Completely at Random Test [156]. Using the multivariate imputation by chained equations (MICE) method of imputation in STATA [157], we created 30 imputed datasets of RSV results with age in months, SARI case status, sex, ethnicity, SES, hospitalisation week, and specimen type (clinician-order versus SHIVERS systematic sampling) included as predictors of missingness. Non-imputed results are provided in Appendix 2.1

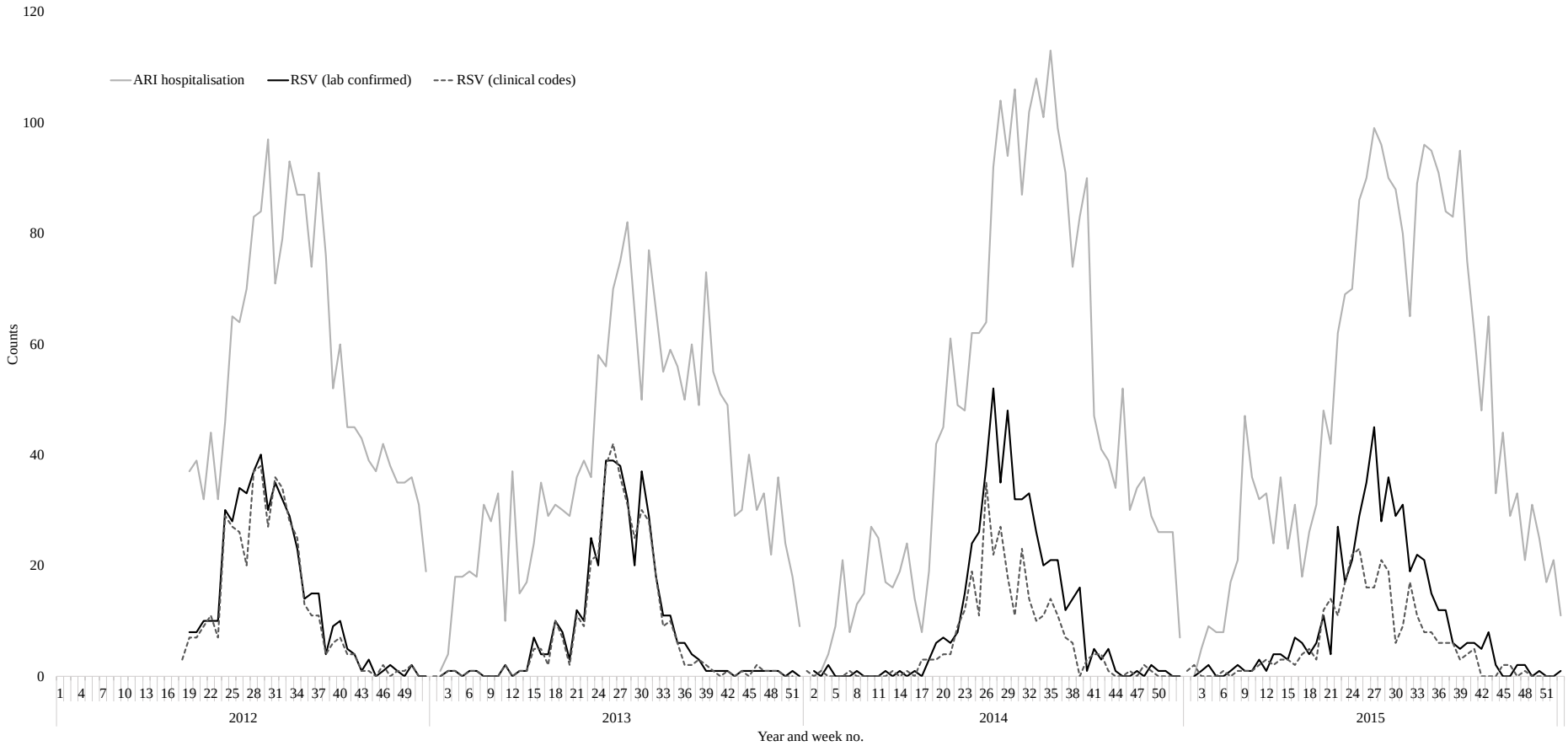


Figure 3.2 Weekly counts of Acute Respiratory Infection (ARI) hospitalisations, RSV laboratory confirmed hospitalisations, and RSV ICD-10 coded hospitalisations among children aged less than five years in Auckland, NZ, 2012–2015

* RSV lab-confirmed cases include all SARI and non-SARI samples tested via the SHIVERS study protocol as well as any samples tested for clinical purposes.

3.4 Results

3.4.1 Study population

During 2012–2015, an average of 84,950 children aged less than five years resided in the study area annually. In total, children in our cohort contributed 131,683 child-years at risk during the winter surveillance period (Table 3.2).

3.4.2 Hospitalised patients

During the surveillance period, there were 5,309 overnight ARI hospitalisations among children aged less than five years, with 433 (8.2%) admitted to ICU and 19 (0.4%) dying in hospital or within 30 days of admission. The median (interquartile range [IQR]) length of hospital stay for children hospitalised with ARI was 2 (1–3) days.

Prospective or clinical RSV testing was performed on 3,923 (73.9%) ARI hospitalisations, including 1,597 (40.7%, 95% CI 39.2–42.2) RSV positive cases. Among the 729 subtyped RSV infections, 384 (52.7%) were RSV subtype A, 343 (47.1%) were RSV subtype B, and two cases were concurrently infected with RSV subtype A and B. Seasonality of RSV by subtype is presented in Appendix 2.2.

The proportion of ARI hospitalisations requiring ICU admission did not differ significantly by RSV positivity (RSV positive = 10.1% versus RSV negative = 10.2%, p-value = 0.926). Among RSV positive children, one child died during the hospital admission and two children died within 30 days of admission. The median (interquartile [IQ]) hospital length of stay of RSV positive children was 3 (2–4) days.

Of the 1,597 RSV positive cases, 1,187 (74.3%) were also tested for other respiratory viruses. Among these RSV positive samples, 368 (31.0%) were co-infected with other viruses, which

included 136 (37.0%) RV co-infections, 114 (31.0%) ADV co-infections, 41 (11.1) influenza co-infections, 14 (3.8%) hMPV co-infections, and 63 (17.1%) samples positive for three or more viruses. Overall, we found RSV co-infections to be more common among older children than single RSV infections (p-value < 0.001). No significant differences in ICU admission or hospital length of stay were found between RSV co-infections and single RSV infections.

Of the 5,309 ARI hospitalisations, 2,999 had additional information on comorbidities including premature birth, low birth weight, chronic lung conditions, and cardiovascular conditions. These ARI hospitalisations included 2,610 patients. Of these patients, 458 (17.6%) had at least one of the assessed comorbidities, the most common of which was premature birth (n=326, 12.5%). Of RSV positive patients, 1,045 had information on comorbidities. Of these cases, 169 (16.2%) had at least one comorbidity, again the most common of which was premature birth (n=121, 11.6%).

3.4.3 Seasonal incidence of RSV-confirmed hospitalisations

The seasonal incidence of RSV-associated ARI hospitalisation, without accounting for non-tested children, was 4.7 (95% confidence interval [CI] 4.5–5.0) per 1,000 children or 12.2 (95% CI 11.6–12.9) per 1,000 child-years at risk (Appendix 2.1). Following imputation for non-testing, the incidence of RSV-confirmed hospitalisation among children aged less than five years was 6.1 (95% CI 5.8–6.4) per 1,000 children or 15.0 (95% CI, 14.3–15.7) per 1,000 child-years at risk (Table 3.2).

Incidence decreased with age, with children 0–2 months old being almost 30 times as likely to have an RSV hospitalisation compared to children aged 2–4 years (Figure 3.3). Māori and Pacific children had an increased risk of RSV hospitalisation compared to children of European or other ethnicities. Similarly, children from more deprived SES areas had an increased risk of RSV hospitalisation compared to children living in the least deprived quintile areas (Figure 3.3).

Following adjustment for SES and ethnicity, rates of RSV hospitalisation remained significantly higher in Māori and Pacific children compared to children of European or other ethnicities (Māori rate ratio [RR] 4.0, 95% CI 3.4–4.7; Pacific RR 2.9, 95% CI 2.5–3.4). Additionally, children from more deprived SES areas remained at increased risk compared with children from the least deprived area (lowest SES area RR 1.3, 95% CI 1.0–1.6; 2nd lowest SES area RR 1.4, 95% CI 1.1–1.7).

3.4.4 Seasonal incidence obtained through hospital discharge codes

During the surveillance periods, 1,247 RSV ARI hospitalisations were identified by RSV specified primary or secondary ICD-10 discharge code (Table 3.1). Of these RSV specified codes, 1,187 (95.2%) were primary discharge codes (Table 3.3).

The seasonal incidence of RSV ICD-10 coded hospitalisations per 1,000 children was 3.7 (95% CI 3.5–3.9) or 9.5 (95% CI, 8.9–10.0) per 1,000 child-years (Table 3.2). Rates obtained using active, lab-confirmed surveillance were 1.7 (95% CI 1.5–1.8) times higher than rates obtained using hospital discharge codes. Active, lab-confirmed surveillance rates were twice the rate obtained from hospital discharge codes in 2014 and 2015 (2014 RR 2.1, 95% CI, 1.8–2.4; 2015 RR 2.1, 95% CI, 1.8–2.4), twice the rate for children aged 12–23 months (RR 2.0, 95% CI 1.7–2.3), and more than three times the rate for children aged 2–4 years (RR 3.2, 95% CI 2.5–4.2).

Compared to RSV PCR positivity, the sensitivity, specificity, and positive predictive value of RSV-associated primary or secondary J121, J210, J205, or B974 discharge codes were 71%, 99%, and 98%, respectively. Further comparisons of RSV laboratory confirmed cases to hospital discharge codes are provided in Appendix 2.3–2.4.

Table 3.2 Seasonal incidence rates of laboratory confirmed and ICD-10 coded respiratory syncytial virus (RSV) associated hospitalisations among children aged less than five years, by year, sub-region, age group, sex, socioeconomic status (SES), and ethnicity in Auckland, New Zealand, 2012–2015

	Child time at risk (years)	All ARI	ARI tested for RSV	RSV laboratory confirmed hospitalisations (adjusted for non-testing)						ICD-10 coded RSV hospitalisations				
				No.	(%) of tested	Rate per 1,000 children*		Rate per 1,000 child-years*			Rate per 1,000 children*		Rate per 1,000 child-years*	
						IR	(95% CI)	IR	(95% CI)	No.	IR	(95% CI)	IR	(95% CI)
Total	131683	5309	3923	1597	(40.7)	6.1	(5.8–6.4)	15.0	(14.3–15.7)	1247	3.7	(3.5–3.9)	9.5	(8.9–10.0)
Year														
2012	33258	1315	931	417	(44.8)	6.8	(6.3–7.4)	17.5	(15.8–19.2)	399	4.6	(4.2–5.1)	11.8	(10.7–13.0)
2013	33066	1128	823	354	(43.0)	5.5	(5.0–6.0)	14.0	(12.6–15.5)	346	4.1	(3.6–4.5)	10.4	(9.3–11.5)
2014	32784	1436	1111	442	(39.8)	6.4	(5.9–7.0)	16.5	(14.9–18.1)	261	3.1	(2.7–3.5)	8.0	(7.0–9.0)
2015	32575	1430	1058	384	(36.3)	5.9	(5.4–6.5)	15.3	(13.8–16.2)	241	2.9	(2.5–3.3)	7.4	(6.4–8.3)
Sub-region														
Central Auckland	55552	2176	1296	504	(38.9)	5.6	(5.2–6.0)	14.6	(13.4–15.7)	374	2.6	(2.3–2.8)	6.8	(6.1–7.5)
South East Auckland	76130	3133	1670	1093	(65.4)	6.5	(6.1–6.8)	16.5	(15.5–17.5)	873	4.5	(4.2–4.8)	11.3	(10.6–12.1)
Age Group														
0–2 months	6254	1151	924	450	(48.7)	35.1	(32.2–38.1)	90.3	(82.4–98.3)	427	26.5	(24.0–29.1)	68	(61.4–74.5)
3–5 months	6428	828	696	314	(45.1)	22.3	(20.1–24.7)	57.4	(51.2–63.6)	265	16.0	(14.1–18.0	41.2	(36.1–46.3)
6–11 months	12961	1213	958	363	(37.9)	13.2	(12.0–14.5)	33.9	(30.3–37.5)	267	8.0	(7.1–9.0)	20.4	(17.9–22.9)
12–23 months.	26068	1042	737	300	(40.7)	6.0	(5.5–6.7)	15.4	(13.7–17.1)	206	3.1	(2.7–3.5)	7.8	(6.7–8.9)
2–4 years.	79972	1075	608	170	(28.0)	1.3	(1.1–1.5)	3.3	(2.8–3.8)	82	0.4	(0.3–0.5)	1.0	(0.8–1.3)

Table continued on next page

	Child time at risk (years)	All ARI	ARI tested for RSV	RSV laboratory confirmed hospitalisations (adjusted for non-testing)						ICD-10 coded RSV hospitalisations				
				No.	(%) of tested	Rate per 1,000 children*		Rate per 1,000 child-years*			Rate per 1,000 children*		Rate per 1,000 child-years*	
						IR	(95% CI)	IR	(95% CI)	No.	IR	(95% CI)	IR	(95% CI)
SES ± ‡														
1 (least deprived)	16358	319	184	78	(42.4)	2.9	(2.4–3.4)	7.4	(5.9–9.0)	59	1.4	(1.1–1.8)	3.6	(2.7–4.5)
2	20097	478	294	133	(45.2)	3.9	(3.4–4.5)	10.2	(8.5–11.9)	103	2.0	(1.6–2.4)	5.1	(4.1–6.1)
3	18983	499	319	123	(38.6)	3.8	(3.3–4.4)	9.8	(8.2–11.4)	94	1.9	(1.6–2.3)	5.0	(3.9–6.0)
4	18161	738	520	219	(42.1)	6.3	(5.6–7.0)	16.2	(14.2–18.3)	175	3.7	(3.2–4.3)	9.6	(8.2–1.1)
5 (most deprived)	58083	3275	2606	1044	(40.1)	8.4	(8.0–8.9)	21.7	(20.3–23.0)	816	5.4	(5.1–5.8)	14.0	(13.1–15.0)
Ethnicity ±														
Māori	19164	1617	1239	509	(41.1)	12.8	(11.8–13.9)	33.1	(30.2–35.9)	401	8.1	(7.3–8.9)	20.9	(18.8–23.0)
PI	36522	2348	1850	720	(38.9)	9.3	(8.7–9.9)	24.0	(22.2–25.8)	570	6.0	(5.6–6.7)	15.6	(14.3–16.9)
Asian	29179	496	321	141	(43.9)	2.7	(2.3–3.1)	7.0	(5.9–8.0)	100	1.3	(1.1–1.6)	3.4	(2.7–4.1)
European/Other	46818	848	513	227	(44.2)	2.9	(2.6–3.2)	7.5	(6.6–8.4)	176	1.5	(1.3–1.7)	3.8	(3.2–4.3)

* Incidence rates were calculated using two definitions; 1) calculating the number of singular RSV-associated ARI hospitalisations (events) divided by the number of children residing in the study area during a season; and 2) dividing the number of events by time at risk during each surveillance period measured as child-years.

± Rates for SES and ethnicity presented in the table are unadjusted for each other. Adjusted rate ratios are provided in text.

‡ SES (Socioeconomic status) was quantified into quintiles using a small area level measure of household deprivation derived from the national census (NZDep2013).

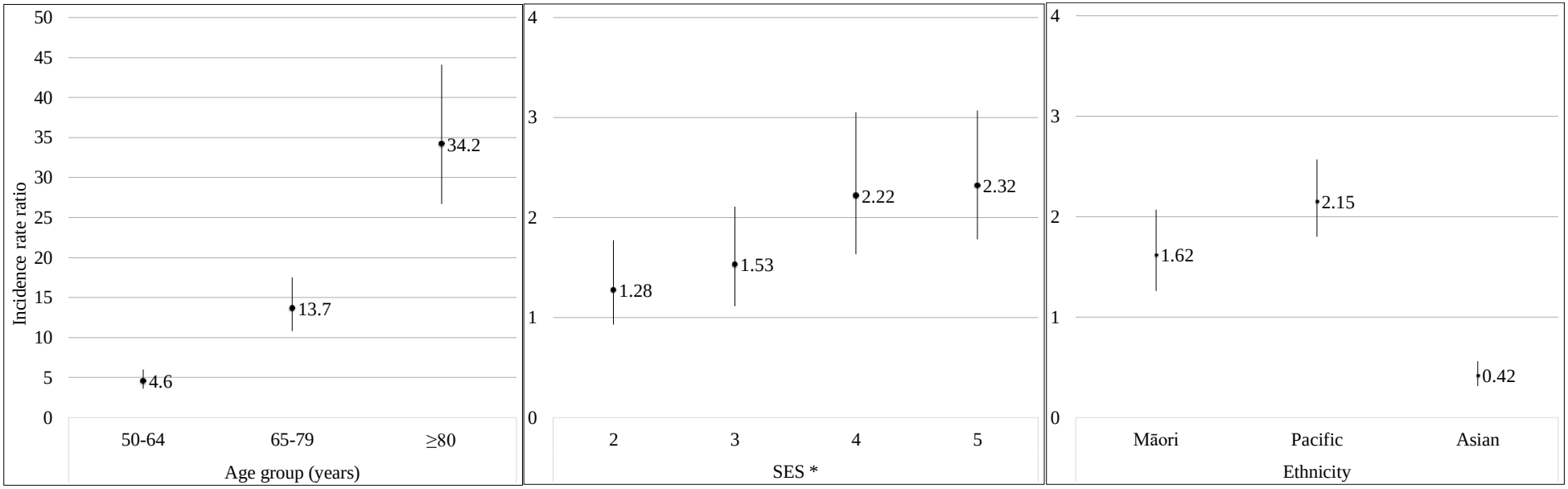


Figure 3.3 Incidence rate ratios for age group (referent 2–4 years old), socioeconomic status (referent – quintile 1), and ethnicity (referent – European/other) of RSV-associated ARI hospitalisations among children less than five years of age in Auckland, New Zealand, 2012–2015

* Rate ratios for SES and ethnicity presented in figure are unadjusted for each other. Adjusted rate ratios are provided in text.
± SES (Socioeconomic status) was quantified into quintiles using a small area level measure of household deprivation derived from the national census (NZDep2013).

Table 3.3 Laboratory confirmed RSV-associated hospitalisations and corresponding primary ICD-10 code among children aged less than five years, 2012–2015

Corresponding primary hospital discharge code *	ICD-10 code	RSV positive		RSV negative		RSV untested		Total	
		N	(%)	N	(%)	N	(%)	N	(%)
Total		**1597**	**(100.0)**	**2251**	**(100.0)**	**1347**	**(100.0)**	**5195**	**(100.0)**
All RSV specified		1081	(67.7)	26	(1.2)	80	(5.9)	1187	(22.8)
RSV as the cause of disease classified to other chapters	B974	76	(4.8)	7	(0.3)	4	(0.3)	87	(1.7)
RSV pneumonia	J121	210	(13.1)	5	(0.2)	21	(1.6)	236	(4.5)
Acute bronchiolitis due to respiratory syncytial virus	J210	791	(49.5)	14	(0.6)	55	(4.1)	860	(16.6)
Acute bronchitis due to respiratory syncytial virus	J205	4	(0.3)	0	(0.0)	0	(0.0)	4	(0.1)
Non-RSV specified respiratory		473	(29.6)	1923	(85.4)	1095	(81.3)	3491	(67.2)
Acute upper respiratory infections	J00-J06	11	(0.7)	187	(8.3)	102	(7.6)	300	(5.8)
Acute lower respiratory infections	A37, J09-J20	420	(26.3)	1528	(67.9)	678	(50.3)	2626	(50.5)
Whooping cough	A37	1	(0.1)	24	(1.1)	8	(0.6)	33	(0.6)
Influenza and Pneumonia	J09-J18	196	(12.3)	619	(27.5)	257	(19.1)	1072	(20.6)
Bronchiolitis	J21	190	(11.9)	779	(34.6)	365	(27.1)	1334	(25.7)
Unspecified ALRI	J22	32	(2.0)	98	(4.4)	47	(3.5)	177	(3.4)
Bronchitis	J20	1	(0.1)	8	(0.4)	1	(0.1)	10	(0.2)
Other and unspecified asthma	J459	8	(0.5)	84	(3.7)	161	(12.0)	253	(4.9)
Wheezing	R062	34	(2.1)	124	(5.5)	154	(11.4)	312	(6.0)
Non-RSV specified non-respiratory		43	(2.7)	302	(13.4)	171	(12.7)	516	(9.9)
Viral infection unspecified	B349	4	(0.3)	37	(1.6)	17	(1.3)	58	(1.1)
Other	xxx	39	(2.4)	265	(11.8)	154	(11.4)	458	(8.8)

* Table 3.3 is only displaying primary ICD-10 discharge codes, of the 1597 RSV positive children, 49 (3.1%) had a secondary RSV specified ICD-10 code.

3.4.5 Direct healthcare cost

Based on the DRG costing methodology, the median (IQR) cost per RSV hospitalisation was $3,155 ($3,071–$4,932) while among non-RSV hospitalisations the median (IQR) cost per hospitalisation was $3,121 ($2,312–$4,651). Hospitalisation costs were not significantly different by RSV positivity in children (p-value = 0.336). After accounting for non-testing, the annual estimated direct healthcare cost of RSV-confirmed hospitalisations among children aged less than five years in the Auckland region was NZ$2.6 million or an average NZ$5,040 per episode (Table 3.4).

Table 3.4 Direct healthcare associated cost for RSV positive hospitalisations by age groups using Diagnosis Related Group (DRG) cost weights in Auckland, New Zealand, 2012–2015

	No. of episodes	Total cost *	Median (IQR) cost	Average cost per episode	Annual cost (NZ$) in study area	Annual cost (US$) in study area ±
RSV positive ‡	1615	$8,139923	$3,155 ($3,071–$4,932)	$5,040	$2,034981	$1,400576
Imputed estimate ¶	2066	$10,413053			$2,603263	$1,791696
By age group						
0–2 months	459	$2,952,299	$4,242 ($3,071–$6,193)	$6,432	$738,075	$507,980
3–5 months	319	$1,607,981	$3,169 ($3,071–$4,932)	$5,041	$401,995	$276,673
6–11 months	365	$1,701,770	$3,155 ($3,071–$4,932)	$4,662	$425,443	$292,811
12–23 months	302	$1,297,951	$3,133 ($3,039–$4,319)	$4,298	$324,488	$223,329
2–4 years	170	$579,921	$3,133 ($3,039–$3,169)	$3,411	$144,980	$99,783

* Total cost from 2012–2015 is calculated as the sum of each individual hospitalisation event cost weight multiplied by the New Zealand fixed cost multiplier for the 2017/18 financial year which was equal to $4,921.

± Currency conversion was based on currency exchange rates from November 2018.

‡ RSV positives include non-unique events i.e. if a child confirmed to have RSV was transferred to another hospital or had two or more RSV positive hospitalisations within 14 days of discharge from their first event. While these events are possibly the same RSV episode, they are indicative of healthcare utilisation and cost and are therefore included in cost estimations.

¶ The average cost per episode for RSV positive hospitalisations was multiplied to the imputed RSV positive estimate to obtain the total, and annual cost.

3.4.6 Extrapolation to national population

If our ethnicity-specific RSV hospitalisation rates were extrapolated to the entire NZ population, we estimate approximately 1,900 children aged less than five years would have an RSV-associated hospitalisation each year with a direct healthcare cost of NZ$8.2 million. Moreover, we estimate Māori and Pacific children to represent approximately 41% and 16% of all RSV hospitalisations, despite comprising 20% and 10% of the NZ child population, respectively.

3.5 Discussion

We found that RSV infection has a high health and economic burden in NZ, accounting for roughly 40% of ARI hospitalisations. Being of indigenous Māori or of Pacific ethnicity or living in more socioeconomically deprived areas were independently associated with increased risk of RSV hospitalisation. Approximately 80% of children with an RSV-associated hospitalisation did not report an underlying condition. Relying on RSV hospital discharge codes under-estimated RSV burden, given the sensitivity of discharge coding of 71% for identifying laboratory-confirmed RSV cases.

Our results are similar to a year-round prospective study of RSV in South Auckland among children age less than two years [76], which suggests that our seasonal incidence approximates to the annual RSV incidence. Among NZ children aged less than five years, RSV-associated hospitalisation rates were roughly three times higher than those reported for influenza (IR = 1.9 per 1,000 children) during the same period [158-161]. Rates in our study are also higher than reported rotavirus hospitalisations rates for NZ children aged less than five years before rotavirus vaccine introduction [162, 163], and highlight the relative contribution of RSV to hospital disease burden. Moreover, we found that an RSV hospitalisation costs on average NZ$5,040 per episode. This is higher than the annual direct cost of rotavirus hospitalisations, which was estimated at

NZ$1,512 per episode among children less than five years in 2006/2007 [38] and would be approximately NZ$2,400 in 2017/18.

When comparing our findings to those reported from a US study that used active lab-confirmed surveillance, we found our proportion positivity for RSV (40%) to be approximately twice the proportion positive reported from the US, moreover our hospitalisation rate of 6.1 per 1,000 children aged less than five years was twice the rate reported from the US [57]. Our findings are consistent with national comparative data showing children less than two years old in NZ to be twice as likely to be hospitalised with bronchiolitis or pneumonia as those living in England or the US [72, 74, 75, 164, 165].

Factors such as differences in healthcare seeking behaviour and thresholds for hospital admission are likely to be contributing to these between country differences. Additionally, the disproportionate burden of RSV disease experienced by Māori and Pacific children will also be contributing to the high burden observed in NZ. While the RSV hospitalisation rates among Māori and Pacific children in our study are comparable to the high rates observed in indigenous populations in Australia [58] and North America [70, 166], in Auckland, Māori and Pacific children comprise approximately 40% of the child population which is in contrast to Australia and North America, where indigenous populations comprise 2–3% of the total population in major urban areas.

Children in the most deprived SES groups also had an increased risk of RSV-associated hospitalisations. Previous studies from NZ have highlighted the disparity in respiratory and other infectious diseases burden [167], linking these to both SES and ethnicity-related factors such as household crowding [168], maternal smoking and perceived experience of healthcare racism [169], as well as barriers to primary healthcare [170], and may explain our finding of independent SES and ethnicity effects. Another potential explanation is that our neighbourhood-level measure

of SES may not accurately capture individual SES. Consequently, social and economic factors associated with RSV disease risk such as smoking, housing density, presence of comorbidities, healthcare seeking behaviour, and poor nutrition are being better captured by ethnicity. Interventions such as the introduction of pneumococcal conjugate vaccines have been associated with reductions in social and ethnic disparities in hospitalisations in NZ [171] and suggest that an RSV vaccine and/or immunoprophylaxis may have a similar impact.

We found lab-confirmed hospitalisation rates to be about 1.7 times higher than discharge coded rates overall and more than double discharge coded rates between 2014–2015 and among children aged greater than one year (Table 3.2). Protocols at hospitals were reported to change from routine testing of all ARIs to testing based on clinical suspicion between 2014–2015 (A Trenholme, personal communication) and may explain the lower sensitivity of discharge codes in detecting RSV positive cases in those years. Such findings have implications for other countries relying on passive surveillance and hospital discharge codes to estimate RSV disease burden, particularly with regards to the potential underestimation of RSV hospitalisation rates among children aged 1-4 years.

The major strength of this study is its use of active laboratory-confirmed surveillance linked with individual-level population data, enabling estimation of RSV hospitalisation rates by key demographic strata. However, our study also has limitations. Firstly, our population estimates of children aged less than five years are higher than population estimates from Statistics NZ; additionally, we are unable to guarantee that all children classified as residents in our study sought healthcare at our surveillance sites. However, as the data sources are continually updated and validated and our surveillance sites are the only hospitals providing acute inpatient paediatric care in the area, we considered this approach as the most robust method in estimating hospitalisation rates. Secondly, our cost estimations did not account for indirect costs associated with loss of

work and out-of-pocket expenses. Third, we did not have population level data on well-established risk factors for severe RSV disease such as premature birth, exposure to second-hand smoking, and other underlying conditions, preventing estimation of RSV hospitalisation rates within these strata. Such rates will be valuable in informing RSV vaccine/therapy use among high-risk groups. Finally, the lack of systematic bacterial and viral co-infection data prevented detailed assessments of the causal role of RSV infection in children presenting with ARIs. However, a recent meta-analysis suggests strong evidence for this association, showing that among young children with RSV-ALRI, ALRI is causally attributable to RSV in about 90% of cases [172].

3.6 Conclusions

We confirm that RSV is a leading cause of hospitalisation among young children and has a high economic cost in NZ. RSV hospitalisation rates in our study are almost twice the rate reported in a similar study from the US. In NZ, being of Māori or Pacific ethnicity or living in a low socioeconomic neighbourhood independently increased the risk of having an RSV-associated hospitalisation. RSV hospitalisation rates obtained though active RSV surveillance are almost twice as high as rates obtained from hospital discharge code data. Our findings highlight the need for effective RSV vaccines and therapies.

4 RSV-associated hospitalisations among children and teenagers aged 5 to 17 years

During the 2012–2015 SHIVERS surveillance period, there were 1,366 ARI hospitalisations among children and teenagers aged 5–17 years. The median (interquartile range [IQR]) length of hospital stay for these patients was 2 (1–4) days. Prospective or clinical RSV testing was performed on 568 (41.6%) ARI hospitalisations, and included 41 (7.2%, 95% CI 5.3–9.6) RSV positive cases. The median (IQR) length of hospital stay for RSV positive patients was 2 (1–5) days. Of the 41 RSV positive hospitalisations, 5 (12.2%) were admitted to the ICU. Given the low number of RSV positive cases among this specific age group over the four-year study period, population-based incidence rates and healthcare associated costs were not estimated.

5 Respiratory virus-related emergency department visits and hospitalisations among infants

5.1 Preface

This chapter addresses objective two of this thesis: estimate the burden of RSV and other respiratory virus-related visits among infants seen only in hospital emergency departments and compare this to RSV and other respiratory virus-related hospital admissions. The research presented in this chapter has been published in the *Paediatrics Infectious Disease Journal*:

Prasad N, Trenholme AA, Huang QS, Duque J, Grant CC, Newbern EC. Respiratory virus-related emergency department visits and hospitalisations among infants in New Zealand. Paediatrics Infectious Disease Journal., 2020; 39(8).

I designed the study with guidance from my supervisors and co-authors. I carried out data management and analysis and drafted the initial manuscript. All co-authors reviewed and approved the final manuscript.

5.2 Introduction

Acute respiratory infections (ARIs) are a leading cause of morbidity and mortality in young children worldwide, particularly infants [173]. Studies to define country specific incidence rates and aetiologies of ARIs among young children are necessary to identify high risk groups and assess the impact of current and potential interventions. Previous research has identified influenza [174], respiratory syncytial virus (RSV) [22], rhinovirus (RV) [175], adenovirus (ADV) [176], and human metapneumovirus (hMPV) [177] as important aetiological agents for ARIs, but few

studies have examined the impact of illnesses caused by these viral infections on hospital emergency department (ED) visits, where many parents seek care for acutely ill infants [178].

In NZ, ARIs are the most common cause of acute overnight hospital admissions, with young children disproportionally affected [71]. Influenza vaccination is recommended for children older than six months in NZ but it is only free for those aged less than four years who have a history of significant respiratory illness [179]. Palivizumab, a licenced immunoprophylaxis for RSV, is not funded in NZ and is rarely used [102]. The aetiology of ARIs in NZ infants admitted to hospital has been described previously [76, 78]. However, to our knowledge there is no published data that describe ARIs in infants who are discharged home from the hospital ED.

In this study, we describe the epidemiology and viral aetiology of ARI events among infants discharged home from the hospital ED and those admitted to hospital. This study increases the evidence base used to inform ARI prevention and management among infants.

5.3 Methods

Note: Details provided in sections 5.3.1–5.3.4 have been previously mentioned in section 2.2.

5.3.1 Study setting

Data used for this study were collected as part of the Southern Hemisphere Influenza Vaccine Effectiveness and Research (SHIVERS) project [131, 132]. Our sample included infants less than one year of age who presented to the hospital ED with suspected ARI including those discharged home from the ED and those admitted to Kidz First Children's Hospital, South Auckland from 2014 to 2016. Suspected ARI cases were identified through a combination of reviewing admission diagnoses and interviewing patients about their presenting signs and symptoms.

In NZ, public hospital care is free. Kidz First Children's Hospital is part of the Middlemore public hospital and is the only secondary care paediatric hospital for the South Auckland population. All patients are triaged in the ED. While some children from South Auckland may present to Starship Children's Hospital (a tertiary care hospital, 17 km away) it is estimated that over 95% of children living in South Auckland present to Kidz First Children's Hospital. Middlemore Hospital is reported to have the highest patient volume across Australasia, with an annual ED volume of approximately 20,000–25,000 [180, 181].

The South Auckland region is predominantly urban with a population of approximately 8,500 infants less than one year of age, of whom 19% are Māori (NZ's indigenous population), 30% Pacific (including ethnic groups from Samoa, Cook Islands, Tonga, Niue, Fiji, Tokelau, Tuvalu, and Kiribati), 22% Asian, and 27% of European or other ethnicities [133]. The predominant circulating influenza strain was influenza A H1N1(pdm09) in 2014 and influenza A (H3N2) in 2015–2016 [160, 161, 182]. Ethical approval for the SHIVERS project was obtained from the NZ Health and Disability Ethics Committee (NTX/11/11/102).

5.3.2 Emergency Department surveillance

During the study period, a study nurse was present in the ED every day from 1 pm to 9 pm to identify infants with suspected ARI who were discharged home from the ED (i.e. not admitted to hospital). Study nurses obtained consent from caregivers and collected nasopharyngeal aspirates. In 2014, ED surveillance lasted for a 10-week period that coincided with the peak NZ influenza season (start of July to mid-September), and in 2015–2016, was extended to a broad 21-week winter period (week 18-39, end of April to end of September).

Data on ED visits from the 2014 winter weeks not under surveillance and those occurring between 9 pm and 1 pm were extracted from the hospital patient management system. These data included

date and time of visit, date of birth, sex, ethnicity, socioeconomic status, viral testing results, and presenting signs and symptoms. ED visits were classified as ARI-associated if infants presented with at least one of the following signs or symptoms: apnoea, cyanosis, shortness of breath, cough, wheeze, increased work of breathing, stridor, or fever. Cases with fever and gastrointestinal symptoms without any other ARI-associated symptoms were excluded.

5.3.3 Hospital surveillance

During the 21-week winter season period in 2014–2016, research nurses identified acute overnight hospital admissions of infants with suspected ARI. All infants with ARI who met the WHO severe acute respiratory infection (SARI) case definition [134], defined as cough and measured or reported fever within the last 10 days were approached for enrolment. To provide an understanding of the respiratory virus hospitalisation burden among ARI patients not meeting the SARI definition, study nurses also enrolled a sample of non-SARI respiratory patients, i.e. those with cough and/or measured or reported fever but not both within 10 days. Each week, six paediatric inpatients fitting the non-SARI respiratory definition were randomly sampled. Similar to ED surveillance, study nurses obtained consent and collected nasopharyngeal aspirates.

5.3.4 Laboratory methods

Specimens collected from consented patients were tested for RSV, RV, ADV, influenza, and hMPV using the CDC real-time RT-PCR protocol at the Institute of Environmental Science and Research [135, 136]. In addition to respiratory virus test results generated by SHIVERS surveillance, hospital laboratories also provided results from clinically ordered tests requested on infants presenting with ARIs during the study period. These specimens were tested using the real time RT-PCR assay at hospital laboratories [137]. Appendix 1.1 shows the performance of the hospital (Counties Manukau) assays compared with CDC's real-time RT-PCR as a gold standard.

Only results from assays with a sensitivity greater than 80% and a specificity greater than 95% were included in the SHIVERS study dataset. Moreover, in 2016, some specimens were only tested for influenza, resulting in differences in the total number of samples tested for each virus (Tables 5.1–5.2).

5.3.5 Statistical analysis

Chi-square tests were used to test for associations between categorical variables. We calculated seasonal incidence rates by calculating the number of virological-confirmed ED visits and hospitalisations divided by the number of infants residing in the South Auckland region. Incidence rates (IRs) were stratified by age group, ethnicity, and socioeconomic status (SES) as these are considered key modifiers of ARI ED/hospital presentations [71]. SES was quantified using a small area-measure of neighbourhood deprivation derived from the 2013 national census (NZDep2013), and was used to separate the cohort into SES quintiles (1=least deprived to 5=most deprived) [145]. Māori and Pacific peoples are overrepresented in the lower SES groups in NZ [155]. Therefore, to control for confounding and evaluate the independence of ethnicity and SES effects, ED visit and hospitalisation rates for each virus were adjusted for these factors.

IRs were corrected for non-testing of each virus by multiplying the proportion of tested patients who were positive for that virus by the number of non-tested ARI patients within each setting by strata defined by study year, age group, SES quintile, and ethnicity. Incidence rate ratios (IRRs) compared age, SES and ethnicity specific rates for each virus. Confidence intervals for IRs and incidence rate ratios (IRRs) were based on the Poisson distribution. All analyses were performed using Stata 14 (College Station, TX: StataCorp LP).

5.4 Results

During the 2014–2016 winter seasons, 3,585 of the 5,412 (66.2%) ARI ED visits among infants were discharged home from the ED with the other 1,827 (33.8%) visits resulting in admission to hospital. Testing and viral positivity rates stratified by key demographic characteristics are presented for ED visits discharged home in Table 5.1 and hospitalisations in Table 5.2.

Of the 1,827 ARI visits admitted to hospital, 835 (45.7%) were SARI and 992 (54.3%) were non-SARI respiratory cases. We obtained at least one viral test result from 746 (89.3%) SARI cases and 834 (84.0%) non-SARI respiratory cases.

Table 5.3 compares key demographics of tested and non-tested infants included in the ED only and hospital admission groups. Children less than three months of age were less likely to be tested in both the ED (p-value = 0.042) and when admitted to hospital (p-value = <0.001) than older infants. Among those admitted to hospital, children in the least deprived quintile (p-value = <0.001) were more likely to be tested while those of Asian ethnicity were less likely to be tested (p-value=0.023).

Table 5.1 ARI-associated emergency department only visits of infants tested for respiratory viruses and the proportion positive for each virus during the 2014–2016 winter seasons

	Influenza			RSV*			RV*			ADV*			hMPV*		
	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested
Total	1150	94	(8.2)	1171	290	(24.8)	1137	202	(17.8)	1169	79	(6.8)	1170	87	(7.4)
Year															
2014	241	37	(15.4)	251	85	(33.9)	237	48	(20.3)	251	21	(8.4)	251	26	(10.4)
2015	503	44	(8.7)	512	109	(21.3)	493	69	(14.0)	512	35	(6.8)	512	34	(6.6)
2016	406	13	(3.2)	408	96	(23.5)	407	85	(20.9)	406	23	(5.7)	407	27	(6.6)
Age group in months															
0–2	227	5	(2.2)	230	51	(22.2)	215	35	(16.3)	230	3	(1.3)	230	7	(3.0)
3–5	297	25	(8.4)	303	83	(27.4)	291	50	(17.2)	303	21	(6.9)	303	25	(8.3)
6–11	626	64	(10.2)	638	156	(24.5)	631	117	(18.5)	636	55	(8.6)	637	55	(8.6)
SES‡															
(least deprived) 1	53	2	(3.8)	54	16	(29.6)	53	7	(13.2)	54	6	(11.1)	54	2	(3.7)
2	76	5	(6.6)	80	17	(21.3)	76	10	(13.2)	80	2	(2.5)	80	1	(1.3)
3	64	3	(4.7)	65	15	(23.1)	65	4	(6.2)	65	4	(6.2)	65	2	(3.1)
4	138	7	(5.1)	139	37	(26.6)	134	23	(17.2)	138	14	(10.1)	138	9	(6.5)
(most deprived) 5	819	77	(9.4)	833	205	(24.6)	809	158	(19.5)	832	53	(6.4)	833	73	(8.8)
Ethnicity															
Māori	299	24	(8.0)	309	78	(25.2)	297	68	(22.9)	308	27	(8.8)	308	21	(6.8)
Pacific	550	56	(10.2)	555	137	(24.7)	542	104	(19.2)	554	36	(6.5)	555	52	(9.4)
Asian	156	10	(6.4)	159	32	(20.1)	154	11	(7.1)	159	8	(5.0)	159	11	(6.9)
European/Other	145	4	(2.8)	148	43	(29.1)	144	19	(13.2)	148	8	(5.4)	148	3	(2.0)

* RSV; respiratory syncytial virus, RV; rhinovirus, ADV; adenovirus, hMPV; human metapneumovirus.

† Only results from hospital assays with a sensitivity greater than 80% and a specificity greater than 95% were included in the SHIVERS study dataset (Appendix 1.1). Moreover, in 2016, some specimens were only tested for influenza, resulting in differences in the total number tested for each virus.

‡ SES was quantified using a small area-measure of neighbourhood deprivation derived from the 2013 national census (NZDep2013) and was used to separate the cohort into SES quintiles (1=least deprived to 5=most deprived).

Table 5.2 ARI-associated hospital admissions of infants tested for respiratory viruses and the proportion positive for each virus during the 2014–2016 winter seasons

	Influenza			RSV*			RV*			ADV*			hMPV*		
	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested	Tested†	Positive	(%) of tested
Total	1523	110	(7.2)	1322	492	(37.2)	927	211	(22.8)	1325	151	(11.4)	1321	87	(6.6)
Year															
2014	612	52	(8.5)	588	242	(41.2)	423	122	(28.8)	591	63	(10.7)	588	49	(8.3)
2015	556	45	(8.1)	546	189	(34.6)	316	43	(13.6)	546	70	(12.8)	545	30	(5.5)
2016	355	13	(3.7)	188	61	(32.4)	188	46	(24.5)	188	18	(9.6)	188	8	(4.3)
Age group (months)															
0–2	623	29	(4.7)	487	184	(37.8)	276	56	(20.3)	489	21	(4.3)	487	19	(3.9)
3–5	413	22	(5.3)	371	148	(39.9)	272	69	(25.4)	372	42	(11.3)	371	28	(7.5)
6–11	487	59	(12.1)	464	160	(34.5)	379	86	(22.7)	464	88	(19.0)	463	40	(8.6)
SES															
(least deprived) ‡ 1	49	1	(2.0)	32	12	(37.5)	25	2	(8.0)	32	1	(3.1)	32	2	(6.3)
2	70	5	(7.1)	61	28	(45.9)	46	5	(10.9)	61	8	(13.1)	61	4	(6.6)
3	91	3	(3.3)	80	30	(37.5)	61	14	(23.0)	80	11	(13.8)	80	4	(5.0)
4	163	8	(4.9)	147	59	(40.1)	103	31	(30.1)	148	18	(12.2)	147	4	(2.7)
(most deprived) 5	1150	93	(8.1)	1002	363	(36.2)	692	159	(23.0)	1004	113	(11.3)	1001	73	(7.3)
Ethnicity															
Māori	523	39	(7.5)	463	171	(36.9)	314	78	(24.8)	463	51	(11.0)	462	24	(5.2)
Pacific	763	63	(8.3)	661	243	(36.8)	472	114	(24.2)	664	81	(12.2)	661	52	(7.9)
Asian	101	3	(3.0)	85	25	(29.4)	58	10	(17.2)	85	11	(12.9)	85	4	(4.7)
European/Other	136	5	(3.7)	113	53	(46.9)	83	9	(10.8)	113	8	(7.1)	113	7	(6.2)

* RSV; respiratory syncytial virus, RV; rhinovirus, ADV; adenovirus, hMPV; human metapneumovirus.

† Only results from hospital assays with a sensitivity greater than 80% and a specificity greater than 95% were included in the SHIVERS study dataset (Appendix 1.1). Moreover, in 2016, some specimens were only tested for influenza, resulting in differences in the total number tested for each virus.

‡ SES was quantified using a small area-measure of neighbourhood deprivation derived from the 2013 national census (NZDep2013) and was used to separate the cohort into SES quintiles (1=least deprived to 5=most deprived).

Table 5.3 Demographic characteristics of acute respiratory infection (ARI) associated Emergency Department (ED) visits and hospital admissions by surveillance period and respiratory viral testing, 2014–2016 winter seasons

	ARI ED visits									ARI hospital admissions						
	Outside surveillance period*		During surveillance period*													
	Total	(column %)	Total	(column %)	Tested for all viruses	(column %)	Not tested	(column %)	P-value†	Total	(column %)	Tested	(column %)	Not tested	(column %)	P-value†
Total	2206	(100.0)	1379	(100.0)	1111	(100.0)	268	(100.0)		1827	(100.0)	870	(100.0)	957	(100.0)	
Age group (months)																
0–2	386	(17.5)	278	(20.2)	212	(19.1)	66	(24.6)	0.042	706	(38.6)	264	(30.3)	442	(46.2)	<0.001
3–5	597	(27.1)	351	(25.5)	283	(25.5)	68	(25.4)	0.973	501	(27.4)	253	(29.1)	248	(25.9)	0.130
6–11	1223	(55.4)	750	(54.4)	616	(55.4)	134	(50.0)	0.108	620	(33.9)	353	(40.6)	267	(27.9)	<0.001
SES																
(least deprived) 1	57	(2.6)	63	(4.6)	52	(4.7)	11	(4.1)	0.685	71	(3.9)	19	(2.2)	52	(5.4)	<0.001
2	94	(4.3)	89	(6.5)	72	(6.5)	17	(6.3)	0.935	79	(4.3)	45	(5.2)	34	(3.6)	0.089
3	92	(4.2)	78	(5.7)	64	(5.8)	14	(5.2)	0.733	111	(6.1)	56	(6.4)	55	(5.7)	0.537
4	255	(11.6)	173	(12.5)	132	(11.9)	41	(15.3)	0.130	188	(10.3)	97	(11.1)	91	(9.5)	0.249
(mots deprived) 5	1708	(77.4)	976	(70.8)	791	(71.2)	185	(69.0)	0.484	1378	(75.4)	653	(75.1)	725	(75.8)	0.729
Ethnicity																
Māori	581	(26.3)	357	(25.9)	286	(25.7)	71	(26.5)	0.801	625	(34.2)	296	(34.0)	329	(34.4)	0.873
Pacific	1084	(49.1)	655	(47.5)	533	(48.0)	122	(45.5)	0.471	900	(49.3)	444	(51.0)	456	(47.6)	0.148
Asian	195	(8.8)	192	(13.9)	151	(13.6)	41	(15.3)	0.469	136	(7.4)	52	(6.0)	84	(8.8)	0.023
European/Other	346	(15.7)	175	(12.7)	141	(12.7)	34	(12.7)	0.998	166	(9.1)	78	(9.0)	88	(9.2)	0.864

* ED surveillance period was for a 10-week period that coincided with the peak influenza season in New Zealand (start of July to mid-September) a study nurse was present in the ED from 1 pm to 9 pm, seven days a week in 2014. In 2015 and 2016, this ED surveillance was extended to a 21-week winter season period (end of April to end of September). Data on ED visits occurring outside surveillance time periods were extracted from the hospital patient management system.

†Chi-square tests were used to test for associations between categorical variables

‡ SES was quantified using a small area-measure of neighbourhood deprivation derived from the 2013 national census (NZDep2013) and was used to separate the cohort into SES quintiles (1=least deprived to 5=most deprived).

5.4.1 Viral aetiology

During the study period, 601 (54.1%) of the 1,111 ED-only visits that were tested for all respiratory viruses were positive for at least one respiratory virus. Of the 870 hospital admissions with testing for all viruses, 639 (73.4%) were positive for at least one respiratory virus. The most common virus detected among the ED-only visits was RSV, with 24.8% (290/1,171) positivity (Table 5.1). Similar to the ED-only sample, the most common virus among hospitalisations was RSV comprising 37.2% (492/1,322) of tested events (Table 5.2).

Among events tested for all viruses, 100 (9.0%) of the ED-only visits and 140 (16.1%) of the hospital admissions were positive for more than one virus. Viral co-detections were significantly more common among hospital admissions than ED-only visits (p-value <0.001). The most common co-detection in both settings was RV with RSV (ED: n=34, 34.0%; hospital: n=37, 26.4%). ADV with RSV (n= 36, 25.7%) was the second most common co-detection in the hospital.

5.4.2 Seasonal incidence

The seasonal ARI-associated ED-only visit rate (142.5 visits per 1,000 infants) was twice (1.96 95% CI 1.86–2.08) as high as the ARI-associated hospitalisation rate (72.6 admissions per 1,000 infants). Respiratory virus-specific ED-only visit rates per 1,000 infants, once corrected for non-testing, were 34.4 for RSV, 24.2 for RV, 11.9 for influenza, 9.9 for hMPV and 9.1 for ADV (Table 5.4). In comparison, respiratory virus-specific hospital-admission rates per 1,000 infants were 24.6 for RSV, 13.9 for RV, 4.6 for influenza, 3.9 for hMPV and 6.8 for ADV (Table 5.4).

Seasonal incidence rates varied by year, with 2016 having lower respiratory viral associated events for influenza, ADV, and hMPV (p-value <0.001). When comparing by age group within each setting, we found infants aged 0–2 months had significantly lower ED-only visit rates (i.e.

were more likely to be admitted to hospital than be seen in the ED only) for all respiratory viruses compared to those aged 6–11 months (p-value <0.001, Table 5.4, Figure 5.1). The largest differences in ED visit rates by respiratory virus when comparing infants aged 0–2 months to those aged 6–11 months were for ADV (Rate Ratio [RR] 0.2, 95% CI 0.1–0.3), influenza (RR 0.2, 95% CI 0.1–0.3), and hMPV (RR 0.2, 95% CI 0.1–0.4).

For hospital admissions, infants aged 0–2 months had significantly higher admission rates compared to those aged 6–11 months when RSV (RR 2.5, 95% CI 2.1–3.1) or RV (RR 1.9, 95% CI 1.5–2.5) were detected. When ADV was detected, the infants aged 0–2 months had significantly lower hospital admission rates than those aged 6–11 months (RR 0.5, 95% CI 0.3–0.8). No significant difference in hospitalisation rates by age group were seen for influenza and hMPV.

Following adjustment for ethnicity, we found infants from the most deprived SES areas to have significantly higher ARI ED-only rates compared to those from the least deprived areas for influenza (RR 4.1, 95% CI 1.3–13.2), RSV (RR 3.0, 95% CI 1.9–4.7), RV (RR 1.9, 95% CI 1.1–3.3), and hMPV (RR 5.0, 95% CI 1.2–20.7). For hospitalisations, while rates for all viruses appeared to increase by deprivation, these increases were not significant (p-value>0.05). When comparing ethnicity specific rates adjusted for SES, Māori and Pacific children had significantly higher ARI ED-only visit and hospital-admission rates compared with children of European or other ethnic groups for all respiratory viruses (p-value <0.001).

Table 5.4 Seasonal, corrected ARI-associated Emergency Department (ED)-only and hospital admission rates for respiratory viruses per 1,000 infants, 2014–2016 winter seasons

		Influenza		RSV*		RV*		ADV*		hMPV*	
		ED	Hospital	ED	Hospital	ED	Hospital	ED	Hospital	ED	Hospital
	Total no. of children	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)	IR† (95% CI)
Total	25674	11.9 (10.6,13.3)	4.6 (3.8,5.5)	34.4 (32.1,36.7)	24.6 (22.7,26.6)	24.2 (22.3,26.2)	13.9 (12.5,15.4)	9.1 (7.9,10.2)	6.8 (5.8,7.9)	9.9 (8.7,11.2)	3.9 (3.1,4.7)
Year											
2014	8344	20.7 (17.5, 23.8)	6.9 (5.1, 8.7)	41.5 (37.0, 45.9)	33.2 (29.3, 37.2)	22.6 (19.4, 25.9)	22.6 (19.4, 25.9)	9.7 (7.6, 11.9)	8.4 (6.4, 10.4)	12.4 (10.0, 14.9)	6.5 (4.8, 8.3)
2015	8665	11.4 (9.1, 13.6)	5.3 (3.8, 6.9)	31.2 (27.5, 35.0)	25.1 (21.7, 28.4)	21.4 (18.3, 24.5)	8.4 (6.4, 10.3)	9.8 (7.7, 11.8)	8.6 (6.6, 10.6)	8.7 (6.7, 10.7)	3.7 (2.4, 5.0)
2016	8665	4.0 (2.7, 5.4)	1.8 (0.9, 2.7)	30.7 (27.0, 34.5)	15.9 (13.2, 18.6)	28.7 (25.1, 32.3)	11.2 (8.9, 13.4)	7.7 (5.8, 9.6)	3.6 (2.3, 4.8)	8.8 (6.8, 10.8)	1.5 (0.7, 2.4)
Age group (months)											
0–2	6253	2.8 (1.4, 4.1)	4.7 (3.0, 6.4)	21.3 (17.6, 24.9)	39.0 (34.1, 43.9)	17.9 (14.5, 21.2)	18.7 (15.3, 22.1)	1.9 (0.8, 3.1)	3.9 (2.3, 5.5)	2.8 (1.4, 4.1)	3.6 (2.1, 5.1)
3–5	6618	12.0 (9.3, 14.8)	3.5 (2.1, 5.0)	39.6 (34.7, 44.6)	29.5 (25.2, 33.8)	25.8 (21.8, 29.8)	17.6 (14.3, 20.9)	8.3 (6.1, 10.6)	7.4 (5.2, 9.5)	11.7 (9.0, 14.4)	4.8 (3.1, 6.5)
6–11	12803	16.3 (14.1, 18.5)	5.2 (3.9, 6.4)	38.1 (34.7, 41.5)	15.3 (13.2, 17.5)	26.5 (23.7, 29.4)	9.8 (8.1, 11.5)	12.8 (10.9, 14.8)	8.0 (6.4, 9.5)	12.5 (10.6, 14.5)	3.6 (2.6, 4.6)
Ethnicity§											
Māori	4894	9.7 (7.0, 12.4)	6.2 (3.4, 9.0)	31.3 (26.3, 36.3)	40.9 (33.4, 48.3)	28.8 (23.4, 34.2)	22.0 (16.7, 27.2)	15.9 (11.3, 20.6)	10.7 (7.0, 14.4)	5.9 (4.0, 7.8)	4.0 (1.8, 6.1)
PI	7802	11.4 (8.6, 14.3)	6.1 (3.5, 8.8)	34.9 (30.1, 39.8)	33.3 (27.2, 39.4)	27.0 (22.3, 31.8)	17.6 (13.4, 21.9)	13.0 (9.2, 16.8)	10.7 (7.1, 14.3)	9.9 (7.4, 12.4)	5.6 (2.9, 8.3)
Asian	5896	3.9 (2.4, 5.4)	0.5 (-0.1, 1.0)	13.3 (10.5, 16.2)	5.5 (3.6, 7.4)	3.3 (1.9, 4.7)	2.2 (1.0, 3.5)	2.9 (1.4, 4.3)	2.1 (0.9, 3.3)	3.3 (1.9, 4.7)	0.7 (0.0, 1.3)
European/ Other	7082	1.1 (0.3, 1.8)	0.7 (0.1, 1.3)	18.4 (15.1, 21.6)	9.0 (6.8, 11.3)	8.7 (6.5, 10.9)	1.8 (0.8, 2.8)	3.8 (2.3, 5.4)	1.3 (0.5, 2.2)	0.7 (0.1, 1.3)	0.9 (0.2, 1.6)
SES‡§											
1	2293	3.4 (-0.5, 7.4)	1.6 (-1.6, 4.9)	13.4 (7.5, 19.3)	18.0 (9.0, 27.0)	14.4 (6.7, 22.0)	4.9 (-0.8, 10.7)	10.7 (3.9, 17.6)	1.3 (-1.3, 4.0)	2.3 (-0.9, 5.5)	2.4 (-1.1, 5.8)
2	3305	4.4 (1.1, 7.7)	4.2 (0.4, 8.0)	14.8 (9.7, 19.8)	20.3 (12.9, 27.6)	10.8 (5.7, 16.0)	4.1 (0.5, 7.8)	2.4 (0.0, 4.7)	6.4 (2.0, 10.8)	0.6 (-0.6, 1.8)	2.7 (-0.1, 5.5)
3	2499	2.9 (0.0, 5.8)	2.4 (-0.3, 5.1)	13.6 (8.4, 18.9)	20.3 (13.0, 27.6)	6.8 (2.7, 10.9)	13.6 (7.0, 20.2)	6.3 (2.3, 10.3)	8.3 (3.3, 13.3)	1.5 (-0.6, 3.6)	2.9 (-0.0, 5.7)
4	3439	6.0 (3.2, 8.7)	2.9 (0.9, 4.9)	35.3 (28.7, 42.0)	23.0 (17.4, 28.6)	22.2 (16.8, 27.7)	13.6 (9.3, 18.0)	14.8 (10.3, 19.2)	6.6 (3.6, 9.6)	7.2 (4.2, 10.2)	1.4 (0.0, 2.7)
5	14138	14.1 (12.2, 15.9)	5.0 (3.9, 6.0)	40.0 (36.6, 43.4)	25.7 (23.2, 28.2)	27.0 (24.5, 29.6)	14.8 (13.0, 16.6)	8.8 (7.4, 10.3)	6.8 (5.6, 8.0)	11.3 (9.7, 13.0)	4.2 (3.2, 5.1)

* RSV; respiratory syncytial virus, RV; rhinovirus, ADV; adenovirus, hMPV; human metapneumovirus.

† IR; Incidence rate per 1,000 infants residing in study area (South Auckland)

‡ SES was quantified using a small area-measure of neighbourhood deprivation derived from the 2013 national census (NZDep2013) and was used to separate the cohort into SES quintiles (1=least deprived to 5=most deprived).

§ SES and ethnicity specific rates have been adjusted for each other.

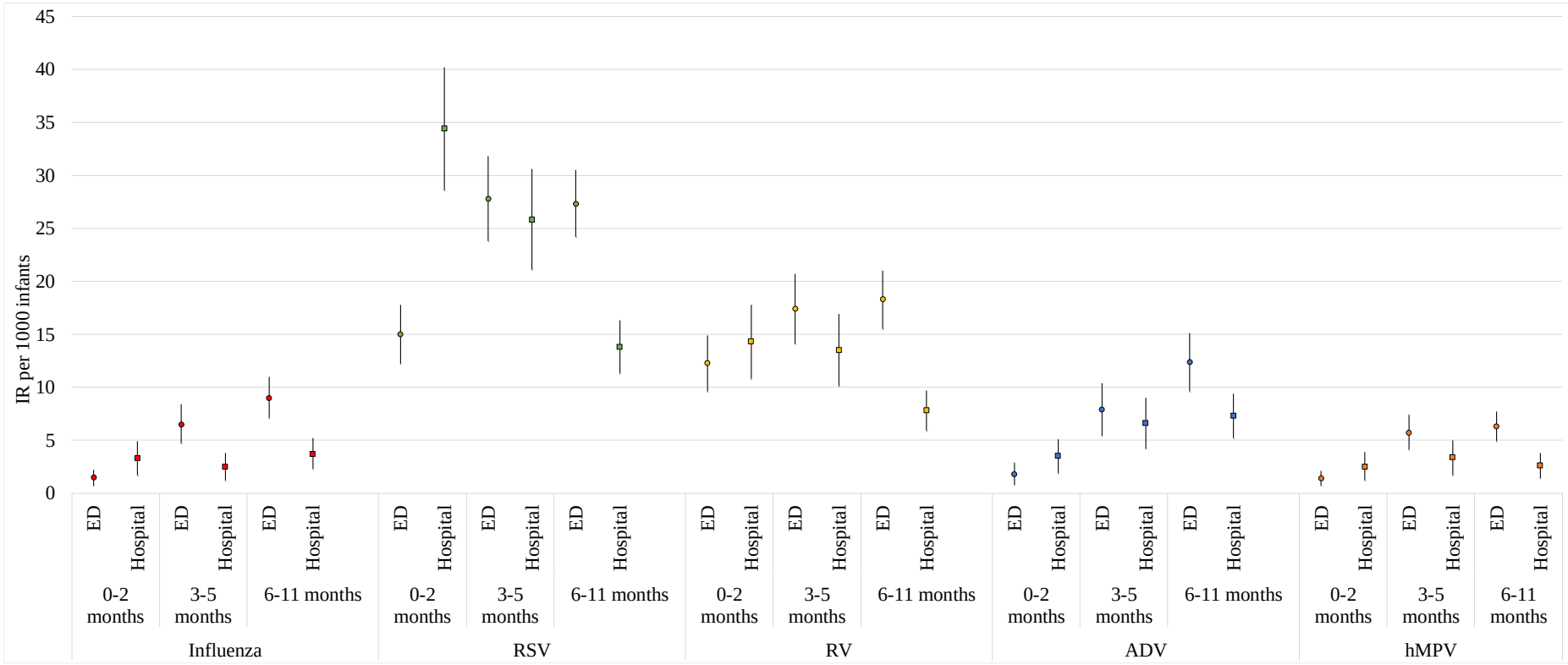


Figure 5.1 Seasonal, corrected ARI-associated emergency department (ED)-only and hospital admission rates for respiratory viruses by age group among infants, 2014-2016 winter seasons

IR indicates incidence rate per 1,000 infants residing in study area (South Auckland); ARI, acute respiratory infection; RSV, respiratory syncytial virus; RV, rhinovirus; ADV, adenovirus; hMPV, human metapneumovirus

5.5 Discussion

While the hospital disease burden due to respiratory viruses has been reported frequently, few studies have examined the contribution of respiratory virus infections to ED visits. In our study, based on active surveillance of acute respiratory clinical presentations during winter, the number of ARI associated ED-only visits in infants was almost twice that of hospital admissions. Additionally, we showed that respiratory viruses were detected in approximately 55% of ARI-associated ED-only visits and 73% of ARI-associated hospital admissions.

We observed changes in respiratory viral ED-only and hospitalisation rates by year. This is likely to reflect seasonal variation, as these trends were also evident in other age groups [160, 161, 182]. Moreover, to our knowledge no major vaccination policy changes were made during the study period that could have impacted our findings.

We found ED-only visit rates to increase with age for all viruses. This is not unexpected as younger infants are more likely to be hospitalised. We did, however, find distinct age effects for different viruses. For example, the age-related increases in ED visit rates were largely driven by ADV, influenza, and hMPV. Moreover, RSV hospital admission rates were highest in infants aged 0–2 months, while for ADV hospital admission rates were highest for infants 6–11 months of age. Such findings are consistent with other studies, which have found RSV to cause more severe disease in the first months of life; whereas, for ADV, severe disease is more frequently seen in slightly older children [183, 184]. Additionally, our findings on influenza and hMPV suggest that, among infants greater than six months of age, ARIs caused by these viruses, while not necessarily severe enough to warrant hospital admission, may cause a considerable burden of disease in terms of ED utilization.

Currently, influenza virus is the only respiratory virus studied that is vaccine preventable [185]. While there is a prophylactic agent available for RSV, the cost greatly limits use [100]. Several vaccines and immunoprophylaxis candidates for RSV and hMPV are in clinical development [104, 186]. Comprehensive disease burden estimates in various clinical settings for specific respiratory viruses are necessary to evaluate the potential effectiveness and inform implementation of potential intervention strategies.

We found that in comparison with infants of other ethnic groups, those of Māori or Pacific ethnicities had significantly higher ED-only visit and hospital admission rates for ARIs when a respiratory virus was detected, even after adjustment for SES. A larger proportion of Māori and Pacific children experience barriers to accessing primary healthcare compared with children of Asian and European/Other ethnicities [187] and consequently may preferentially access ED services. If this were the main driver for ED presentations, we would expect Māori and Pacific children seen in the ED to have less severe disease and hence lower rates of hospital admission. However, we found Māori and Pacific children to also have increased rates of hospital admission, suggesting true differences in disease burden and severity.

Disparities in respiratory infectious disease burden and severity by ethnicity have been previously reported in NZ [71, 76, 165]. Moreover, Aboriginal children in Australia [68] and native American and African American children in North America [69, 70] are also reported to have higher respiratory infection associated morbidity and mortality. Ethnic differences in respiratory infectious diseases are thought primarily to be due to social and economic factors, as ethnic groups with increased risk of infection and disease are also overrepresented in lower socioeconomic groups. However, when we adjusted and stratified rates by ethnicity and SES in our study, we found ethnicity to have a stronger effect than SES on respiratory virus associated ED visit and hospitalisation risk (Table 5.4). A likely explanation is that our measure of SES,

which is an area-level value of neighbourhood deprivation, may not accurately represent individual and household SES. Consequently, social and economic factors associated with increased respiratory infection risk and severity such as poor housing, over-crowding, maternal smoking, and poor nutrition are potentially being better captured by ethnicity.

Additionally, the consistently higher ED visit and hospitalisation rates among Māori and Pacific children for all respiratory viruses suggests that the increased risk of ARI in these children is more likely to be due to factors related to the child and their environment than with a particular respiratory virus. Nonetheless, the introduction of the pneumococcal conjugate vaccine has been associated with a reduction in social and ethnic disparities in infectious disease burden in NZ [171] and Australia [188], suggesting a respiratory pathogen vaccine, particularly for a common infection such as RSV, may help decrease health inequalities.

Our study has several limitations. Firstly, ED surveillance was not for full days and was carried out for a shorter period in 2014; consequently, we had to rely on patient management data to identify ARI ED presentations outside these surveillance periods. Secondly, surveillance was only carried out during the winter seasons. For most of the viruses studied, this period would capture the majority of cases [76, 189]; however, ADV and RV circulate year-round in NZ [76]. Thus, the true impact of these two viruses on ED visit and hospitalisation burden is likely to be underestimated. A final limitation was that the study only included one geographical location and was only undertaken among infants. This allowed description of the substantial ARI ED-only disease burden in this population but does limit the generalizability of study findings. Given the potential that now exists for new respiratory virus infection prevention and treatment interventions, it would be beneficial to assess the differences in ED and inpatient disease burdens in various geographical areas and wider age groups.

5.6 Conclusions

Respiratory viruses cause considerable healthcare burden in terms of ED visits and hospital admissions among infants. Respiratory virus infection associated ED visits rates, including those for the vaccine preventable disease influenza, were almost twice as high as hospitalisation rates. RSV was the most common virus identified among infants in both healthcare settings.

Respiratory virus infections resulting in ED visits should be included in measurements of ARI disease burden to more accurately measure the impact of vaccines, immunoprophylaxis therapies, and other preventative measures. Vaccine and immunoprophylaxis candidates, particularly for a common virus such as RSV, in conjunction with interventions that address health equity more broadly are required to reduce the high and unequal childhood respiratory viral disease burden in NZ.

6 The health and economic burden of RSV-associated hospitalisations in adults

6.1 Preface

This chapter addresses Objective three of this thesis: to estimate the health and economic burden of RSV-associated hospitalisations among adults aged 18 years or more. The research presented in this chapter has been published in *PLoS One.*

Prasad N, Newbern EC, Trenholme AA, Thompson MG, McArthur CM, Wong CA, Jelley L, Aminisani N, Huang QS, Grant CC. The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. PLoS One 2020; 15(6): e0234235.
https://doi.org/10.1371/journal.pone.0234235

I designed the study with guidance from my supervisors and co-authors. I carried out data management and analysis and drafted the initial manuscript. All co-authors reviewed and approved the final manuscript.

6.2 Introduction

Respiratory syncytial virus (RSV) is well established as a major cause of acute respiratory infections (ARI) in children, but the burden of disease in adults has been less completely studied. Recent studies have reported RSV as a considerable cause of morbidity and mortality in adults [5] sometimes equalling or exceeding rates caused by seasonal influenza [81, 190, 191].

While previous studies have been informative, uncertainties about RSV disease burden among adults remain. Most estimates of RSV-associated hospitalisation rates are from studies conducted in the USA and appear to vary by location and calendar year. The methods used to estimate RSV

disease burden have also varied, with a few studies using active surveillance [81, 190-193], while others have been based on statistical models correlating clinical data with viral activity captured through passive surveillance [83, 194, 195]. Moreover, laboratory methods used to confirm RSV have changed over time, with molecular methods having higher sensitivity than previously used serologic and virus isolation techniques [53]. Finally, few studies among adults' report RSV hospitalisation rates by fine age strata or other demographic characteristics [5].

No licensed RSV vaccine is currently available; however, several adult RSV vaccines candidates are in development [104, 196]. More comprehensive estimates of RSV disease burden in adults will help inform the introduction of such interventions.

In this study, we utilised ARI surveillance data to estimate the incidence of RSV-associated hospitalisations and direct healthcare associated costs among adults aged 18 years and older in Auckland, NZ. We present RSV-associated hospitalisation rates estimated by two complementary methods. Our findings provide evidence to inform RSV treatment and preventative strategies in adult populations.

6.3 Methods

In this study, we retrospectively established a cohort of adult residents aged 18 years or more and identified RSV positive ARI hospitalisations within this cohort using data from the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) project. SHIVERS was an active ARI surveillance project conducted in two public hospitals which provide all inpatient services for the population residing in the central, eastern and southern regions of Auckland [131, 132]. The study area is predominantly urban with an estimated 734,530 adults aged 18 years or more in 2015, of whom 9% are Māori (NZ's indigenous population), 16% Pacific (including ethnic groups from Samoa, Cook Islands, Tonga, Niue, Fiji, Tokelau, Tuvalu,

and Kiribati), 23% Asian, and 52% of European or other ethnicities [133]. Ethical approval for the SHIVERS project was obtained from the NZ Ministry of Health, Health and Disability Ethics Committee (NTX/11/11/102).

Note: Details provided in section 6.3.1–6.3.2 have been previously provided in section 2.2.

6.3.1 Hospital surveillance

From 30th April 2012 to 31st December 2015, research nurses evaluated adults admitted to inpatient wards for suspected ARI. Suspected ARI cases were identified through a combination of reviewing admission diagnoses and interviewing patients about their presenting signs and symptoms [131]. Among suspected ARI patients, those meeting the WHO severe acute respiratory infection (SARI) case definition of cough and measured or reported fever within the last 7 days in 2012, and within 10 days from 2013 onwards, were enrolled. Study nurses obtained consent from eligible patients; completed detailed case report forms on a range of factors including comorbidities, influenza vaccination, antibiotic treatment and clinical outcomes; and collected nasopharyngeal swabs.

To provide an understanding of the respiratory virus hospitalisation burden among ARI patients not meeting the SARI definition, in 2013–2015 study nurses enrolled a sample of non-SARI respiratory patients. Sampling in 2013 was during the peak winter period (12th August to 6th October) and included weekly random selection of two adult inpatients who fitted the non-SARI respiratory definition at all participating facilities. In 2014 and 2015, this surveillance was extended to randomly enrol approximately six adult non-SARI respiratory patients weekly in both hospitals from week 18 to 39 (end of April – end of September).

In addition to respiratory virus test results generated by SHIVERS surveillance, hospital laboratories also provided results from clinically ordered tests performed on SARI and non-SARI

respiratory patients during the study period. These results were included after validation of the hospital respiratory virus PCR assay. This clinician identified sample was especially valuable in expanding the number of laboratory tested non-SARI patients including in the analysis, since fewer non-SARI patients were systematically enrolled in the SHIVERS study.

6.3.2 Laboratory methods

Collected specimens were tested for RSV, influenza, rhinovirus, adenovirus, and human metapneumovirus using the United States Centers for Disease Control and Prevention real-time reverse transcription (RT)-PCR protocol [135, 136] at the Institute of Environmental Science and Research, or using the AusDiagnostic PCR protocol and real-time PCR assays at hospital laboratories [137]. A sample of positive specimens were further sub-typed. Further information on performance of hospital assays compared to CDC's real-time RT-PCR as a gold standard are provided in Appendix 1.1.

6.3.3 Incidence rate denominator sources

We used national administrative datasets including hospital discharges from the National Minimum Dataset, primary healthcare enrolments from Primary Health Organisation Enrolment Collection, births from the National Maternity Collection, deaths from the National Mortality Collection, and other public hospital non-admitted events from the National Non-Admitted Patient Collection [153] to identify and obtain individual level demographic data on adults aged 18 years or more residing in the SHIVERS study area during surveillance periods. These datasets use a unique patient identifier (National Health Index (NHI) numbers) enabling linkage. This population data was linked to SHIVERS data using NHI numbers to identify those with ARI and RSV-confirmed hospitalisations.

6.3.4 Cost estimation

Each inpatient event in the National Minimum Dataset is allocated a Diagnosis Related Group (DRG) code [146]. The DRG coding system categorises hospitalisations into clinically similar events with comparable resource use. These codes, together with information on hospital length of stay and additional interventions such as mechanical ventilation, are used to calculate a cost weight and therefore a cost for each inpatient hospital admission. DRGs are the principal means of reimbursing hospitals for inpatient care in most high-income countries including NZ [197]. We calculated hospitalisation costs by multiplying each cost weight provided in the NMDS with the NZ fixed cost multiplier applicable for the 2017/18 financial year [146].

6.3.5 Statistical analysis

Full-year surveillance data showed that RSV follows a well-defined seasonal pattern with 89.5% of RSV positive hospitalisations detected during the broad winter surveillance period (Figure 6.1). As SHIVERS non-SARI respiratory testing was only conducted during winter seasons, we restricted our analyses to weeks 18–39 of 2012–2015.

Chi-square tests were used to test associations between categorical variables and Student's t-tests for continuous variables. Among hospitalised cases, logistic regression with adjustment for age and ethnicity was used to test for association of comorbidities, influenza vaccination, and antibiotic treatments with RSV positivity.

For incidence calculations, if an RSV positive patient was transferred to another hospital and/or had multiple RSV positive hospitalisations within 14 days of discharge from their first hospitalisation, they were considered a singular illness episode. Incidence rates were calculated by dividing the number of RSV-associated ARI hospitalisations (singular episodes) by the number of adults residing in the study area. Confidence intervals for incidence rates and rate ratios were

based on the Poisson distribution. Rates were stratified by Auckland sub-region, age, sex, ethnicity, and SES as they are considered key modifiers of ARI hospitalisation risk. SES was quantified using NZ's small area measure of neighbourhood deprivation derived from the national census (NZ Deprivation Index 2013) [145]. This SES measure was used to divide the study sample into SES quintiles (quintile 1 – least deprived to quintile 5 – most deprived).

In NZ, Māori and Pacific peoples have lower reported life expectancy than other ethnic groups [198], and are also overrepresented in the lower SES groups [155]. To control for confounding and evaluate the independent effects of these factors, RSV hospitalisation rates and rate ratios for age group, ethnicity, and SES were adjusted for each other.

The correction of incidence rate calculations for non-testing for RSV among ARI patients was done using two methods. First, we multiplied the proportion of those tested who were positive for RSV by the number of non-tested ARI patients within strata formed by study year, sub-region, age group, SES quintile, and ethnicity (multiplier method). Second, we corrected test results using the multivariate imputation by chained equations (MICE) method [157], which has been shown to yield unbiased estimates when accounting for missing outcome data [199]. For imputation, we verified that non-tested patients were missing at random, using a Missing Completely at Random Test [156], before creating 30 imputed datasets of RSV results with age, ethnicity, SES, SARI case definition, sex, week of hospitalisation, and specimen type (clinician-ordered versus SHIVERS systematic sampling) included as predictors of missingness. To ensure correction of non-testing was only done for singular RSV illness episodes, patients with two or more untested ARI hospitalisations within 14 days of each other were considered a singular episode. All analyses were performed using Stata 14 (College Station, TX: StataCorp LP).

6.4 Results

6.4.1 Study population

Based on our linked data methodology, we identified an annual average of 731,204 adults aged 18 years or more residing in the study area during 2012–2015. This was similar to the 2015 Statistics NZ population estimates (734,530) [133].

6.4.2 Hospitalised patients

The temporal distribution of RSV hospitalisations among adults demonstrated a consistent peak during the NZ winter (May-September) (Figure 6.2). Over the four winter seasons, there were 8,776 ARI hospitalisations among adults aged 18 years or more, including 3,804 (43.4%) SARI events and 4,972 (56.7%) non-SARI events. Of ARI hospitalisations, 4,600 (52.4%) were tested for RSV (Figure 6.2). Of the 348 unique RSV-associated hospitalisation episodes identified, there were 226 (7.4%) from the 3,046 SARI tested hospitalisations and 122 (7.9%) from the 1,554 non-SARI tested hospitalisations

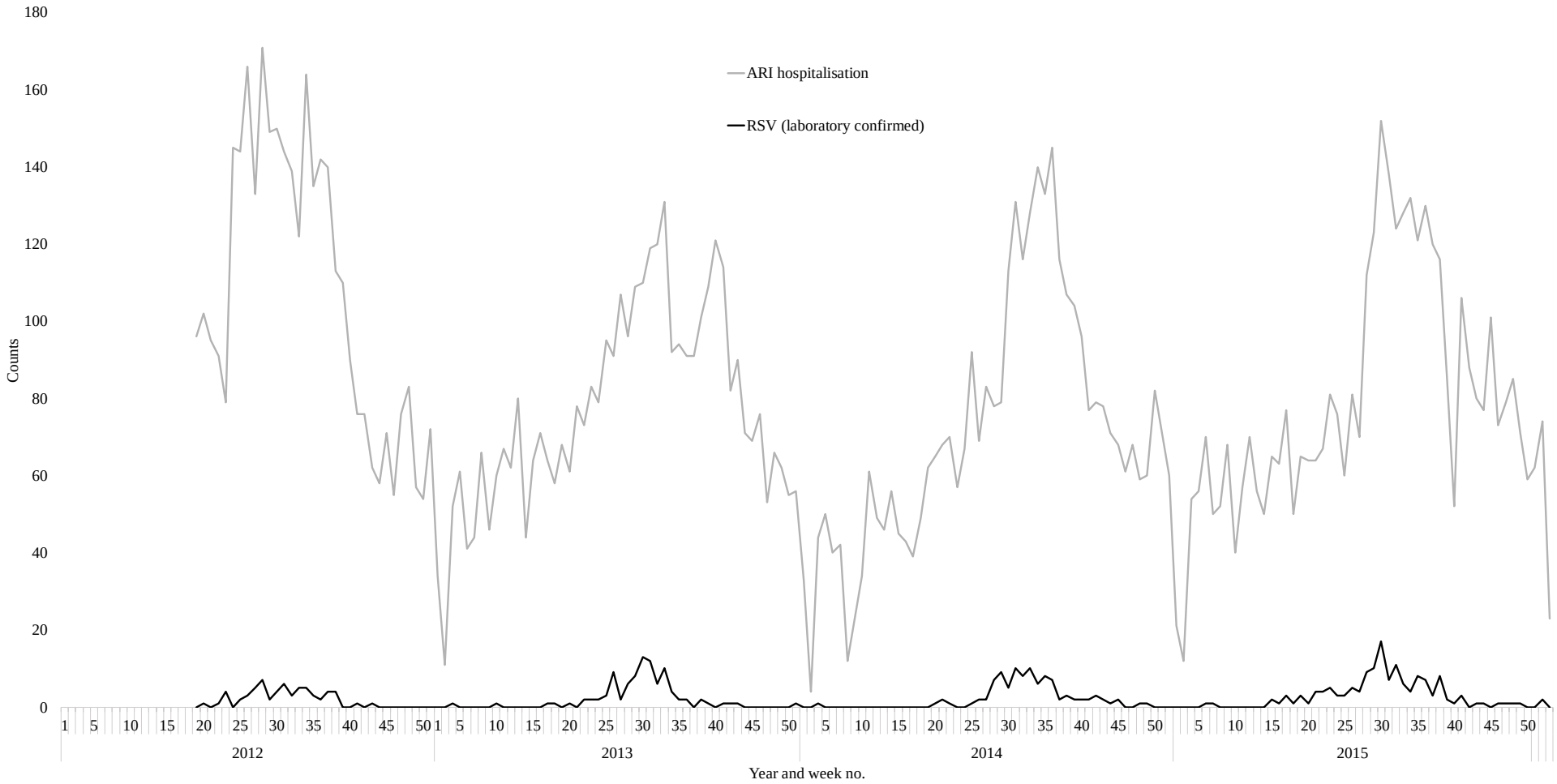


Figure 6.1 Weekly counts of acute respiratory infection (ARI) hospitalisations and respiratory syncytial virus (RSV) laboratory-confirmed hospitalisations among adults aged 18 years and older in Auckland, New Zealand, 2012–2015

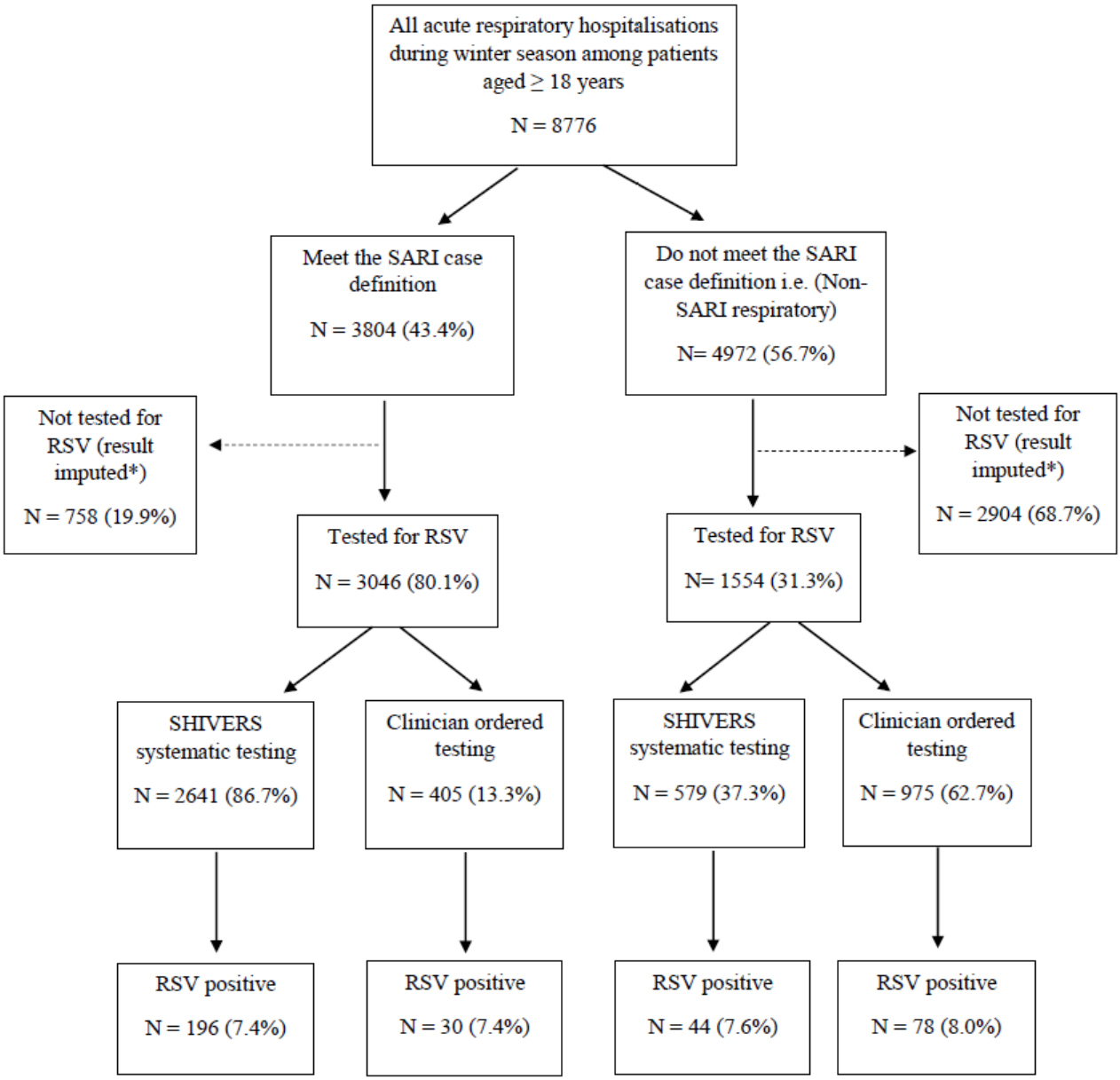


Figure 6.2 Flowchart detailing retrospective cohort of adults aged 18 years and older in Auckland, New Zealand in 2012–2015 and number of acute respiratory infection (ARI) and respiratory syncytial virus (RSV)-tested hospitalisations

* For incidence rate calculations, correction of non-testing among ARI patients was done using two methods; first by multiplying the proportion positive for RSV in each demographic strata to non-tested ARI patients in each group; and second by using the multivariate imputation by chained equations (MICE) method of imputation in STATA.

Older adults and those of Asian ethnicity were less likely to be tested (Table 6.1). The patients tested through the SHIVERS study and those tested based on clinician's orders differed by age, SES, ethnicity, SARI case definition, and length of hospital stay (Appendix 3.1).

Among RSV positive samples, 103 (29.6%) were subtyped of which 54 (52.4%) were RSV-A and 49 (47.5%) RSV-B. There were 47 (18.0%) co-detections of RSV with other viruses. Of the 261 RSV positive samples tested for other respiratory viruses, 26 (10.0%) were influenza co-detections, 13 (5.0%) rhinovirus, 6 (2.3%) were adenovirus, and 3 (1.1%) were human metapneumovirus co-detections.

The median (interquartile range [IQR]) hospital length of stay in days among all ARI hospitalisations was 3 (2–6). Of ARI hospitalisations, 179 (2.0%) were admitted to the intensive care unit (ICU), 244 (2.8%) died during their hospital stay, and 312 (3.6%) died within 30 days of discharge. The median (interquartile range [IQR]) hospital length of stay for RSV positive adults was 3 (2–6) days. Among RSV positive cases, 4 (1.1%) died during a hospital admission and 11 (3.2%) died within 30 days of hospital discharge.

Hospital length of stay did not differ by RSV positivity (p-value=0.590). The proportion of ARI hospitalisations requiring ICU admission also did not differ significantly by RSV positivity (RSV positive = 8/348 (2.3%) vs RSV negative = 132/4,252 (3.1%); p-value = 0.400).

Of 8,776 ARI hospitalisations, 3,421 (39.0%) had additional information on comorbidities, current influenza vaccination status, and antibiotic treatment following hospital admission (Figure 6.3). These ARI hospitalisations included 3,209 patients. Of these patients, 1,606 (50.1%) were regular smokers, 1,800(56.1%) patients had a current influenza vaccination, and 2,844 (88.6%) received antibiotics during the hospital admission. In terms of comorbidities, 1,370 (42.7%) patients had a chronic lung disease, and 1,196 (37.3%) had a cardiovascular condition. No factors were significantly associated with RSV positivity following adjustment for age and ethnicity.

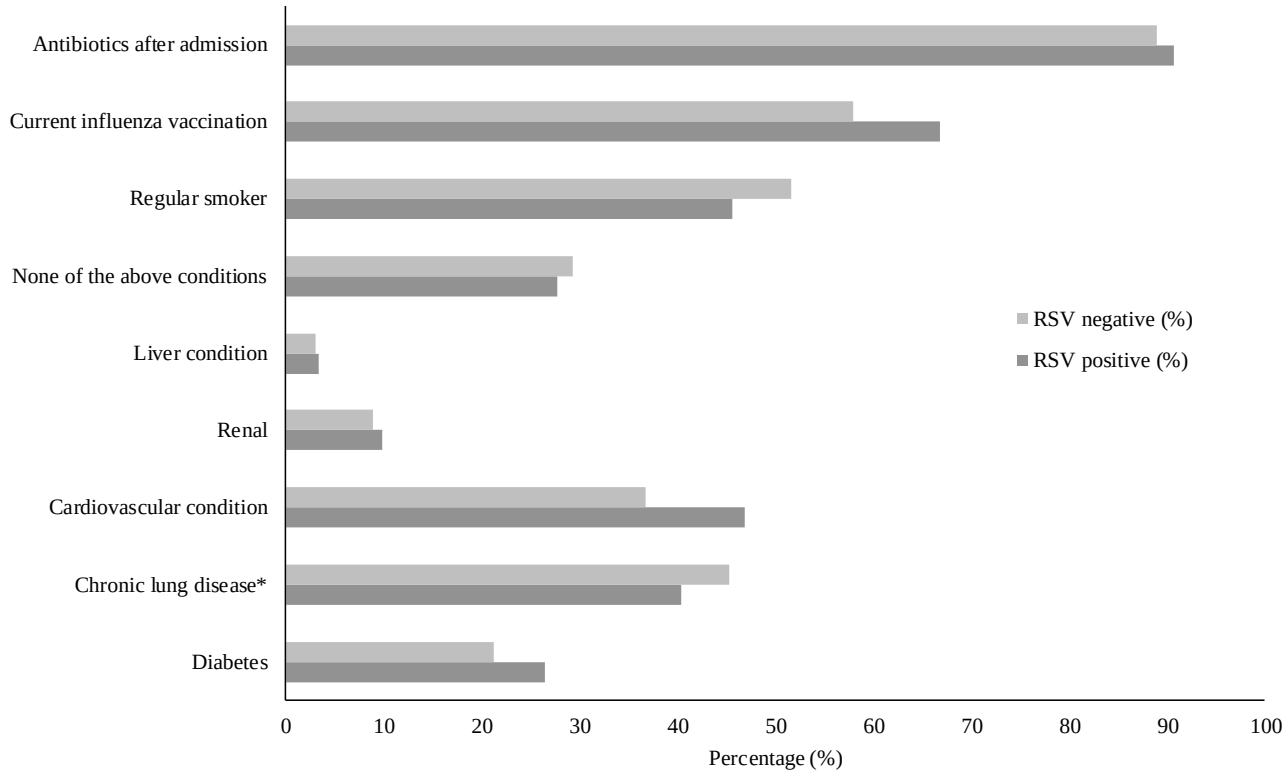


Figure 6.3 Risk factors among acute respiratory infection (ARI) hospitalisations in adults aged 18 years or more in Auckland, New Zealand, 2012–2015 by respiratory syncytial virus (RSV) result

* Includes asthma, COPD, and bronchiectasis.

6.4.3 Seasonal incidence of RSV-confirmed hospitalisations

The seasonal incidence of RSV hospitalisation without accounting for non-tested adults was 11.9 (95% confidence interval [CI] 10.7–13.2) per 100,000 adults (Table 6.2). Following correction for non-testing, the incidence of RSV-associated ARI hospitalisations was 22.7 (95% CI: 21.0–24.5) per 100,000 persons using the multiplier method and 23.6 (95% CI 21.0–26.1) per 100,000 adults using multiple imputation (Table 6.2). Rates were not significantly different based on the method used for correction; however, multiple imputation estimates had slightly wider confidence intervals due to the incorporation of uncertainty inherent in imputation. Subsequent presentation of incidence estimates used data derived from multiple imputation.

Following adjustment for age group, SES, and ethnicity; incidence was shown to increase with age, with adults aged 80 years or older being approximately 30 times as likely to have an RSV-associated hospitalisation compared to those aged 18–49 years (Rate ratio [RR] 31.3, 95% CI 22.3–44.0). Adults from SES quintiles 3–5 were at higher risk of an RSV-associated hospitalisation compared to adults in the least-disadvantaged SES group (quintile 1), following adjustment for age group and ethnicity. Similarly, RSV hospitalisation rates adjusted for age group and SES were higher in Māori (RR 2.8, 95% CI 2.0–4.0) and Pacific adults (RR 3.5, 95% CI 2.6–4.7) compared to those of European or other ethnicities.

Table 6.1 Comparison of tested and non-tested ARI hospitalisations stratified by SARI case definition among adults aged 18 years or older in Auckland, New Zealand 2012–2015

	All ARI hospitalisations		SARI				non-SARI acute respiratory				
	Total		Tested		non-tested		p-value*	Tested		non-tested		p-value*
	N	(Col %)	N	(Col %)	N	(Col %)		N	(Col %)	N	(Col %)	
Total	8776	(100.0)	3046	(100.0)	758	(100.0)		1554	(100.0)	3418	(100.0)	
Age Group (years)												
18–49	2117	(24.1)	982	(32.2)	185	(24.4)	<0.001	385	(24.8)	565	(16.5)	<0.001
50–64	1974	(22.5)	754	(24.8)	159	(21.0)	0.009	375	(24.1)	686	(20.1)	0.059
65–79	2677	(30.5)	824	(27.1)	212	(28.0)	0.917	484	(31.1)	1157	(33.9)	0.519
≥80	2008	(22.9)	486	(16.0)	202	(26.6)	<0.001	310	(19.9)	1010	(29.5)	<0.001
Sex												
Female	4682	(53.4)	1673	(54.9)	392	(51.7)	0.125	855	(55.0)	1762	(51.6)	0.376
Male	4094	(46.6)	1373	(45.1)	366	(48.3)	0.124	699	(45.0)	1656	(48.4)	0.403
SES†												
1 (least deprived)	931	(10.6)	318	(10.4)	77	(10.2)	0.783	171	(11.0)	388	(11.4)	0.767
2	1216	(13.9)	438	(14.4)	110	(14.5)	0.870	227	(14.6)	511	(15.0)	0.236
3	1335	(15.2)	432	(14.2)	113	(14.9)	0.703	225	(14.5)	516	(15.1)	0.414
4	1258	(14.3)	399	(13.1)	103	(13.6)	0.764	220	(14.2)	522	(15.3)	0.589
5 (most deprived)	4036	(46.0)	1459	(47.9)	355	(46.8)	0.903	711	(45.8)	1481	(43.3)	0.100
Ethnicity												
Māori	1585	(18.1)	560	(18.4)	130	(17.2)	0.406	266	(17.1)	629	(18.4)	0.063
Pacific	2552	(29.1)	1026	(33.7)	246	(32.5)	0.858	426	(27.4)	854	(25.0)	0.045
Asian	811	(9.2)	321	(10.5)	93	(12.3)	0.029	119	(7.7)	278	(8.1)	0.070
European/Other	3828	(43.6)	1139	(37.4)	289	(38.1)	0.395	743	(47.8)	1657	(48.5)	0.571

* Characteristics of tested and non-tested cases were compared using chi-square tests.† SES quantified using a small area level measure of household deprivation derived from the national census (NZDep2013). This measure was used to divide the study sample into quintiles with SES 1 as least deprived and SES 5 as most deprived.

Table 6.2 Seasonal incidence rates (IR) of acute respiratory infection (ARI) and laboratory-confirmed respiratory syncytial virus (RSV)-associated ARI hospitalisations among adults 18 years and older by year, Auckland sub-region, demographic factors in Auckland, New Zealand, 2012–2015

		ARI hospitalisations				Incidence rates (IR) per 100,000 adults		
						Crude - Not corrected for non-testing	Corrected for non-testing*	
							Multiplier method	Multiple imputation
	No. of adults	Total	No. tested for RSV	No. confirmed with RSV	(%) of tested	IR (95% CI)	IR (95% CI)	IR (95% CI)
Total	2924815	8776	4600	348	(7.6)	11.9 (10.7– 13.2)	22.7 (21.0–24.5)	23.6 (21.0– 26.1)
Season								
2012	708332	2637	951	59	(1.3)	8.2 (6.1– 10.3)	23.2 (19.8–26.9)	25.5 (18.2– 32.9)
2013	726127	2036	932	83	(1.8)	11.3 (8.8– 13.7)	24.9 (21.4–28.8)	29.2 (23.2– 35.2)
2014	736724	2023	1315	86	(1.9)	11.7 (9.2– 14.1)	17.9 (15.0–21.3)	19.1 (15.2– 23.0)
2015	753632	2080	1402	120	(2.6)	15.9 (13.1– 18.8)	23.6 (20.3–27.4)	25.1 (20.4– 29.7)
Region								
Central Auckland	1435862	4061	2063	158	(3.4)	11.0 (9.3– 12.8)	21.6 (19.3–24.2)	22.7 (19.3– 26.0)
South East Auckland	1488953	4715	2537	190	(4.1)	12.8 (10.9– 14.7)	23.7 (21.3–26.3)	24.4 (21.1– 27.8)
Age Group (years)								
18–49	1838952	2117	1367	64	(1.4)	3.5 (2.6– 4.3)	5.4 (4.4–6.6)	5.9 (4.3– 7.5)
50–64	658708	1974	1129	93	(2.0)	14.2 (11.3– 17.1)	24.8 (21.2–28.9)	24.2 (18.2– 30.2)
65–79	327234	2677	1308	118	(2.6)	36.4 (29.6– 43.2)	74.0 (64.9–83.8)	72.9 (57.4– 88.3)
≥65	427155	4685	2104	191	(4.2)	44.7 (38.6– 51.5)	99.5 (90.3–10.9)	99.2 (82.4–115.9)
≥80	99921	2008	796	73	(1.6)	74.5 (57.4– 91.5)	184.1 (158.5–212.8)	190.8 (137.6– 244.0)
Sex								
Female	1543948	4682	2528	198	(4.3)	12.9 (11.1– 14.7)	23.8 (21.4–26.3)	23.9 (20.7– 27.1)
Male	1380867	4094	2072	150	(3.3)	10.9 (9.1– 12.7)	21.4 (19.1–24.0)	23.3 (19.8– 26.7)

Table continued on next page

		ARI hospitalisations				Incidence rates (IR) per 100,000 adults		
						Crude - Not corrected for non-testing	Corrected for non-testing*	
							Multiplier method	Multiple imputation
	No. of adults	Total	No. tested for RSV	No. confirmed with RSV	(%) of tested	IR (95% CI)	IR (95% CI)	IR (95% CI)
SES †‡								
1	525511	931	474	35	(0.8)	6.7 (4.5– 8.9)	13.1 (10.2–16.6)	13.9 (9.0– 18.7)
2	566525	1216	624	49	(1.1)	8.5 (6.1– 10.9)	16.7 (13.6–20.5)	17.3 (12.7– 22.0)
3	512159	1335	676	52	(1.1)	10.6 (7.8– 13.4)	20.1 (16.4–24.4)	22.1 (16.5– 27.7)
4	383620	1258	639	57	(1.2)	13.6 (9.9– 17.3)	29.2 (24.0–35.1)	28.1 (20.2– 36.0)
5	937001	4036	2187	155	(3.4)	17.1 (14.3– 19.8)	30.5 (27.1–34.3)	31.7 (26.9– 36.6)
Ethnicity †								
Māori	249970	1585	826	43	(0.9)	17.3 (12.2– 22.5)	33.3 (26.5–41.2)	34.3 (24.7– 43.9)
Pacific	482596	2552	1452	121	(2.6)	25.2 (20.6– 29.9)	44.1 (38.4–50.5)	45.3 (37.2– 53.4)
Asian	684059	811	440	32	(0.7)	4.7 (3.1– 6.3)	8.6 (6.6–11.1)	9.2 (6.0– 12.4)
European/Other	1508190	3828	1882	152	(3.3)	10.1 (8.5– 11.7)	20.5 (18.3–22.9)	21.4 (17.8– 25.0)

* Correction for non-testing among ARI patients was done using two methods; first by multiplying the proportion positive for RSV in each demographic strata to non-tested ARI patients identified in each group; and second by using the multivariate imputation by chained equations (MICE) method of imputation.
†Rate for SES and ethnicity presented in table are unadjusted. Adjusted rate ratios are provided in text.
‡SES quantified using a small area level measure of neighbourhood deprivation derived from the national census (NZDep2013).

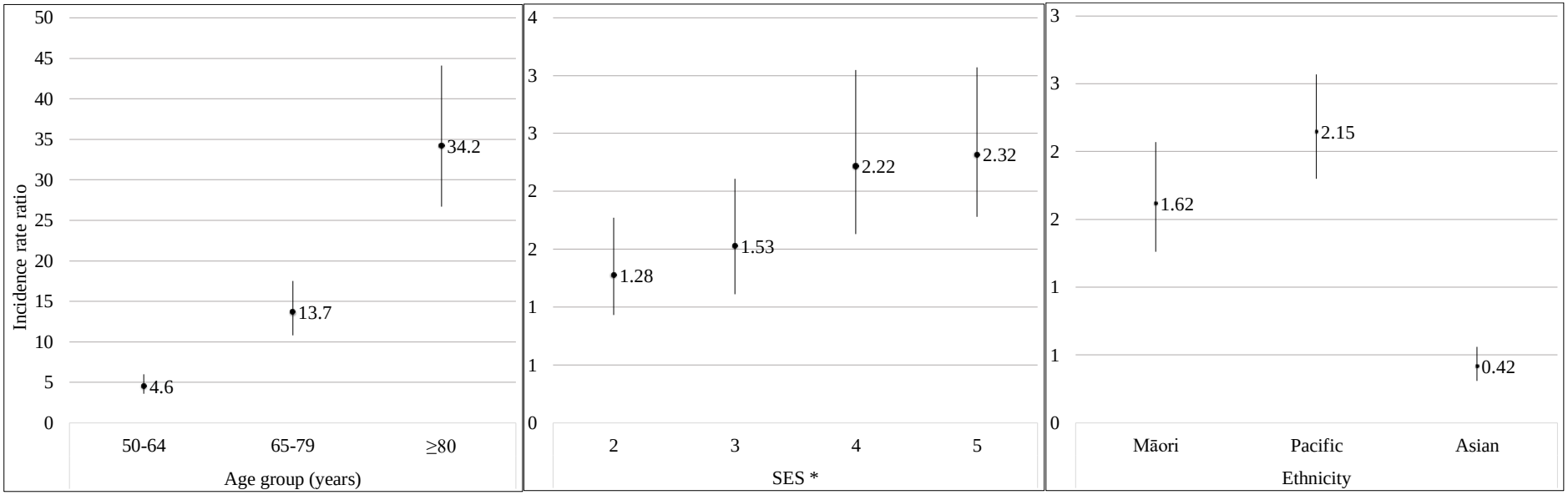


Figure 6.4 Incidence rate ratios for age group (referent 18–49 years old), socioeconomic status (referent – quintile 1), and ethnicity (referent – European/other) of respiratory syncytial virus (RSV) associated acute respiratory infection (ARI) hospitalisations among adults 18 years or older in Auckland, New Zealand, 2012–2015

* Incidence rate ratios for age, socioeconomic status and ethnicity in figure are unadjusted. Adjusted rate ratios are provided in text.
† SES quantified using a small area level measure of neighbourhood deprivation derived from the national census (NZDep2013) with SES 1 as least deprived and SES 5 as most deprived

6.4.4 Direct healthcare costs

Based on the DRG costing methodology, the median (IQR) cost per RSV hospitalisation among adults was NZ$3,724 ($2,500–$5,028) while among non-RSV hospitalisations the median (IQR) cost per hospitalisation was $3,951 ($2,424–$5,028). Hospitalisation costs were not significantly different by RSV positivity in adults (p-value = 0.254). After accounting for non-testing, the annual direct healthcare cost of RSV-confirmed hospitalisations in Auckland was NZ$818,399 or an average NZ$4,758 per hospitalisation. This is equivalent to US$525,138 or an average US$3,053 per hospitalisation, using November 2019 currency exchange rates.

6.5 Discussion

We present estimates of RSV hospitalisations rates among adults aged 18 years or more from population-based ARI surveillance. We show RSV to be associated with approximately 8% of ARI hospitalisations during winter seasons in this age group and to cost an average NZ$4,758 per episode. Increasing age, Māori or Pacific ethnicity and low neighbourhood SES were all associated with an increased risk of RSV-associated hospitalisation in this population.

Of year-round RSV-associated SARI hospitalisations, 90% of RSV occurred during the winter season suggesting that seasonal incidence approximates annual incidence. We observed disparities in RSV-associated hospitalisation rates by age, ethnicity and SES. Such disparities have been reported for RSV-associated hospitalisation rates in children [70], but to our knowledge this is the first study to demonstrate such inequalities among adults. Ethnic differences in respiratory infectious diseases are thought primarily to be due to social and economic factors, as ethnic groups with increased risk of infection and disease tend to be overrepresented in lower socioeconomic groups. However, in our study we found both ethnicity and SES to have independent effects on RSV-associated hospitalisation risk. A potential explanation is that our

neighbourhood-level measure of SES may not accurately capture individual SES. Consequently, social and economic factors associated with RSV disease risk such as smoking, housing density, presence of comorbidities, healthcare seeking behaviour, and poor nutrition are potentially being better captured by ethnicity. As our investigation is exploratory, further investigation is warranted to guide policy development. Nevertheless, our findings highlight the value of assessing RSV related health disparities among different socio-ethnic adult populations in other countries.

Our estimates of RSV positivity among adult ARI hospitalisations is comparable to one US study using active ARI surveillance and laboratory confirmation among hospitalised adults aged 65 years or more [81]. When comparing our estimates to studies reporting RSV hospitalisation rates using hospital surveillance [190, 191], we found our rates (23.6 per 100,000 adults aged ≥18 years and 99.2 per 100,000 adults aged ≥65 years) to be lower than those reported in these studies (55 per 100,000 adults aged ≥18 years and 189–254 per 100,000 adults aged ≥65 years). One possible reason for differences could be the approach used to extrapolate RSV positivity in untested patients. In our study, all ARI patients were actively identified by study nurses during a broad winter season, and RSV positivity for those without study testing was estimated while accounting for demographic and clinical differences using a traditional multiplier method and a multiple imputation method. In the US studies, RSV hospitalisation rates were estimated by multiplying the proportion of enrolled patients positive for RSV by the total number of residents with an ICD-9 classified ARI hospitalisation during influenza seasons [190, 191]. Additionally, one of the studies took place during a single year when there was a novel influenza A H1NI pandemic [190], thus rates estimated that year may not be representative of all years

The relative burden of influenza compared to that due to RSV also differed in comparison to these earlier studies. In the studies by Falsey et al. and Widmer et al., the proportion of ARI hospitalisations in adults positive for influenza were found to be similar to those for RSV. In our

study, the proportion of hospitalised adults with influenza (approximately 24%) and the influenza-related hospitalisation rate (approximately 72 per 100,000) [159-161] were higher than those for RSV, despite influenza vaccination coverage in adult populations in NZ being similar to those of the US study locations. It is possible that these differences are due to the effects of different circulating influenza strains. In our study, influenza H3N2 was the predominant strain every year except 2014, and has been shown to result in more severe illness than RSV [200], whereas in the US studies, influenza H1N1 was generally the predominant strain.

The RSV-associated hospitalisation rates among adults aged 65 years or more (99 per 100,000 adults) reported in this study were similar to estimates reported by studies using indirect statistical modelling. Zhou et al. modelled hospitalisation and viral surveillance data in 13 US states from 1993–1994 through 2007–2008 and estimated an RSV hospitalisation rate of 86 per 100,000 adults aged 65 years or more [83]. Similarly, Fleming et al. modelled viral surveillance and hospitalisation data from the UK from 1995–2009 and estimated an RSV hospitalisation rate of 156 per 100,000 adults aged 65 years or more [194]. Finally, similar to our findings, Zhou et al. estimated hospitalisation rates due to influenza in adults to be considerably higher than that for RSV, particularly in years dominated by influenza H3N2 [83].

When carrying out analyses among hospitalised cases, we did not find any assessed comorbidity to be significantly associated with RSV positivity following adjustment for age and ethnicity. This lack of association is likely due to the higher risk of hospitalisation for non-RSV illnesses in adults with comorbidities i.e. selection bias that occurs when both exposure and outcome are associated with hospitalisation. Thus, in order to accurately measure the effect of comorbidity on RSV disease risk, population level comorbidity data should be used to estimate RSV-associated hospitalisation rates in specific co-morbidity strata. Such estimates will be valuable in identifying

adult groups who are at particularly high-risk from RSV-associated disease and priority groups for future RSV vaccines and treatments.

A strength of this study is its use of ARI surveillance across multiple seasons linked with individual-level population data, to estimate RSV hospitalisation rates by demographic characteristics important for NZ. Nonetheless, our study has important limitations. First of which was the lack of RSV testing for all ARI patients and differences in testing by SARI case definition. However, our estimates were similar using two different correction methods for non-testing. Additionally, by using multiple imputation we were able to provide more realistic measures of uncertainty for our rate estimates. Secondly, our estimations of cost are based on direct healthcare associated cost and do not account for indirect costs associated with loss of work hours and out-of-pocket expenses. Finally, the lack of systematic bacterial and viral co-infection data prevented detailed assessments of the causal role of RSV infection in adult ARIs. However, a recent meta-analysis suggests strong evidence for this association, showing that among individuals with RSV-ARI, ARI is causally attributable to RSV in about 88% of cases [201].

6.6 Conclusions

In a setting outside of the US, where most studies assessing the burden of RSV in older have been conducted, we confirm that RSV has a considerable hospitalisation burden and associated economic cost in adults. In our study from 2012–2015, RSV burden was less than that for influenza. RSV disproportionally affects adults by age. Being of indigenous Māori or Pacific ethnicity or from a low socioeconomic area were associated with RSV hospitalisation risk. An effective RSV vaccine or treatment may offer benefits for older adults.

7 RSV-associated hospitalisations among adults with chronic medical conditions

7.1 Preface

This chapter addresses Objective four of this thesis: to investigate risks posed by specific chronic comorbidities among adults on RSV-associated hospitalisations. The research presented in this chapter has been published in *Clinical Infectious Diseases.*

Prasad N, Walker TA, Waite B, Wood T, Trenholme AA, Baker MG, McArthur CM, Wong CA, Grant CC, Huang QS, Newbern EC. Respiratory syncytial virus associated hospitalisations among adults with chronic medical conditions, Clinical Infectious Diseases, ciaa730, https://doi.org/10.1093/cid/ciaa730

I was provided with population level co-morbidity data, which was defined by co-authors (Walker TA, Waite B, and Newbern EC). I carried out data management and analysis, with guidance from my supervisors and co-authors, and drafted the initial manuscript. All co-authors reviewed and approved the final manuscript.

7.2 Introduction

Respiratory syncytial virus (RSV) is increasingly recognised as an important cause of morbidity and mortality among adults, with older age groups disproportionally affected [81, 191]. As with influenza [202], cardiopulmonary conditions have been associated with increased risk of RSV hospitalisation in older adults [51, 81], however, there remains limited information on the role of these conditions among younger adults. Furthermore, the role of other common chronic medical

conditions (CMCs), such as diabetes and renal disease, on RSV-associated-outcomes remains poorly understood.

Using an acute respiratory illness (ARI) surveillance platform established in a defined adult population, we estimated risk of RSV-associated hospitalisations among adults aged 18–80 years with CMCs including chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular accidents (CVA), diabetes mellitus (DM), and end-stage renal disease (ESRD), compared to adults without these respective conditions.

7.3 Methods

7.3.1 Study design and population

This study was an extension of two previous Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) studies [131, 132]; one estimating the RSV hospitalisation rate among adults ([203] and Chapter 6) and the other estimating the rate of influenza hospitalisations among adults stratified by the same CMCs [202]. SHIVERS was an active ARI surveillance project conducted from 2012 to 2015 in two public hospitals in Auckland, NZ, which provide all inpatient respiratory services for the population residing in the central, eastern and southern regions of Auckland.

The study area is predominantly urban with approximately 700,000 adults aged 18–80 years in 2015, of whom 9% are Māori (NZ's indigenous population), 16% Pacific (including ethnic groups from Samoa, Cook Islands, Tonga, Niue, Fiji, Tokelau, Tuvalu, and Kiribati), 23% Asian, and 52% of European or other ethnicities [133]. Ethical approval for the SHIVERS project was obtained from the NZ Health and Disability Ethics Committee (NTX/11/11/102).

Using NZ's National Health Index (NHI) number, which is a unique identifier assigned to all healthcare users in NZ, we combined the SHIVERS surveillance data with national administrative datasets including: the National Minimum Dataset of hospitalisations; the Primary Health Organisation Collection describing primary care enrolments; the National Maternity and Mortality Collections; the National Non-Admitted Patient Collection of outpatient visits; community pharmacy dispensing data; and TestSafe laboratory data [153]. Through this data linkage, we were able to obtain individual-level demographic, CMC, and ARI hospitalisation records for adults aged 18–80 years residing in the study area during 2012–2015.

Note: Details in the following two paragraphs and section 7.3.2 have been previously mentioned in section 2.2.

For SHIVERS, research nurses evaluated adults admitted to inpatient wards with a suspected ARI. Suspected ARI cases were identified through a combination of reviewing admission diagnoses and interviewing patients about their presenting signs and symptoms. Among suspected ARI cases, those meeting the WHO severe acute respiratory infection (SARI) case definition, defined as cough and measured or reported fever within the last 7 days in 2012 and last 10 days in 2013–2015 were enrolled [134]. To estimate the respiratory virus hospitalisation burden among ARI cases not meeting the SARI definition (i.e. those with cough and/or measured or reported fever but not both within 10 days), a convenience sample of non-SARI respiratory cases were enrolled during the 2013–2015 winter seasons. Sampling in 2013 was during the peak winter period (12th August to 6th October) and included weekly random selection of two adult inpatients who fitted the non-SARI respiratory definition at all participating facilities. In 2014 and 2015, this surveillance was extended to randomly enrol approximately six adult non-SARI respiratory patients weekly in both hospitals from week 18 to 39 (end of April – September). Nurses obtained consent from eligible patients and collected nasopharyngeal samples.

In addition to respiratory virus test results generated by SHIVERS, hospital laboratories provided results from clinically ordered tests performed on ARI patients during the study. These results increase the proportion of tested participants, particularly for non-SARI cases, since few were systematically enrolled in SHIVERS.

7.3.2 Laboratory methods

Specimens were tested for RSV using the United States Centers for Disease Control and Prevention real-time reverse transcription (RT)-PCR protocol [135, 136] at the Institute of Environmental Science and Research, or using the AusDiagnostic PCR protocol and real-time PCR assays at hospital laboratories [137]. Further information on laboratory methods and comparisons of the performance of different assays are provided in Appendix 1.1.

7.3.3 Chronic medical condition (CMC) case definitions

Methods used to define the CMC status of our study population have been described previously [202] and further details are provided in Appendix 4.1–4.2. In brief, machine learning techniques in the form of predictive partial least squares (PLS) models were developed to define each adult's CMC status by training the study population's health data (prescribed medications, medication class combinations, and laboratory test results) to CMC-specific hospitalisation *ICD-10* codes. Such methods have been previously used to assign CMC statuses to a population [204]. As *ICD-10* codes were expected to be specific, other health data were used to improve the model's sensitivity. Variables that discriminated between highly related CMCs in univariate logistical regression were included as predictors in the PLS model training (Appendix 4.2). The model generated weights for each variable based on the strength of association between the variable and the presence of CMC specific ICD-10 codes.

If an individual's health data met the threshold for the model-predicted CMC status (based on model weighting), the individual was assigned that CMC status. The optimal threshold for assigning each model-predicted CMC status was determined by randomly sampling 100,000 individuals and applying the Youden modified optimality criterion [205] using expected CMC prevalence according to the NZ Health Survey [153] and case definitions derived from study data sources (Appendix 4.2b).

CHF, CAD, and DM statuses were assigned based on associations between hospitalisation *ICD-10* codes, pharmaceutical claims, and laboratory test results modelled for each condition. Asthma and COPD statuses were based on models including hospitalisation *ICD-10* codes and pharmaceutical claims, as pulmonary function test results were incomplete. COPD, CVA and ESRD data were restricted to adults aged 50 years or more. Models were not used to predict CVA and ESRD because their predicted prevalence were not comparable with reported estimates [153]. CVA status was assigned using *ICD-10* discharge codes, and ESRD by qualifying *ICD-10* discharge codes or laboratory results. The variables used to define CVA and ESRD status are shown in Appendix 4.2b.

7.3.4 Statistical analysis

RSV follows a well-defined seasonal pattern with 90% of RSV positive hospitalisations among adults detected during winter surveillance (Figure 6.1). As SHIVERS non-SARI respiratory testing was only conducted during winter seasons, we restricted our analyses to the 2012–2015 winter periods (week 18–39, end of April to end of September of each year).

Chi-square tests were used to test for associations between categorical variables and Student's t-tests for continuous variables. We used logistic regression to assess associations of CMCs with age and ethnicity in the study population.

We assessed if specific CMCs were independently associated with hospital length of stay (LOS) among RSV positive adults by modelling LOS as a continuous outcome using negative binomial regression and including all CMCs, while adjusting for age and ethnicity. Low numbers of RSV-associated Intensive Care Unit (ICU) admissions and deaths on our study population prevented similar assessments.

Incidence rates (IR) were calculated by dividing the number of RSV-associated ARI hospitalisations (singular episodes) by the number of adults, stratified by CMC status. As certain age and ethnic groups have higher rates of RSV (Chapter 6) and CMCs (Appendix 4.3), estimates were stratified by major age group and adjusted for age and ethnicity. The low number of RSV hospitalisations in our study prevented stratification by both age and ethnicity.

RSV hospitalisation incidence rate ratios (IRR) were calculated by comparing rates among individuals with CMCs to those without the corresponding CMCs (i.e. COPD vs. no COPD). Confidence intervals for IRs and IRRs were based on the Poisson distribution. IRs and IRRs with non-overlapping 95% CIs and p-value<0.05 were considered significantly different.

We attempted to estimate IR and IRRs while also adjusting for SES (quantified using NZ's small area measure of neighbourhood deprivation derived from the national census (NZ Deprivation Index 2013) [145]), however, we found that in certain age stratified models the high collinearity between the ethnicity and SES variables resulted in non-convergence. Previous related analysis has suggested that the neighbourhood-level measure of SES used in our analyses may not detect individual SES, which may be more accurately captured by ethnicity. Consequently, we chose to focus on age and ethnicity adjusted models. All analyses were performed using Stata 14 (College Station, TX: StataCorp LP).

Missing data

Not all ARI hospitalisations were tested for RSV. We verified that non-tested patients were missing at random using a Missing Completely at Random Test [156]. Our primary focus was to estimate the relative risks of RSV hospitalisation posed by specific CMCs (i.e. IRRs). To investigate if missing data had an impact on IRR estimates, we used the multivariate imputation by chained equations (MICE) method of imputation. We created 30 imputed datasets of RSV results with age, ethnicity, socioeconomic status, SARI case definition, week of hospitalisation, all assessed CMC statuses, and specimen type (clinician-ordered versus SHIVERS systematic sampling) included as predictors of missingness. Imputed IRRs (Table 7.3) were not significantly different from non-imputed IRRs for CMCs, thus we focused on non-imputed results.

7.4 Results

7.4.1 Study population

Our study source population comprised on average 706,000 adults aged between 18–80 years annually. A total of 174,514 (19.7%) of our study population had at least one identified CMC with the highest prevalence (44.1%) in those aged 65 years and older. The most common CMCs in the population were asthma (12.0%) and DM (7.2%) (Table 7.1). People of Māori and Pacific ethnicity were more likely to have a CMC compared to those of European or Other ethnicity (p-value<0.001), after controlling for age (Appendix 4.3).

7.4.2 Hospitalisations

During the 2012–2015 winter seasons, there were 6,911 ARI hospitalisations among adults aged 18-80 years, of which 3,875 (56.1%) were tested for RSV. Tested ARI hospitalisations included 2,591 (66.9%) SARI and 1,284 (33.1%) non-SARI cases. Of SARI cases, 184 (7.1%) were positive for RSV while among non-SARI cases 97 (7.6%) were positive for RSV, resulting in a

total of 281 (7.3%) RSV-associated ARI hospitalisations. Among the 227/281 (80.8%) RSV-associated patients with at least one identified CMC, the most common CMCs were asthma (173/281, 61.6%), COPD (137/281, 48.8%), and DM (92/281, 32.7%).

Appendix 4.4 provides proportion positive for RSV by SARI and non-SARI case definitions by each CMC and age group. The proportion positive for RSV was not found to be significantly different by SARI case definition for any CMC overall and within specific age groups.

Among RSV positive cases, 8 (2.8%) were admitted to the ICU, 4 (1.4%) died during hospitalisation, and 4 (1.4%) died within 30 days of hospital discharge. CMCs were present in 5 (62.5%) RSV positive cases admitted to ICU, of which three had asthma.

The median (range) LOS among RSV-associated hospitalisations was 3 (1–19) days. In a negative binomial regression model, while adjusting for age, ethnicity, and studied CMCs; among RSV positive adults, LOS were significantly longer for patients with CHF (IRR 1.3, 95% CI 1.1–1.7) or COPD (IRR 1.8, 95% CI 1.1–3.0).

Table 7.1 Estimated chronic medical condition prevalence by age and number of hospitalisations that were RSV tested and positive, Auckland, New Zealand, 2012–2015

			Chronic medical condition*													
	Overall		COPD		Asthma		CHF		CAD		CVA		DM		ESRD	
	n	(%)*	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†
Total Population	883999	(100.0)	31652	(3.6)	106389	(12.0)	7876	(0.9)	28553	(3.2)	5431	(0.6)	64026	(7.2)	2336	(0.3)
RSV positive/Tested hospitalisations	281/3875	(7.3)	137/1542	(8.9)	173/2238	(7.7)	50/689	(7.3)	83/1046	(7.9)	9/134	(6.7)	92/1083	(8.5)	9/180	(5.0)
By Age Group																
Age 18–49 years	597167	(100.0)	†		61110	(10.2)	617	(0.1)	2543	(0.4)	†		17086	(2.9)	†	
RSV positive/Tested hospitalisations	64/1367	(4.7)			30/621	(4.8)	6/63	(9.5)	6/80	(7.5)			16/171	(9.4)		
Age 50–64 years	188157	(100.0)	15046	(8.0)	26676	(14.2)	2011	(1.1)	10129	(5.4)	1597	(0.8)	26220	(13.9)	879	(0.5)
RSV positive/Tested hospitalisations	93/1129	(8.2)	50/609	(8.2)	57/688	(8.3)	12/194	(6.2)	30/337	(8.9)	2/36	(5.6)	26/414	(6.3)	6/77	(7.8)
Age 65–80 years	98675	(100.0)	16606	(16.8)	18603	(18.9)	5248	(5.3)	15881	(16.1)	3062	(3.1)	20720	(21.0)	898	(0.9)
RSV positive/Tested hospitalisations	124/1379	(9.0)	87/933	(9.3)	86/929	(9.3)	32/432	(7.4)	47/629	(7.5)	6/83	(7.2)	50/497	(10.1)	2/66	(3.0)

*COPD; Chronic obstructive pulmonary disease, CHF; congestive heart failure, CAD; coronary artery disease, CVA; cerebrovascular accident, DM; diabetes mellitus, ESRD end-stage renal disease.
† Percentages (%) are of total population and by age group strata.
‡ Modelled COPD, CVA, and ESRD data was not included for adults aged 18–49 years.

7.4.3 Seasonal ARI hospitalisation rates and rate ratios for each CMC (Table 7.2)

Chronic obstructive pulmonary disease (COPD)

RSV hospitalisation rates in adults aged 50 years or more with COPD increased significantly with age from 69.9 to 135.2 per 100,000 adults. In both age groups (50–64 years and 65–80 years), RSV hospitalisation rates were roughly ten times higher for adults with COPD versus those without.

Asthma

RSV hospitalisation rates in adults with asthma increased significantly with age, ranging from 13.6 to 119.6 per 100,000 adults. Across all ages, adults with asthma had 7–8 times higher RSV hospitalisation rates than those without asthma.

Congestive Heart Failure (CHF)

RSV hospitalisation rates in adults with CHF ranged from 79.3–137.4 per 100,000 adults by age. RSV hospitalisations were over 36 times higher when adults aged 18–49 years had CHF. Adults aged 50 years or more with CHF also had significantly increased rates of RSV hospitalisations compared to those without CHF.

Coronary Artery Disease (CAD)

RSV hospitalisation rates in adults with CAD ranged from 33.4–72.9 per 100,000 adults. CAD was associated with higher RSV hospitalisation rates for adults of all ages with rates 11 times higher for adults aged 18–49 years with CAD versus those without.

Cerebrovascular Accidents (CVA)

Among adults aged 50 years or more with a history of a CVA, RSV hospitalisation rates ranged from 24.4–52.8 per 100,000 adults. In the 50–64 years and 65–80 years age groups, CVAs were not found to be significantly associated with higher RSV hospitalisation rates.

Diabetes mellitus (DM)

RSV hospitalisation rates in adults with DM ranged from 15.2–52.8 per 100,000 adults. Adults aged 65–80 years with DM had significantly higher RSV hospitalisation rates compare to younger adults with DM. RSV hospitalisation rates were significantly higher for adults with DM versus those without in the 18–49 years and 65–80 years age groups.

End Stage Renal Disease (ESRD)

RSV hospitalisation rates among adults aged 50 years or more with ESRD ranged from 39.7–87.7 per 100,000 adults. The IRRs for RSV hospitalisation were significantly increased for adults with versus without ESRD in the 50–64 years age group.

Table 7.2 Incidence rates (IR) per 100,000 and incidence rate ratios (IRR) of RSV hospitalisations by major age groups and chronic medical condition (CMC), Auckland New Zealand, 2012–2015, *adjusted for ethnicity and age*

Chronic medical condition *	Age group					
	18–49 years		50–64 years		65–80 years	
	IR (95% CI)	IRR (95% CI) †	IR (95% CI)	IRR (95% CI) *	IR (95% CI)	IRR (95% CI) *
No COPD	‡		7.3 (5.1– 9.5)	Ref	13.9 (9.4– 18.4)	Ref
COPD			69.9 (49.0– 90.8)	9.58 (6.18– 14.84)	135.2 (101.8– 168.6)	9.72 (6.33– 14.94)
No Asthma	2.0 (1.3– 2.7)	Ref	6.6 (4.4– 8.8)	Ref	14.6 (9.9– 19.3)	Ref
Asthma	13.6 (8.6– 18.6)	6.69 (4.06– 11.04)	49.8 (36.3– 63.3)	7.55 (4.92– 11.59)	119.6 (92.1– 147.1)	8.18 (5.48– 12.23)
No CHF	3.1 (2.3– 3.9)	Ref	12.6 (9.8– 15.3)	Ref	29.9 (23.8– 36.1)	Ref
CHF	112.2 (10.5– 213.9)	36.45 (14.11– 94.16)	79.3 (27.1– 131.5)	6.31 (3.14– 12.70)	137.4 (81.9– 192.9)	4.59 (2.91– 7.24)
No CAD	3.1 (2.3– 3.9)	Ref	10.4 (7.8– 13.0)	Ref	28.9 (22.2– 35.6)	Ref
CAD	33.4 (4.8– 62.0)	10.79 (4.41– 26.41)	55.0 (33.5– 76.6)	5.29 (3.30– 8.47)	72.9 (51.5– 94.3)	2.52 (1.74– 3.67)
No CVA	‡		14.0 (11.1– 16.9)	Ref	36.9 (30.0– 43.8)	Ref
CVA			24.4 (-9.7– 58.4)	1.74 (0.42– 7.17)	52.8 (10.5– 95.1)	1.43 (0.63– 3.26)
No DM	2.7 (1.9– 3.5)	Ref	13.4 (10.2– 16.7)	Ref	31.2 (23.9– 38.5)	Ref
DM	15.2 (6.6– 23.8)	5.63 (2.97– 10.69)	16.2 (9.6– 22.8)	1.21 (0.74– 1.95)	52.8 (36.1– 69.4)	1.69 (1.13– 2.54)
No ESRD	‡		13.3 (10.5– 16.1)	Ref	37.4 (30.5– 44.3)	Ref
ESRD			87.7 (6.7– 168.6)	6.57 (2.55– 16.94)	39.7 (-15.2– 94.6)	1.06 (0.26– 4.29)

*COPD; Chronic obstructive pulmonary disease, CHF; congestive heart failure, CAD; coronary artery disease, CVA; cerebrovascular accident, DM; diabetes mellitus, ESRD end-stage renal disease.

† Incidence rate ratio (IRR) compares RSV hospitalisation rates between adults with versus without each CMC

‡ Modelled COPD, CVA, and ESRD data was not included for adults aged 18–49 years

Table 7.3 Incidence rates (IR) per 100,000 and incidence rate ratios (IRR) of RSV hospitalisations by major age groups and chronic medical conditions (CMC), Auckland New Zealand, 2012–2015– ***Corrected for non-testing and adjusted for ethnicity and age***

Chronic Medical Contrition*	Age group					
	18–49 years		50–64 years		65–80 years	
	IR (95% CI)	IRR† (95% CI)	IR (95% CI)	IRR (95% CI)	IR (95% CI)	IRR (95% CI)
No COPD	‡		11.8 (8.1– 15.6)	Ref	25.2 (16.3– 34.1)	Ref
COPD			136.5 (93.2– 179.8)	11.54 (7.74– 17.20)	286.6 (212.7– 360.5)	11.40 (7.62– 17.06)
No Asthma	3.7 (2.3– 5.0)	Ref	10.9 (7.0– 14.9)	Ref	26.7 (17.8– 35.7)	Ref
Asthma	23.9 (14.9– 32.8)	6.51 (4.07– 10.41)	92.4 (66.3– 118.6)	8.47 (5.68– 12.65)	253.0 (188.2– 317.7)	9.49 (6.43– 13.99)
No CHF	5.1 (3.3–7.9)	Ref	22.0 (16.2– 27.7)	Ref	58.1 (44.5– 71.8)	Ref
CHF	205.8 (90.5–424.9)	40.19 (15.62–105.89)	164.9 (59.4– 270.3)	7.37 (3.76– 14.43)	312.8 (164.0– 461.7)	5.31 (3.18– 8.87)
No CAD	5.3 (3.7– 6.9)	Ref	18.3 (13.5– 23.1)	Ref	58.6 (44.4– 72.8)	Ref
CAD	81.3 (10.5– 152.1)	14.63 (5.82– 36.79)	101.5 (59.3– 143.8)	5.51 (3.55– 8.57)	147.2 (98.3– 196.1)	2.50 (1.76– 3.57)
No CVA	‡		24.9 (19.0– 30.8)	Ref	74.0 (57.4– 90.7)	Ref
CVA			67.1 (-56.2– 190.4)	2.26 (0.49– 10.41)	125.8 (17.7– 233.9)	1.62 (0.68– 3.88)
No DM	4.7 (3.3– 6.1)	Ref	24.6 (17.7– 31.6)	Ref	64.0 (47.5– 80.5)	Ref
DM	28.4 (12.4– 44.4)	6.00 (3.35– 10.76)	28.0 (16.1– 39.9)	1.13 (0.70– 1.83)	105.1 (65.9– 144.4)	1.63 (1.07– 2.49)
No ESRD	‡		24.0 (18.1– 29.9)	Ref	75.3 (59.2– 91.5)	Ref
ESRD			163.0 (24.6– 301.3)	6.60 (2.86– 15.24)	103.4 (-31.2– 238.0)	1.23 (0.32– 4.78)

*COPD; Chronic obstructive pulmonary disease, CHF; congestive heart failure, CAD; coronary artery disease, CVA; cerebrovascular accident, DM; diabetes mellitus, ESRD end-stage renal disease.

† Incidence rate ratio (IRR) compares RSV hospitalisation rates between adults with versus without each CMC

‡ Modelled COPD, CVA, and ESRD data was not included for adults aged 18–49 years

7.5 Discussion

The increasing recognition of RSV as an important cause of morbidity and mortality in adults has encouraged development of RSV vaccine candidates for this population [152, 196]. Prior to the introduction of such interventions, more comprehensive estimates of RSV disease burden in adults by key CMC strata are needed to establish high-risk groups as well as to assess the potential impact and cost-effectiveness of interventions in these populations.

In this study, we report population-based risk estimates of seasonal RSV-associated ARI hospitalisations among adults with CMCs. In age-stratified analyses, we found RSV hospitalisation risk to be higher among adults with certain CMCs compared to those without the corresponding condition. The highest relative risks of RSV hospitalisation were seen among adults with COPD, CHF, or asthma. Risk varied by CMC and age group. The risk of RSV hospitalisation was increased in all age groups for COPD, asthma, CHF, and CAD. In contrast, for DM and ESRD, a significant risk of RSV hospitalisation was only present in certain age groups. CVA was not found to be associated with RSV hospitalisation in our analysis. Finally, among hospitalised RSV positive adults, CHF and COPD were found to be independently associated with increased length of hospital stay.

Our findings are consistent with the seminal Falsey et al. study that found a higher prevalence of RSV-associated outpatient visits and hospital admissions in adults with chronic cardiopulmonary conditions compared to healthy elderly adults [81]. Previous studies of patients with chronic lung diseases have often grouped different diseases together or have focused on older adults or on adults with COPD [81, 206], making it difficult to ascertain the impact of specific chronic respiratory conditions by age group. In our study, we show that asthma also increases the risk of RSV hospitalisation, even among younger adults.

Similar to previous studies investigating the risk of cardiovascular conditions on RSV-associated disease and healthcare utilisation [81, 207, 208], we show that both CHF and CAD increase the risk of RSV-associated ARI hospitalisation. This risk was particularly high among adults aged 18–49 years, highlighting this sub-population as an important group for RSV preventative strategy prioritisation. In contrast, we found that CVA did not increase the risk of RSV hospitalisation among adults aged 50 years or more. This was similar to findings from a related influenza study [202] and is possible that reliance on ICD-10 discharge data to determine CVA status in our methodology did not allow for sufficient capture of CVA disease and its associated RSV hospitalisation risk.

To our knowledge, this is the first study to provide population-based incidence and risk of RSV-associated ARI hospitalisation among adults with DM or ESRD. We found presence of DM or ESRD was associated with an increased risk of RSV hospitalisation among some age groups (DM: 14–49 and 65–80 years; ESRD: 50–64 years), however, in general RSV hospitalisation rates were higher for older adults with cardiopulmonary conditions than for those with DM or ESRD. The overall number of RSV hospitalisations in patients with ESRD was low and may have contributed to the statistical insignificance seen for this association.

While the prevalence of all CMCs was higher in older adults, as was the overall incidence of RSV hospitalisations, the risk of RSV hospitalisations in adults with CMCs compared to those without (i.e. IRRs) did not appear to increase with age. In fact, the risks of RSV hospitalisation associated with presence of CMCs were often highest in the 18–49 years age group. Among older adults, frailty, immunosenescence, and/or the presence of multiple CMCs may reduce differences in hospitalisation rates between those with or without a specific CMC, potentially explaining the higher IRRs seen in younger adults. Such findings have implications for identifying RSV vaccine priority groups, suggesting that all older adults could be considered at risk of severe RSV-

associated outcomes and that younger adults with CMCs, particularly asthma, CHF, and CAD should also be considered.

The major strengths of our study include its ability to estimate the risk of RSV hospitalisation at a population-level, thus providing a more accurate representation of RSV disease burden compared to analysing hospitalised patients alone, which can be influenced by selection bias (Berkson's bias) that occurs when both exposure and outcome are associated with hospitalisation [209]. Other strengths of our study include expanding the types of CMCs studied and studying CMCs within specific age groups. Finally, our use of administrative data and statistical modelling to classify presence or absence of individual CMCs is more accurate than relying on ICD-10 codes alone and resulted in CMC prevalence comparable to national estimates [153].

Nonetheless, our study has important limitations. Firstly, not all ARI patients were tested for RSV, resulting in underestimation of RSV hospitalisation rates. However, our primary focus was to present the relative risk of RSV-associated ARI hospitalisation posed by specific CMCs rather than incidence due to these conditions, which did not change after accounting for non-testing (Table 7.2–7.3). Secondly, the low numbers of RSV hospitalisations prevented further stratification of rates and rate ratios of each CMC by age and ethnicity. Such analyses would have been valuable given the observed ethnic inequalities in RSV hospitalisations among NZ adults [203] (Chapter 6). Additionally, the low number of RSV-confirmed ICU admissions and deaths in our study prevented investigation of the role of CMCs on such severe outcomes. Finally, there were insufficient data to investigate other CMCs such as immunosuppression, chronic liver disease, or disabling neurologic disease, which are considered priorities for influenza vaccination [210]. Consequently, we did not assess the impact of combinations of CMCs on hospitalisation rates. It is likely that the presence of multiple CMCs could alter the risk of RSV-associated ARI hospitalisation.

7.6 Conclusions

In summary, we show that adults with specific CMCs experience a significantly increased risk of RSV-associated ARI hospitalisation. While RSV hospitalisation rates increase with age, younger adults with CMCs experience a markedly increased risk for RSV hospitalisation compared with younger adults without these CMCs. Our findings support the prioritisation and investigation of RSV vaccine impact in these specific populations.

8 Modelling the impact of respiratory syncytial virus vaccine and immunoprophylaxis strategies in New Zealand

8.1 Preface

This chapter addresses Objective five of this thesis: to assess the health impact of a potential RSV maternal vaccine or a seasonal infant immunoprophylaxis using mathematical modelling. The research presented in this chapter is currently under review.

Prasad N, Read J.M, Jewell C, Waite B, Trenholme AA, Grant CC, Huang QS, Newbern EC, Hogan AB. Modelling the impact of respiratory syncytial virus (RSV) vaccine and immunoprophylaxis strategies in New Zealand. Under review

I designed the study with guidance from my supervisors and co-authors. I wrote the code for the model and carried out model fitting with guidance from co-authors (Read JM, Jewell C, Hogan AB). I also drafted the initial manuscript. All co-authors reviewed and approved the final manuscript.

8.2 Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute respiratory tract infections (ARI) in children worldwide [3, 4]. In New Zealand (NZ), RSV accounts for approximately 40% of ARI hospitalisations among children aged less than five years [189]. Almost all children have an RSV infection by two years of age [19], with infants aged less than six months experiencing the greatest burden of severe disease [4]. Immunoprophylaxis through the neutralizing monoclonal antibody (mAb) palivizumab is currently the only licensed preventative strategy for RSV.

However, due to its requirement of monthly dosing and high costs, its use is limited to high-risk infants [211] and rarely used in NZ [101].

There are several RSV vaccines and new mAbs in clinical trials and preclinical development [104]. The RSV F nanoparticle maternal vaccine is currently the most advanced vaccine candidate in clinical development. In an initial Phase 3 trial, the vaccine did not meet its primary endpoint, of reducing medically significant RSV lower respiratory tract infections (LRTI), despite an overall efficacy of 39.4% (95% confidence intervals [CI], 5.3–61.2) against medically significant RSV LRTI for 90 days after vaccination. However, the vaccine did meet secondary objectives of reducing RSV LRTI hospitalisations and severe hypoxemia, with benefits through to 180 days after vaccination. Consequently, the vaccine is undergoing an additional Phase 3 trial [105]. In terms of new immunoprophylaxis through mAbs, the candidate MEDI8897, which is administered once seasonally, demonstrated a 70.0% (95% CI 51.9–90.3) efficacy in reducing medically-significant RSV LRTI in healthy pre-term infants over the 150 day follow-up period [106]. It is currently being trialled for use in both pre-term and full-term infants.

Such recent advancements highlight the need to update the mathematical models used to evaluate potential RSV preventative strategies. Several mathematical modelling studies of RSV vaccination and mAbs have been published [118, 119, 127, 130, 212]. In particular, Cromer et al. [118] and Rainisch et al. [119] compared the impact of RSV maternal vaccination and mAbs, using a cohort model and decision tree model respectively. While informative, these studies assumed effectiveness values that were higher than reported from recent clinical trials. Additionally, differences in climate, demographics, and contact patterns can impact RSV transmission [86], emphasising the need to develop and fit RSV models to specific areas. Finally, as RSV is not a notifiable disease, surveillance methods and RSV burden data can also vary considerably by location [4].

In this study, we estimated the impact of an RSV maternal vaccine and a seasonal infant mAb on RSV hospitalisations, under varying levels of coverage, duration of protection, and effectiveness, using a mathematical model fitted to population-based, active hospital surveillance data collected in Auckland, NZ.

8.3 Methods

Note: Details in section 8.3.1 have been previously mentioned in section 2.2.

8.3.1 Setting and population-based data

Data for this study were sourced from the Southern Hemisphere Influenza Vaccine Effectiveness and Research (SHIVERS) project [132]. SHIVERS was an active ARI surveillance project conducted in two public hospitals serving the central, southern, and eastern regions of Auckland from 30th April 2012 to 31st December 2015. The SHIVERS hospital sites provide all respiratory inpatient services for the population residing in these regions. The Auckland region is a predominantly urban area with a sub-tropical climate. According to Statistics NZ population estimates, the central, southern, and eastern regions of Auckland have a combined population of approximately one million including 36,000 children aged less than two years [133]. Ethical approval for the SHIVERS project was obtained from the NZ Health and Disabilities Ethics Committee (NTX/11/11/102).

During the study, research nurses reviewed daily records to identify all admissions with suspected ARI. All patients meeting the WHO severe acute respiratory infection (SARI) case definition (cough and fever within the last 10 days) were included [134]. Study nurses obtained consent and collected nasopharyngeal swabs from cases. To provide an understanding of the respiratory virus burden among ARI patients not meeting the SARI definition (cough and/or fever but not both within last 10 days), from 2013 to 2015 study nurses enrolled non-SARI respiratory patients.

Sampling of non-SARI respiratory patients in 2013 was during the peak winter/spring period (12th August to 6th October) and included weekly selection of two paediatric and two adult inpatients who fitted the non-SARI respiratory definition at each facility. During 2014 and 2015, this surveillance was extended to randomly enrol approximately six paediatric and six adult non-SARI respiratory patients weekly at each facility between April and September.

In addition to respiratory virus test results generated by the SHIVERS project, hospital laboratories provided results from clinical-ordered tests performed on ARI patients during the study period. These results were included after validation of the hospital PCR assay performance (Appendix 1.1). Collected specimens were tested for RSV using the United States Centers for Disease Control and Prevention real-time reverse transcription (RT)-PCR protocol [135, 136] at the Institute of Environmental Science and Research, or using the AusDiagnostic PCR protocol and real-time PCR assays at hospital laboratories [137].

To account for changes in testing criteria and to correct for non-testing among ARI patients, we applied the proportion positive for RSV among SARI and non-SARI cases to non-tested SARI and non-SARI patients for each age group by study week.

8.3.2 Model structure and parameters

We modelled RSV transmission in a population using a deterministic, compartmental Susceptible (S) – Exposed (E) – Infectious (I) – Recovered (R) – Susceptible (S) transmission (SEIRS) model, similar to work by Moore et al. and Hogan et al. [89, 130]. The model divided the population into four age groups: children aged less than three months (S_1, E_1, I_1, R_1), children aged 3–5 months (S_2, E_2, I_2, R_2), children aged 6–23 months (S_3, E_3, I_3, R_3), and individuals aged two years and older (S_4, E_4, I_4, R_4).

According to Statistics NZ population estimates, there are on average 279 live births per week in Auckland [213], informing the birth rate used in the model. The average life expectancy for an Auckland resident is 81 years [198]. We assumed that deaths only took place in the older age group, thus the weekly ageing/death rate in age group 4 ($\eta 4$) was equal to 1/ (52*79). The weekly ageing rates from age group 1 to 2, age group 2 to 3, and age group 3 to 4 were 1/13, 1/13, and 1/78 respectively. Given the seasonal fluctuations in RSV transmission observed in temperate climates and with annual epidemics occurring between April – September [189] in NZ, we captured seasonality using a cosine function [86].

Mixing between age groups was based on NZ-specific contact rates as reported by Prem et al. [112]. As these rates were in five-year age groups, we used more finely stratified contact data for children aged less than two years as reported by Jan van Hoek et al. [214].

Epidemiological parameters were based on data published in the peer reviewed literature or estimated during model fitting (Table 1). Drawing on previous observation and modelling studies, we assumed average values for a latent period ($1/\sigma$) of four days [25, 120], a duration of infectiousness ($1/\gamma$) of ten days [26, 120] and immunity following infection ($1/\nu$) of 230 days [46, 89]. We assumed that infants are born with temporary immunity to RSV infection though transplacental transfer of antibodies, however, the level of protection conferred is uncertain [20, 21, 215]. Informed by data from serological studies of RSV specific antibodies [44, 45], we initially reduced susceptibility to infection by 66% in infants younger than three months ($\alpha_{1=}$ 0.33) and included this as a fitted parameter. As this parameter is derived from limited observations, we also assessed the impact on fitted parameters when assuming no natural maternally derived immunity in the model.

Studies suggest that susceptibility to RSV infections decreases with age due to development of immunity following RSV exposure and/or maturation of the immune and respiratory system [45, 47, 216]. Given the limitations of our data, and to avoid over-parameterising our model, we chose to focus on age and its effect on RSV susceptibility. Like RSV-specific maternal antibodies, the level of protection from RSV infection acquired with prior infection and/or age is uncertain. Based on serological and previous modelling studies [45, 217], we assumed infants aged 3–5 months were 100% susceptible to RSV infection and included a reduced susceptibility parameter in the 6–23 month and 24 months and older age groups. We initially reduced susceptibility to infection by 10% in infants aged 6–23 months (α_3=0.90) and by 50% in those aged 24 months or older (α_4=0.50) and allowed these parameters to vary during model fitting.

8.3.3 Model fitting

Our model output represents the total number of RSV cases in the population while our data are RSV hospitalisations based on population-based surveillance. We therefore scaled our model results by parameters P_1, P_2, P_3, and P_4 which represent the proportion of RSV infections in each age group that are hospitalised and detected with the virus. This was estimated as the sum of all cases in the data for an age group divided by the sum of the modelled incidence over 209 weeks, which was the SHIVERS surveillance time period.

We estimated parameters β_0, β_1, φ and α_1, α_3, α_4 by fitting the model to weekly hospitalisations for the four age groups in our model. We developed the model in R software [218]. Model fitting was done through maximum likelihood estimation using the bbmle package [219]. We assumed that the number of RSV hospitalisations each week represented Poisson samples with expectation pI, where p is probability of a case being hospitalised and detected with RSV, and I is the true incidence in each age group. Confidence intervals for fitted parameter estimates were based on the quadratic approximation at the maximum likelihood estimate [219].

8.3.4 Model with vaccination or immunoprophylaxis

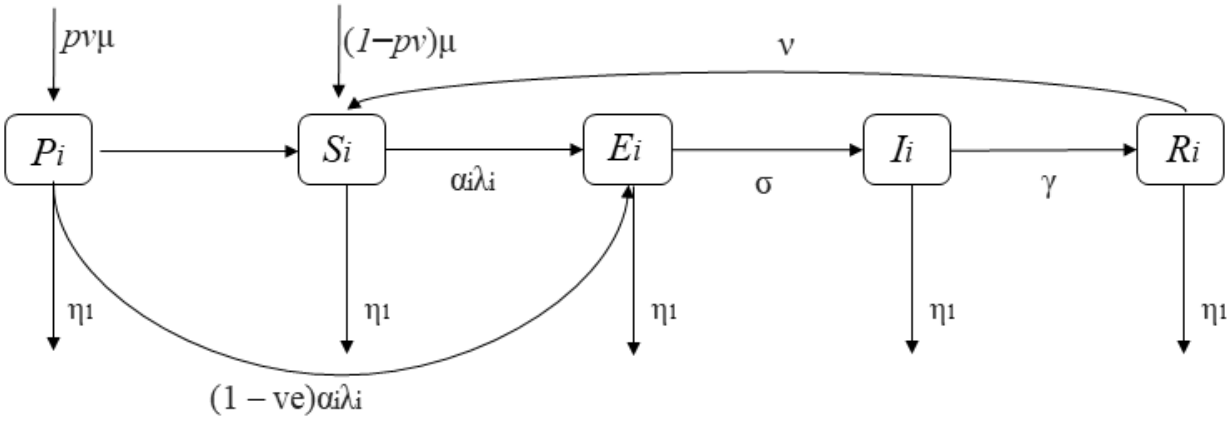
We considered two RSV preventative strategies: first, a maternal vaccination where infants are born with or without maternal vaccine derived protection, and secondly, a seasonal immunoprophylaxis in the form of a single dose mAb administered to infants aged less than six months.

To investigate the impact of maternal vaccination, we assumed the duration of protection from a maternal vaccine to be 180 days, which was the duration of follow-up to assess efficacy in the recent RSV-F maternal vaccine trial [105]. Immunised infants were born into a P_i group, and had susceptibility reduced by factor 1-*ve*, where *ve* is a proxy of a vaccine effectiveness. Informed by results from the RSV-F phase 3 trial [105], we tested a default scenario where effectiveness waned over time starting at 40% effectiveness and halving after 90 days, however, we also tested scenarios where vaccine effectiveness was 50% initially and then waned to 30% after 90 days, and where effectiveness remained at 40% throughout the 180 day period.

To investigate the impact of an RSV mAb, we assumed infants aged less than six months were administered the mAb one month prior to or during the NZ RSV season. The duration of protection from a mAb was 150 days, which was the duration of follow-up used to assess efficacy in the recent MEDI8897 trial [106]. Like maternal vaccination, immunised infants had susceptibility reduced by factor 1-ve, based on mAb effectiveness. We tested a default scenario of 60% effectiveness. This was 10% lower than the reported efficacy from the recent MEDI8897 phase 3 trial [106], to account for effectiveness in all infants not just pre-term infants who have a greater risk of severe RSV-associated outcomes [66]. However, we also tested scenarios where mAb effectiveness was 50% and 70%.

For both preventative strategies, the default coverage was set at 50%, informed by recent maternal vaccination coverage data from NZ [220, 221]. However, we also tested scenarios of 30% and 80% coverage. A schematic representation of the model is presented in Figure 8.1 while all model equations are provided in section 8.3.5. The R code for the models and fitting process are provided in Appendix 4.5.

a. Maternal vaccine



b. Seasonal mAb

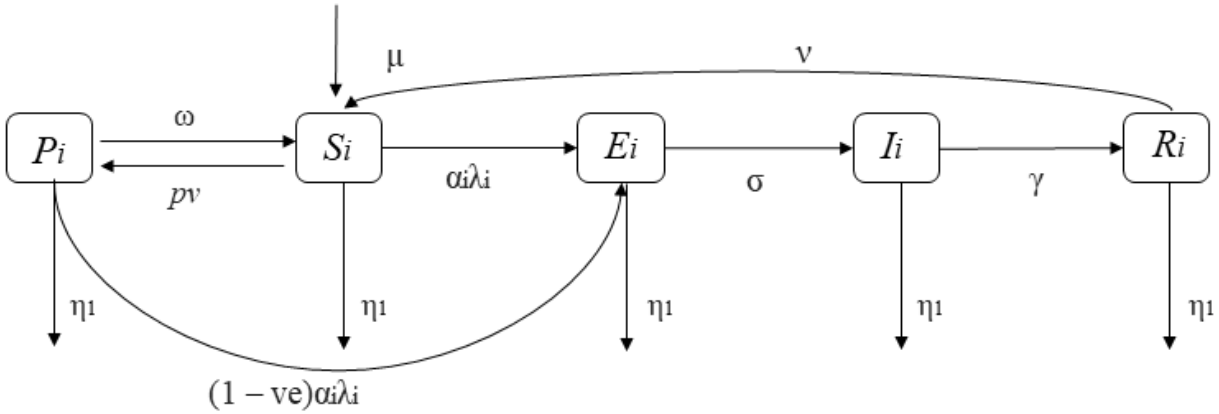


Figure 8.1 Schematic diagram for model assessing impact of a maternal RSV vaccine or a seasonal newborn mAb

The compartments S_i, E_i, I_i, R_i, and P_i represent the susceptible, exposed, infectious, recovered, and protected populations respectively for each age group *i*. The parameters λ_i represent transmission rates in each age group *i* while parameters σ, γ , and ν represent the latent, recovery, and immunity rates respectively. Reduced susceptibility to infection due to either maternally derived antibodies (i = 1) or with age (i = 3,4) are represented by α_i. Vertical lines represent births and ageing. Births and ageing are shown for the youngest age group only for visual clarity. The parameter *pv* represents the proportion vaccinated or administered a mAb. Infants protected by immunisation or mAb have susceptibility to infection reduced by factor 1 – *ve*.

8.3.5 Model equations

Model equations (without intervention)

The transmission rate was calculated as:

$$\lambda_i = \beta_0(1 + \beta_1 \cos(\frac{2\pi t}{52} + \varphi))\frac{1}{N_i}\sum_{j=1}^{4} M_{i,j}\, I_j \qquad (2.0)$$

This was chosen to represent the distinct seasonality of RSV. Similar seasonal forcing has been shown to accurately model RSV seasonality in temperate climates and accounts for the increase in observed RSV infections during winter periods [89, 120]. In the equation above β_0 is the transmission coefficient, β_1 is the amplitude of seasonal forcing, and φ represents the phase shift. The mixing matrix $M_{i,j}$ is the number of contacts that an individual in age group *j* has with individuals in age group *i*.

In the equations below, λ_i represents transmission rates in each age group *i* while parameters σ, γ, and ν represent the latent, recovery, and immunity rates respectively. Live births are represented by μ. Reduced susceptibility to infection due to maternally derived antibodies is represented by α_1. while reduced suseptibility due to development of immunity following RSV exposure and/or maturation of the immune and respiratory systems are represented by α_3, α_4. Ageing is represented by η_i.

$$\frac{dS_1}{dt} = \mu - \alpha_1\lambda_1 S_1 - \eta_1 S_1 + \nu R_1 \quad (2.1)$$

$$\frac{dE_1}{dt} = \alpha_1\lambda_1 S_1 - \eta_1 E_1 - \sigma E_1 \quad (2.2)$$

$$\frac{dI_1}{dt} = \sigma E_1 - \eta_1 I_1 - \gamma I_1 \quad (2.3)$$

$$\frac{dR_1}{dt} = \gamma I_1 - \eta_1 R_1 - \nu R_1 \quad (2.4)$$

$$\frac{dS_2}{dt} = \eta_1 S_1 - \lambda_2 S_2 - \eta_2 S_2 + \nu R_2 \quad (2.5)$$

$$\frac{dE_2}{dt} = \eta_1 E_1 + \lambda_2 S_2 - \eta_2 E_2 - \sigma E_2 \quad (2.6)$$

$$\frac{dI_2}{dt} = \eta_1 I_1 + \sigma E_2 - \eta_2 I_2 - \gamma I_2 \quad (2.7)$$

$$\frac{dR_2}{dt} = \eta_1 R_1 + \gamma I_2 - \eta_2 R_2 - \nu R_2 \quad (2.8)$$

$$\frac{dS_3}{dt} = \eta_2 S_2 - \alpha_3\lambda_3 S_3 - \eta_3 S_3 + \nu R_3 \quad (2.9)$$

$$\frac{dE_3}{dt} = \eta_2 E_2 + \alpha_3\lambda_3 S_3 - \eta_3 E_3 - \sigma E_3 \quad (3.0)$$

$$\frac{dI_3}{dt} = \eta_2 I_2 + \sigma E_3 - \eta_3 I_3 - \gamma I_3 \quad (3.1)$$

$$\frac{dR_3}{dt} = \eta_2 R_2 + \gamma I_3 - \eta_3 R_3 - \nu R_3 \quad (3.2)$$

$$\frac{dS_4}{dt} = \eta_3 S_3 - \alpha_4 \lambda_4 S_4 - \eta_4 S_4 + \nu R_4 \quad (3.3)$$

$$\frac{dE_4}{dt} = \eta_3 E_3 + \alpha_4 \lambda_4 S_4 - \eta_4 E_4 - \sigma E_4 \quad (3.4)$$

$$\frac{dI_4}{dt} = \eta_3 I_3 + \sigma E_4 - \eta_4 I_4 - \gamma I_4 \quad (3.5)$$

$$\frac{dR_4}{dt} = \eta_3 R_3 + \gamma I_4 - \eta_4 R_4 - \nu R_4 \quad (3.6)$$

Model equations (with maternal vaccination)

Immunised infants had susceptibility reduced by factor 1-*ve*, where *ve* represents maternal vaccine effectiveness. The transmission rate for individuals in age group i was calculated as:

$$\lambda = \beta_0(1 + \beta_1 \cos(\frac{2\pi t}{52} + \varphi))\frac{1}{N_i}\sum_{j=1}^{4} M_{i,j} I_j \quad (3.7)$$

The proportion vaccinated is represented by *pv*. Protection from vaccination is assumed to last for up to 180 days (six months), therefore *ve* was set to 0 in age groups 3 and 4. The model equations are:

$$\frac{dS_1}{dt} = (1 - pv)\mu - \alpha_1\lambda_1 S_1 - \eta_1 S_1 + \nu R_1 \quad (3.8)$$

$$\frac{dE_1}{dt} = \alpha_1\lambda_1 S_1 + (1 - ve)\alpha_1\lambda_1 P_1 - \eta_1 E_1 - \sigma E_1 \quad (3.9)$$

$$\frac{dI_1}{dt} = \sigma E_1 - \eta_1 I_1 - \gamma I_1 \quad (4.0)$$

$$\frac{dR_1}{dt} = \gamma I_1 - \eta_1 R_1 - \nu R_1 \quad (4.1)$$

$$\frac{dP_1}{dt} = (pv)\mu - (1 - ve)\alpha_1\lambda_1 P_1 - \eta_1 P_1 \quad (4.2)$$

$$\frac{dS_2}{dt} = \eta_1 S_1 - \lambda_2 S_2 - \eta_2 S_2 + \nu R_2 \quad (4.3)$$

$$\frac{dE_2}{dt} = \eta_1 E_1 + \lambda_2 S_2 + (1 - ve)\lambda_2 P_2 - \eta_2 E_2 - \sigma E_2 \quad (4.4)$$

$$\frac{dI_2}{dt} = \eta_1 I_1 + \sigma E_2 - \eta_2 I_2 - \gamma I_2 \quad (4.5)$$

$$\frac{dR_2}{dt} = \eta_1 R_1 + \gamma I_2 - \eta_2 R_2 - \nu R_2 \quad (4.6)$$

$$\frac{dP_2}{dt} = \eta_1 P_1 - (1 - ve)\lambda_2 P_2 - \eta_2 P_2 \quad (4.7)$$

$$\frac{dS_3}{dt} = \eta_2 S_2 - \alpha_3 \lambda_3 S_3 - \eta_3 S_3 + \nu R_3 \quad (4.8)$$

$$\frac{dE_3}{dt} = \eta_2 E_2 + \alpha_3 \lambda_3 S_3 + (1 - ve)\alpha_3 \lambda_3 P_3 - \eta_3 E_3 - \sigma E_3 \quad (4.9)$$

$$\frac{dI_3}{dt} = \eta_2 I_2 + \sigma E_3 - \eta_3 I_3 - \gamma I_3 \quad (5.0)$$

$$\frac{dR_3}{dt} = \eta_2 R_2 + \gamma I_3 - \eta_3 R_3 - \nu R_3 \quad (5.1)$$

$$\frac{dP_3}{dt} = \eta_2 P_2 - (1 - ve)\alpha_3 \lambda_3 P_3 - \eta_3 P_3 \quad (5.2)$$

$$\frac{dS_4}{dt} = \eta_3 S_3 - \alpha_4 \lambda_4 S_4 - \eta_4 S_4 + \nu R_4 \tag{5.3}$$

$$\frac{dE_4}{dt} = \eta_3 E_3 + \alpha_4 \lambda_4 S_4 + (1 - ve)\alpha_4 \lambda_4 P_4 - \eta_4 E_4 - \sigma E_4 \tag{5.4}$$

$$\frac{dI_4}{dt} = \eta_3 I_3 + \sigma E_4 - \eta_4 I_4 - \gamma I_4 \tag{5.5}$$

$$\frac{dR_4}{dt} = \eta_3 R_3 + \gamma I_4 - \eta_4 R_4 - \nu R_4 \tag{5.6}$$

$$\frac{dP_4}{dt} = \eta_3 P_3 - (1 - ve)\alpha_4 \lambda_4 P_4 - \eta_4 P_4 \tag{5.7}$$

Model equations (with seasonal mAb)

Immunised infants had susceptibility reduced by factor $1 - ve$, where ve is a proxy of a mAb effectiveness. The transmission rate for immunised children was calculated as:

$$\lambda = \beta_0(1 + \beta_1 \cos(\frac{2\pi t}{52} + \varphi)) \frac{1}{N_i} \sum_{j=1}^{4} M_{i,j} I_j \quad (5.8)$$

The proportion immunised is represented by pv. To investigate the impact of a seasonal mAb, equations were numerically solved with a condition that $pv = pv$ for weeks one month prior to or within the winter season period (where the winter season was defined as weeks 18–39 of each year), and $pv = 0$ otherwise. Protection from a mAb is assumed to last for up to 150 days (five months) after administration, therefore mAb effectiveness was set to 0 in age group 4. The model equations are:

$$\frac{dS_1}{dt} = \mu - \alpha_1 \lambda_1 S_1 - \eta_1 S_1 + \nu R_1 - pv S_1 + \omega P_1 \quad (5.9)$$

$$\frac{dE_1}{dt} = \alpha_1 \lambda_1 S_1 + (1 - ve)\alpha_1 \lambda_1 P_1 - \eta_1 E_1 - \sigma E_1 \quad (6.0)$$

$$\frac{dI_1}{dt} = \sigma E_1 - \eta_1 I_1 - \gamma I_1 \quad (6.1)$$

$$\frac{dR_1}{dt} = \gamma I_1 - \eta_1 R_1 - \nu R_1 \quad (6.2)$$

$$\frac{dP_1}{dt} = pvS_1 - (1-ve)\alpha_1\lambda_1 P_1 - \eta_1 P_1 - \omega P_1 \quad (6.3)$$

$$\frac{dS_2}{dt} = \eta_1 S_1 - \lambda_2 S_2 - \eta_2 S_2 + \nu R_2 - pvS_2 + \omega P_2 \quad (6.4)$$

$$\frac{dE_2}{dt} = \eta_1 E_1 + \lambda_2 S_2 + (1-ve)\lambda_2 P_2 - \eta_2 E_2 - \sigma E_2 \quad (6.5)$$

$$\frac{dI_2}{dt} = \eta_1 I_1 + \sigma E_2 - \eta_2 I_2 - \gamma I_2 \quad (6.6)$$

$$\frac{dR_2}{dt} = \eta_1 R_1 + \gamma I_2 - \eta_2 R_2 - \nu R_2 \quad (6.7)$$

$$\frac{dP_2}{dt} = pvS_2 + \eta_1 P_1 - (1-ve)\lambda_2 P_2 - \eta_2 P_2 - \omega P_2 \quad (6.8)$$

$$\frac{dS_3}{dt} = \eta_2 S_2 - \alpha_3\lambda_3 S_3 - \eta_3 S_3 + \nu R_3 + \omega P_3 \quad (6.9)$$

$$\frac{dE_3}{dt} = \eta_2 E_2 + \alpha_3\lambda_3 S_3 + (1-ve)\alpha_3\lambda_3 P_3 - \eta_3 E_3 - \sigma E_3 \quad (7.0$$

$$\frac{dI_3}{dt} = \eta_2 I_2 + \sigma E_3 - \eta_3 I_3 - \gamma I_3 \quad (7.1)$$

$$\frac{dR_3}{dt} = \eta_2 R_2 + \gamma I_3 - \eta_3 R_3 - \nu R_3 \quad (7.2)$$

$$\frac{dP_3}{dt} = \eta_2 P_2 - (1 - ve)\alpha_3 \lambda_3 P_3 - \eta_3 P_3 - \omega P_3 \quad (7.3)$$

$$\frac{dS_4}{dt} = \eta_3 S_3 - \alpha_4 \lambda_4 S_4 - \eta_4 S_4 + \nu R_4 + \omega P_4 \quad (7.4)$$

$$\frac{dE_4}{dt} = \eta_3 E_3 + \alpha_4 \lambda_4 S_4 + (1 - ve)\alpha_4 \lambda_4 P_4 - \eta_4 E_4 - \sigma E_4 \quad (7.5)$$

$$\frac{dI_4}{dt} = \eta_3 I_3 + \sigma E_4 - \eta_4 I_4 - \gamma I_4 \quad (7.6)$$

$$\frac{dR_4}{dt} = \eta_3 R_3 + \gamma I_4 - \eta_4 R_4 - \nu R_4 \quad (7.7)$$

$$\frac{dP_4}{dt} = \eta_3 P_3 - (1 - ve)\alpha_4 \lambda_4 P_4 - \eta_4 P_4 - \omega P_4 \quad (7.8)$$

8.3.6 Model outputs

The number and proportion of hospitalisations averted in children aged less than two years was estimated, stratified by age group, for each of the vaccination and mAb default strategies, and when coverage and effectiveness levels were varied. We assessed the public health impact during the first ten years following vaccine or mAb introduction, as well as the impact once the intervention was well-established within the population. Uncertainty in model outputs was estimated from the distribution of 500 model simulations (Figure 8.4). Each simulation used a

different combination of parameter values with fitted parameters values sampled from the uncertainty range obtained from maximum likelihood estimation (Table 8.1).

8.4 Results

8.4.1 Model fit and outcomes

Our fitted base RSV SEIRS model captured the characteristics of RSV hospitalisations by time and age group in Auckland (Figure 8.2). Fitted parameter values with 95% CIs are shown in Table 8.1. When testing the assumption of no natural maternally derived protection, we found that our model was unable to fit to the data. Both the base and intervention model outputs replicated the seasonal pattern of RSV infection observed in Auckland (Figure 8.3).

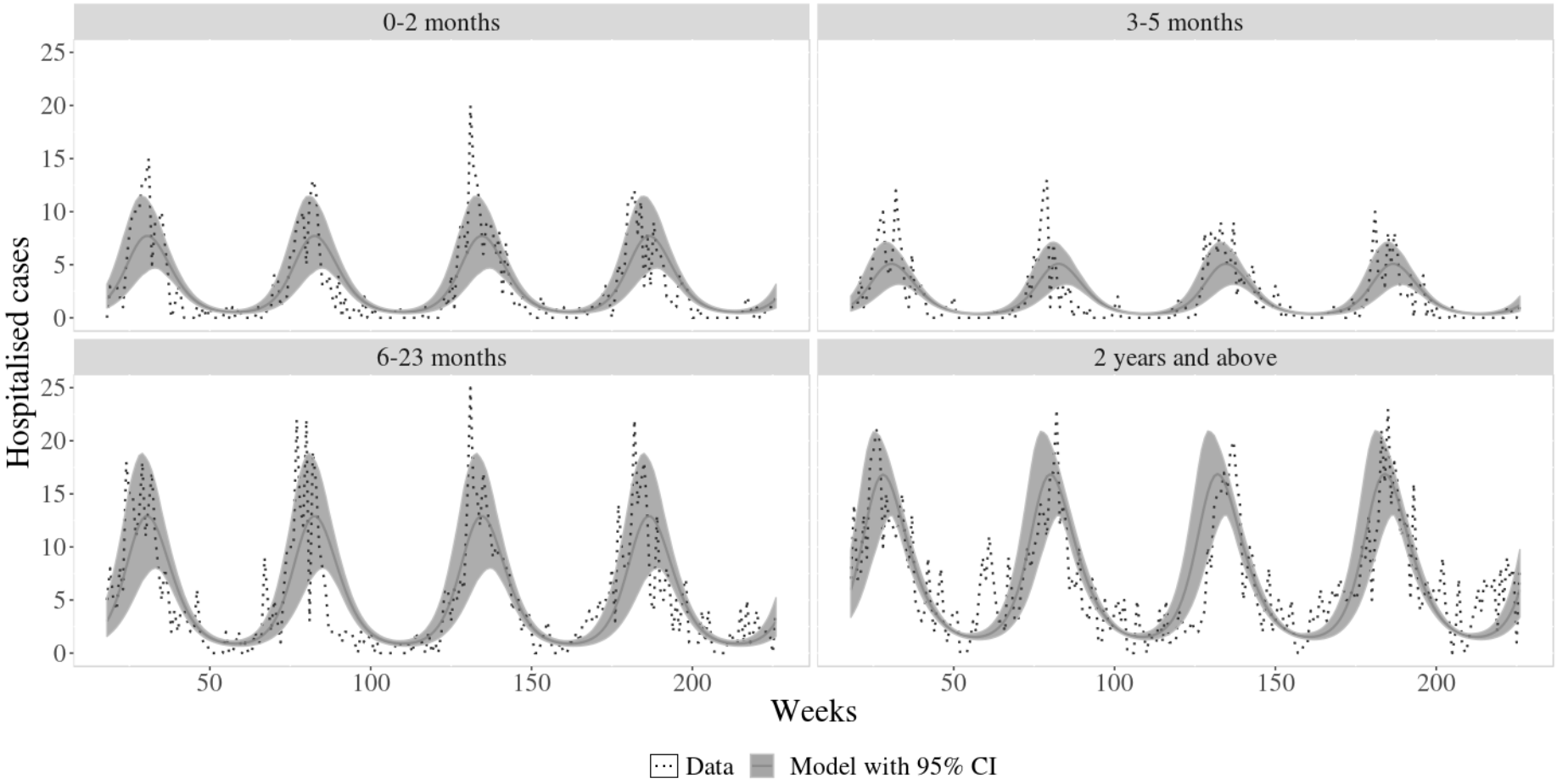


Figure 8.2 Model output with 95% confidence intervals (CI) against RSV hospitalisation data (dots) for each age group.

The shaded area represents 95% CI for model outputs which were estimated from the distribution of 500 model simulations. Each simulation used a different combination of parameter values based on the fitted parameter uncertainty from maximum likelihood estimation, as shown in Table 8.1.

Table 8.1 Fixed and fitted model parameter values

Parameters	Definition	Fixed/Fitted	Value(s) with 95% CIs for fitted parameters	Reference
$1/\sigma$	Latent period (days)	Fixed	4	[25, 120]
$1/\gamma$	Infectious period (days)	Fixed	10	[26, 120]
$1/\nu$	Duration of immunity following infection (days)	Fixed	230	[46, 89]
β_0	Transmission coefficient	Fitted	0.032 (0.030 – 0.035)	
β_1	Amplitude of seasonal forcing	Fitted	0.191 (0.180 – 0.203)	
φ	Phase of seasonal forcing	Fitted	-0.707 (-0.708 – -0.797)	
α_1	Reduced susceptibility in 0–2 months age group due to RSV-natural maternal antibodies	Fitted	0.329 (0.289 – 0.372)	[44, 45]
α_3	Reduced susceptibility in 6–23 months age group due to development of immunity/exposure	Fitted	0.918 (0.804 – 1.00)	[45, 217]
α_4	Reduced susceptibility in ≥24 months age group due to development of immunity/exposure	Fitted	0.345 (0.304 – 0.398)	[45, 217]
P_1	Proportion of infected that are hospitalised and detected in age group 0–2 months		0.69	
P_2	Proportion of infected that are hospitalised and detected in age group 3–5 months		0.09	
P_3	Proportion of infected that are hospitalised and detected in age group 6–23 months		0.04	
P_4	Proportion of infected that are hospitalised and detected in age group ≥24 months		0.0004	
pv	Vaccine/mAb coverage		50%*	[220, 221]
$1/\omega$	Duration of vaccine induced protection (days) Duration of mAb‡ induced protection (days)		180 150	[46, 105, 106]
ve	Vaccine effectiveness mAb‡ effectiveness		40% – 20%* 60%*	[105, 106]

* Default values

‡ mAb; monoclonal antibody

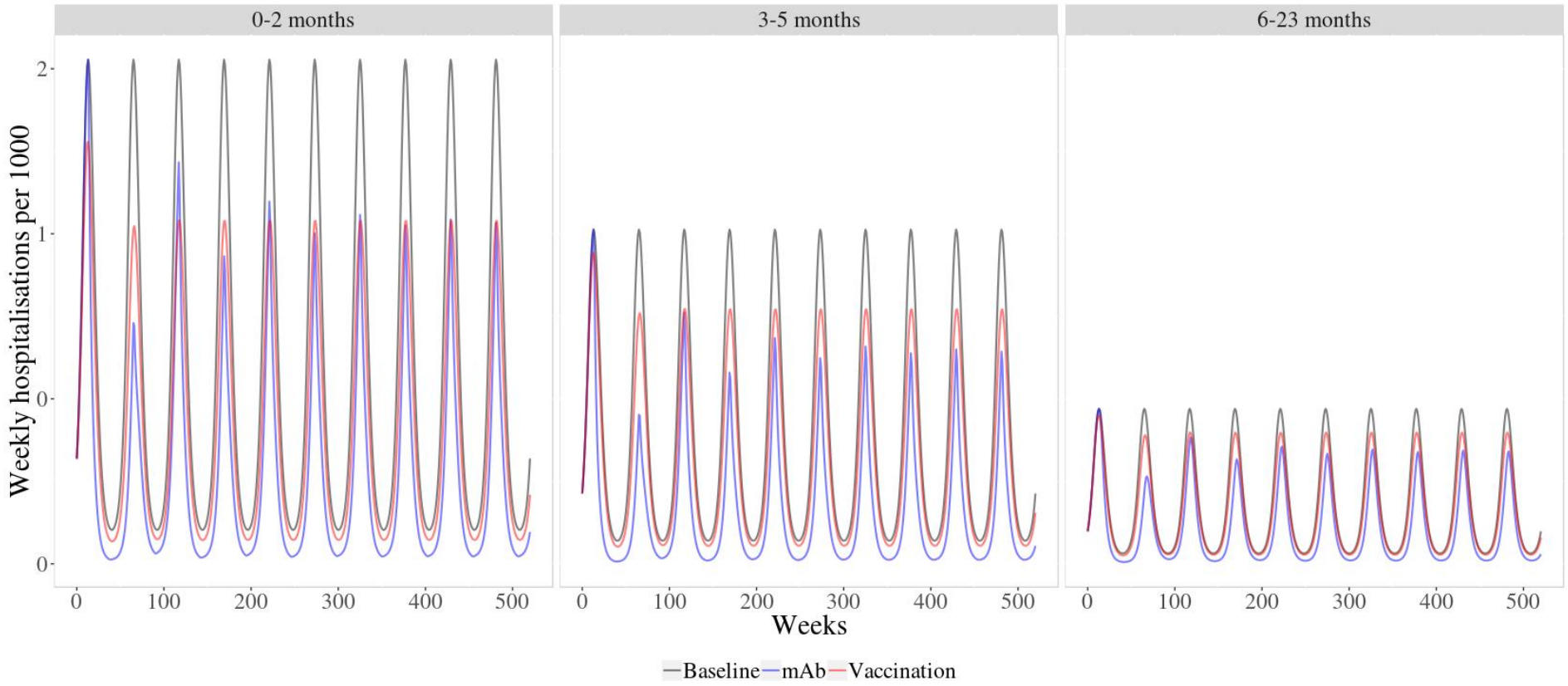


Figure 8.3 Weekly RSV hospitalisations per 1,000 children by age group for baseline, default maternal vaccine, and default seasonal infant monoclonal antibody (mAb) scenarios for ten years following implementation

The black line represents the base model while the blue and red lines represent outputs of the seasonal mAb and vaccination model at default values, respectively.

8.4.2 Averted hospitalisations

Both RSV preventative strategies modelled reduced the number of hospitalisations compared to baseline among children less than two years old (Table 8.2). At default values, the RSV maternal vaccine had a small impact in the first year following implementation. By the second year, the vaccine showed a consistent reduction in hospitalisations compared to baseline among all children aged less than two years (Figure 8.3).

A seasonal RSV mAb at default values showed minimal impact on hospitalisations among children aged less than two years in the first year but had a larger impact in the second year following implementation. A seasonal mAb displayed an alternating seasonal pattern 3–5 years after implementation but changed to an annual seasonal pattern by the sixth year (Figure 8.3).

Once well-established in the population, the default maternal vaccine scenario of 50% coverage and 180 days duration of protection with 40% effectiveness for the first 90 days, and a 20% effectiveness thereafter, resulted in a 31% reduction in hospitalisations per 1000 children aged 0–2 months, a 23% reduction among children aged 3–5 months, and a 15% reduction among children aged 6–23 months, compared to baseline. If coverage of a vaccine with our default effectiveness values was increased from 50% to 80%, there was an additional 22%, 15%, and 9% reduction in hospitalisations among children aged 0–3 months, 3–5 months, and 6–23 months respectively, compared to the default scenario. The impact of a maternal vaccine was greatest in children aged 0–2 months, except in scenarios that assumed there was no waning vaccine effectiveness, where the impact was greatest in children aged 3–5 months.

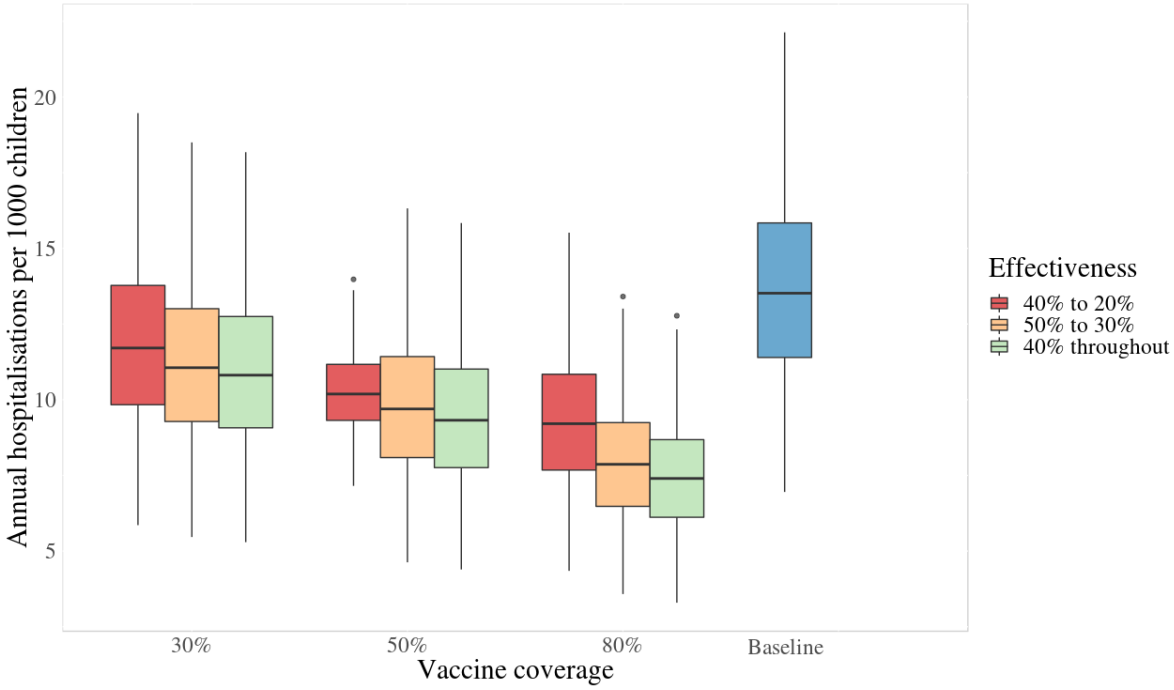
A seasonal mAb among infants aged less than six months at default values of 50% coverage and 60% effectiveness for 150 days, resulted in a 55% reduction in hospitalisations per 1000 children aged 0–2 months, a 60% reduction among children aged 3–5 months, and a 44% reduction among

children aged 6–23 months, compared to baseline. If coverage of a mAb with 60% effectiveness was increased from 50% to 80%, there was an additional 8%, 8%, and 4% reduction in hospitalisations among children aged 0–3 months, 3–5 months, and 6–23 months respectively, compared to the default scenario. The impact of a seasonal mAb on averted hospitalisations was greatest in children aged 3–5 months for all scenarios.

Table 8.2 Annual hospitalisations averted in terms of cases per 1,000 children and percentage reduction for each age group compared to baseline (no intervention) for a range of scenarios among children aged less than two years

	Annual hospitalisations averted (0–2 months)		Annual hospitalisations averted (3–5 months)		Annual hospitalisations averted (6–23 months)	
	Cases per 1,000	(%)	Cases per 1,000	(%)	Cases per 1,000	(%)
Maternal vaccine impact with duration of protection of 180 days						
Expected coverage (50%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	9.5	(31.3)	4.7	(23.3)	1.3	(14.5)
Higher effectiveness (50% first 90 days, 30% next 90 days)	12.0	(39.8)	6.6	(32.6)	1.9	(20.2)
Sustained protection (40% for 180 days)	11.7	(38.5)	8.0	(39.4)	2.2	(23.7)
Higher coverage (80%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	14.1	(46.7)	7.1	(35.1)	2.1	(22.4)
Higher effectiveness (50% first 90 days, 30% next 90 days)	17.5	(57.7)	9.7	(47.7)	2.8	(30.6)
Sustained protection (40% for 180 days)	16.7	(55.2)	11.4	(56.5)	3.3	(35.4)
Lower coverage (30%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	6.0	(19.7)	2.9	(14.5)	0.8	(8.9)
Higher effectiveness (50% first 90 days, 30% next 90 days)	7.7	(25.5)	4.2	(20.7)	1.2	(12.6)
Sustained protection (40% for 180 days)	7.5	(24.9)	5.1	(25.4)	1.4	(14.9)
Seasonal mAb‡ impact with duration of protection of 150 days						
Expected coverage (50%)						
Default effectiveness (60%)	16.8	(55.4)	12.2	(60.2)	4.1	(44.1)
Higher effectiveness (70%)	18.7	(61.9)	13.6	(67.0)	4.6	(49.8)
Lower effectiveness (50%)	14.6	(48.2)	10.7	(52.6)	3.5	(38.1)
Higher coverage (80%)						
Default effectiveness (60%)	17.9	(59.0)	12.9	(63.5)	4.3	(46.6)
Higher effectiveness (70%)	19.9	(65.8)	14.3	(70.4)	4.9	(52.5)
Lower effectiveness (50%)	15.6	(51.6)	11.3	(55.7)	3.7	(40.3)
Lower coverage (30%)						
Default effectiveness (60%)	15.1	(49.9)	11.1	(54.9)	3.7	(40.2)
Higher effectiveness (70%)	17.0	(56.0)	12.4	(61.4)	4.2	(45.5)
Lower effectiveness (50%)	13.1	(43.2)	9.7	(47.8)	3.2	(34.5)

*The public health impact shown in the table above is once an intervention is well-established within a population. ‡mAb; monoclonal antibody



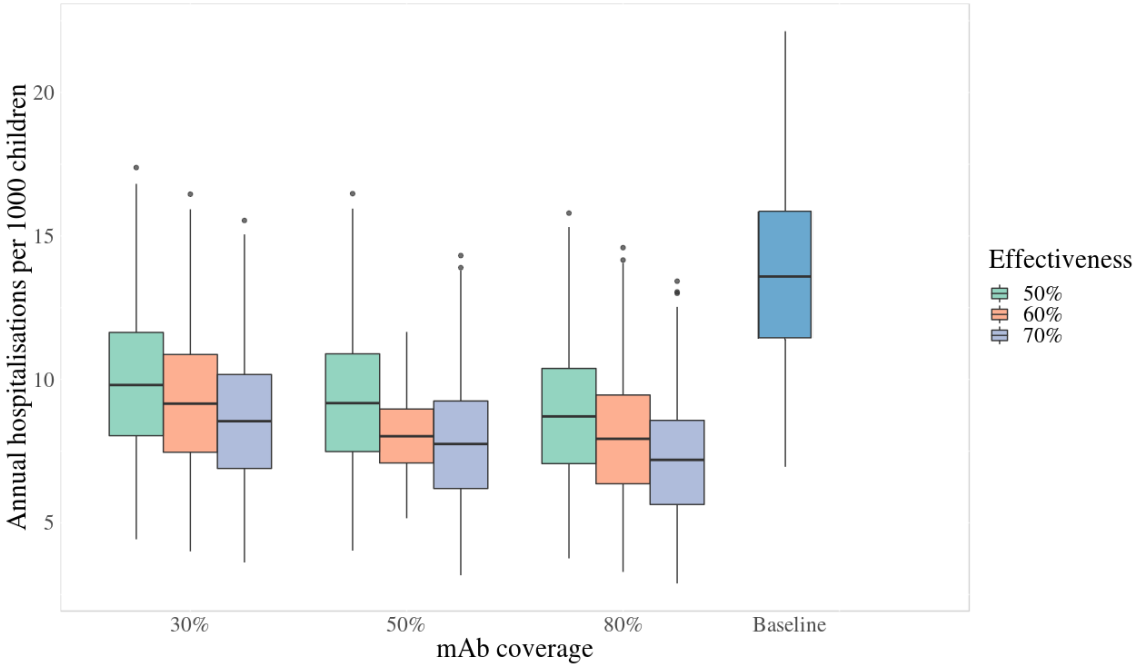


Figure 8.4 Estimated annual RSV hospitalisations per 1,000 children aged less than two years for baseline and different vaccination and seasonal monoclonal antibody (mAb) effectiveness and coverage scenarios

Distribution (2.5%, 25%, 75%, and 97.5% quantile and median) of each modelled scenario by age group, which were estimated from the distribution of 500 model simulations. Each simulation used a different combination of parameter values, sampling from the fitted parameter uncertainty range from maximum likelihood estimation, as shown in Table 8.1. Figures by finer age groups among children aged less than two years are provided in Appendix 4.6.

8.5 Discussion

In this study, we report the impact of a potential RSV maternal vaccine or a seasonal infant mAb on RSV hospitalisations, given a range of coverage and effectiveness measures using a dynamic transmission model. This model assumed effectiveness and duration of protection values informed from recent Phase 3 trial results and found both preventative strategies to reduce hospitalisations in children aged less than two years.

When assuming a similar coverage to that for existing maternal vaccination programmes in NZ, an RSV maternal vaccine with waning effectiveness that approximates the recent RSV F vaccine Phase 3 results could reduce RSV hospitalisations by more than a fifth in children aged less than two years. In contrast, a seasonal mAb administered to infants aged less than six months with 60% effectiveness could approximately halve RSV hospitalisations in the same age group. Overall, a seasonal mAb showed a greater health impact due to its ability to protect a wider age range of children than a maternal vaccine.

RSV is the most commonly detected pathogen among young children with ARI hospitalisations, highlighting the need for new pharmaceutical interventions to reduce health system burden and cost. Given the challenges in achieving protective efficacy in infants through active immunisation, either an RSV maternal vaccination or an infant mAb are realistic public health strategies. Maternal vaccination strategies for influenza and pertussis currently exist, thus the same systems can be leveraged for implementation of an RSV maternal vaccine. However, such a strategy will require access to and acceptability of vaccination among pregnant women. While no newborn monoclonal antibodies are currently recommended in NZ [222], the previous success of licensed immunoprophylaxis for RSV (Palivizumab) may aid in the licensure and acceptability of a new mAb candidate. Moreover, producers of MEDI8897 expect the product to have vaccine-like

pricing [107]. As the modelled health impacts from both strategies in our study were not extremely different, pricing of these interventions together with comprehensive cost-effectiveness analysis will be crucial for implementation.

In our model, a maternal vaccine providing protection for a 180-day period showed an impact in terms of averted hospitalisations among children aged 6–23 months, indicating indirect effects. This contrasts with a related mathematical modelling study from Western Australia that found the effect of a RSV maternal vaccine to be negligible for children 6–23 months of age [130]. Potential explanations for this include differences in demographics and contact rates by location, as well as our inclusion of RSV ARI hospitalisation data among all ages, which may have resulted in a better capture of RSV transmission and disease among older children and consequently shown greater impact of a modelled preventative strategy. Additionally, the Western Australian model used cohort ageing to model transitions between age groups while we applied continuous ageing, which due to the exponential distribution of the duration of each compartment, could result in a larger modelled indirect effects.

Previous studies comparing RSV vaccines and/or mAbs [118, 119, 130] have assumed effectiveness values higher than recent clinical trial results. In terms of the relative impact of RSV mAb and maternal vaccinations on hospitalisations, in studies by Rainisch et al. and Cromer et al., when assuming 100% uptake of both candidates, a mAb was estimated to prevent approximately 1.7–1.8 times more hospitalisations than a maternal vaccine among infants aged less than six months [118, 119]. In our study, if assuming 100% uptake at the default effectiveness values for each candidate, a seasonal mAb prevented 1.2 times more hospitalisations than a maternal vaccine among infants aged less than six months. The greater impact of a maternal vaccine found in our study is likely due to our longer assumed duration of protection, informed by recent clinical trial results, as well as our capture of indirect effects. Additionally, we noted a greater impact on

hospitalisations with increased coverage for a maternal vaccine than for a seasonal mAb. Such findings suggest that a maternal vaccine may be more cost-effective than previously estimated. It also highlights the strengths of our study, which incorporates characteristics of RSV preventative strategies currently in Phase 3 trials and validates the model against comprehensive RSV surveillance data.

Our study also has several important limitations. Firstly, the starting values for our fitted parameter for maternally derived immunity were based upon limited data. However, we found our model was unable to fit to data if we assumed no such immunity and our fitted values aligned closely with previous modelling and seroprevalence study findings [44, 45, 130]. Secondly, we utilised scaling parameters to fit the modelled incidence to number of RSV hospitalisations reported in our data, however, due to limited information on the proportion of RSV infections that are hospitalised by age, validation of these parameters was challenging. Examination of emergency care presentation and hospitalisation rates due to RSV in NZ show that infants aged 0–2 months are three times as likely to be hospitalised than those aged 6–11 months [223], supporting our assumptions. Nevertheless, better data on RSV disease burden in the community and hospitalisation risk will be valuable for future RSV modelling work. Thirdly, given our data we chose to characterise susceptibility to infection by age group, rather than including additional compartments to represent history of infection. Finally, our modelling relied on hospitalisation data thus did not assess the health impact of preventive strategies in other settings. Furthermore, a RSV vaccine or mAb may have benefits that extend beyond preventing direct RSV-associated events, as evidence suggests that severe RSV in infancy is associated with recurrent wheeze and development of asthma later in life [224, 225]. Additionally, data from the recent RSV F nanoparticle maternal vaccine Phase 3 trial reported a reduction in “all cause” medically significant LRTI events (i.e. without a requirement of RSV) [105]. As these additional benefits of

an RSV preventative strategy were not accounted for in our model, findings from our study are likely to be a conservative estimate of the true health and economic impact.

8.6 Conclusions

In summary, our study suggests that an RSV maternal vaccination and a seasonal mAb could reduce RSV hospitalisation burden by approximately 20-50% and 40-60% in children aged less than two years, respectively. Overall, a seasonal mAb had a greater modelled impact than a maternal vaccine as it provided protection to a wider age range, however, a year-round maternal vaccination demonstrated indirect effects among children aged 6–23 months. Additional data on the burden of RSV in the community and in other health care settings together with cost-effectiveness analyses will be key to the implementation of either of these preventative strategies. Finally, as RSV vaccine candidates are also being developed for older children and adults, further modelling and cost-effectiveness work to estimate the impact of combined strategies will be necessary.

9 Overall thesis discussion and conclusions

9.1 Summary of findings

The overall aim of this thesis was to estimate the burden of RSV among young children and adults in Auckland, NZ by key socio-demographic and health factors using active, population-based hospital surveillance data linked with national administrative data. Additionally, a mathematical model was developed and parametrised to RSV burden data to assess the impact of potential RSV preventative strategies currently in clinical development.

This aim was broken down into five objectives. The main findings from each of these objectives can be summarised as follows:

1. Using an active, population-based, hospital ARI surveillance project between 2012 and 2015, there were on average 6.1 (95% CI 5.8–6.4) RSV-associated ARI hospitalisations per 1,000 children aged less than five years, annually. Of all ARI hospitalisations among children in this age group, approximately 40% were RSV positive. The average cost of an RSV-associated hospitalisation was NZ$5,040. Approximately 80% of children with an RSV-associated hospitalisation did not have an underlying condition. The highest incidence of RSV hospitalisation was among children aged less than three months. Being of Māori or Pacific ethnicity or living in a neighbourhood with low socioeconomic status independently increased the risk of an RSV-associated hospitalisation. RSV-associated hospital discharge codes had an overall sensitivity of 71% for identifying laboratory-confirmed RSV cases, however, this sensitivity was considerably lower among children aged 2–4 years.

2. In a sub-study among infants comparing ARI visits seen only in the hospital ED to hospital admissions; it was found that almost twice as many ARI virus infections are managed solely

in the ED. RSV was associated with the highest rates in both the ED and hospital. RSV-associated rates changed significantly by age in months among infants; infants aged 0–2 months were more likely to be admitted to hospital compared to those aged 6–11 months i.e. 6–11-month-old infants were more likely to be seen only in the ED. Finally, Māori and Pacific children had significantly higher ED visit and hospitalisation rates for all respiratory viruses compared to children of other ethnicities.

3. When investigating the burden of RSV-associated hospitalisations in adults aged 18 years and above, it was estimated that between 2012 and 2015, there were on average 23.6 (95% CI 21.0–26.1) RSV-associated ARI hospitalisations per 100,000 adults. Of all ARI hospitalisations among adults in this age group, approximately 8% were positive for RSV. The average cost of an RSV-associated hospitalisation was NZ$4,758. The highest incidence was among adults aged 80 years or more. Being of Māori or Pacific ethnicity or living in a neighbourhood with low socioeconomic status independently increased the risk of an RSV-associated hospitalisation.

4. In an additional study among adults, investigating risks posed by specific chronic comorbidities on RSV-associated hospitalisation rates, it was found that risks were significantly higher among adults with COPD, asthma, congestive heart failure, and coronary artery disease compared to adults without these conditions. End-stage renal disease was only found to increase risk of RSV hospitalisation among adults aged 50–64 years, while diabetes mellitus only increased risk among adults aged 65–80 years. No increased risk was seen for adults with cerebrovascular accidents. Among RSV positive adults, COPD and congestive heart failure were independently associated with increased length of hospital stay. In general,

RSV hospitalisation risk was high in older adults regardless of comorbidity, however, in younger adults having a comorbidity significantly increased risk.

5. Finally, by using a compartmental mathematical model parameterised to active RSV hospital surveillance data, it was estimated that either a maternal RSV vaccine or a seasonal infant immunoprophylaxis through mAbs could reduce RSV-associated hospitalisations in children aged less than two years. A maternal vaccine with effectiveness of 40–50% in the first 90 days and 20–30% for the next 90 days would reduce RSV hospitalisations by 31–40% in children younger than 3 months, by 23–33% in children aged 3–5 months, and by 15–20% in children aged 6–23 months. A seasonal infant mAb with 50–70% effectiveness for 150 days would reduce RSV hospitalisations by 48–62%, 53–67% and by 38–50% in children aged 0–2 months, 3–5 months and 6–23 months, respectively.

9.2 Implications of findings

Results from this thesis show that RSV causes a high and unequal burden of disease in Auckland, NZ. Such findings highlight the urgent need for improved RSV surveillance and preventive strategies. In this thesis, a research surveillance project designed primarily for influenza was leveraged to investigate RSV epidemiology and suggests that current national influenza surveillance platforms could be extended to improve national RSV surveillance.

RSV-associated hospitalisation rates among children aged less than five years reported in this thesis were almost twice as high as rates reported from a similar study in the US. This comparatively high burden appeared to be driven by the greater risk of hospitalisation among Māori or Pacific children as well as among children living in a neighbourhood with low socioeconomic status. Our findings also suggest that other studies relying on passive surveillance

and hospital discharge codes may be underestimating the burden of RSV in children aged 2–4 years, given the low sensitivity of discharge codes in identifying laboratory-confirmed RSV cases in this age group.

In addition to the high hospitalisation burden, RSV was also found to pose a significant burden among infants in terms of ED visits. Such estimates outside the hospital setting should be included for more accurate quantification of RSV-associated disease burden and cost. RSV positive ED visit rates increased with age in months among infants, indicating that as age increases and disease severity decreases, a greater proportion of RSV infections present outside the hospital setting. These findings suggest that RSV-associated ED visits in slightly older children (i.e. aged 1–4 years) may also be high.

Given the high burden of RSV disease and that most children hospitalised with RSV do not have an underlying condition, future RSV preventative strategies should ideally target all young children. However, if targeted approaches are necessary, the priority group should be infants aged less than three months who have the greatest risk of RSV-associated hospital admissions.

Finally, the introduction of the pneumococcal conjugate vaccine has been associated with a reduction in social and ethnic disparities in infectious disease burden in NZ [171]. This suggests that an RSV preventative strategy in conjunction with policies that address health inequalities more broadly (e.g. improving access to primary health care and housing standards) are necessary for reducing the high and disproportionate childhood RSV disease burden in NZ. Correspondingly, concerted efforts should be made to ensure equitable access to RSV preventative strategies once they are available

Few studies have assessed the burden of RSV among adults. Findings from this thesis show that while RSV can cause severe disease in adults, RSV-associated hospitalisations rates were lower

than influenza-associated hospitalisation rates among adults in NZ during the SHIVERS study period. RSV burden among adults relative to influenza appeared to change with the predominant influenza virus strain, highlighting the importance of surveillance for both viruses in adults. Similar to children, RSV disproportionally affected adults of Māori or Pacific ethnicity as well as those living in a neighbourhood with low socioeconomic status and highlights the value an adult RSV preventative strategy may have in reducing health inequalities in NZ.

When carrying out analyses among hospitalised adults, no comorbidity was significantly associated with RSV positivity following adjustment for age and ethnicity. This lack of association was likely due to the higher risk of hospitalisation for non-RSV illnesses in adults with comorbidities i.e. selection bias that occurs when both exposure and outcome are associated with hospitalisation. As such, in order to accurately measure the effect of comorbidity on RSV disease risk, modelled population-level comorbidity data was used to estimate RSV-associated hospitalisation rates in specific co-morbidity strata.

When investigating the role of comorbidities on RSV hospitalisation risk at a population level, adults with comorbidities were found to have a great risk of RSV-associated hospitalisation compared to adults with no such comorbidities. It was also noted that this risk did not appear to increase with age. In fact, the risks of RSV hospitalisation associated with presence of a comorbidity were often highest in the 18–49-year age group. It is likely that among older adults, frailty, immunosenescence, and/or the presence of multiple comorbidities reduced differences in hospitalisation rates between those with or without a specific condition, potentially explaining the higher risk seen in younger adults. Such findings have implications for identifying RSV vaccine priority groups, suggesting that all older adults could be considered at risk of severe RSV-associated outcomes and that younger adults with certain comorbidities such as asthma, CHF, and CAD should also be prioritised.

In the fifth objective of this thesis, a dynamic transmission model was used to assess the impact of a potential RSV maternal vaccine or a seasonal mAb. Assuming effectiveness and duration of protection values informed from recent Phase 3 trial results, at a range of coverage scenarios, it was found that either a maternal vaccine or seasonal mAb could reduce RSV-associated hospitalisations among children aged less than two years. A seasonal mAb had a greater impact than a maternal vaccine due to its ability to protect a wider age range, however, a maternal vaccine did show indirect effects, and had more impact with increased coverage, potentially improving its cost-effectiveness. Moreover, an RSV maternal vaccine could potentially be implemented easily by leveraging current maternal vaccination platforms. As such, assessment of the impact of both strategies at other healthcare setting levels together with comprehensive cost-effectiveness analysis will be important for decision-making and implementation.

9.2.1 Use of linked administrative data

This thesis demonstrates the value of using national administrative datasets for RSV and infectious disease research more broadly. While hospital admissions and laboratory testing data used in this thesis were obtained from a research project that had notable advantages over data collected from passive surveillance, the benefits from using linked national administrative datasets to estimate denominators, stratified by key demographic and health factors, remain. Moreover, administrative datasets can be used to fill in key elements and values missing from surveillance data, extending its use and application.

The population level analyses using administrative data carried out in this thesis is not only useful for accurately highlighting disparities in disease risk but is also important for reducing selection, effect modification, and confounding bias. Finally, the methods employed in the thesis can be easily applied to more recent RSV and other infectious disease data to inform disease burden estimates and optimal preventative strategies.

9.3 Recommended future work and research

The findings of this thesis suggest the following as key priorities for future work and research:

Evaluate current national influenza surveillance platforms in NZ including assessment of the incremental cost of performing RSV surveillance

Assess the performance of current influenza surveillance case definitions in primary and secondary healthcare settings (such as influenza-like-illness and severe-acute respiratory illness, respectively) in detecting RSV. Evaluate the feasibility and incremental cost of expanding case definitions, sampling, and testing strategies to include RSV. As RSV disease burden is well recognised and documented among young children in hospital, this expanded surveillance would be particularly important for RSV burden estimation in adults and among patients presenting to primary healthcare. Such surveillance will also be vital for establishing 'baseline' burden of disease estimates, which will be crucial for assessing the impact of future RSV preventative strategies.

Investigate the community burden of RSV-associated disease in New Zealand

Monitor and test for RSV-associated illness among cases not presenting to primary and secondary healthcare settings. Such burden estimations are particularly important for assessing the indirect economic costs of RSV (i.e. loss of work, out-of-pocket expenses) as well for informing key parameters used in mathematical models to assess impact and cost-effectiveness of potential RSV preventative strategies.

Assess long-term outcomes associated with severe RSV-associated disease in New Zealand

Evidence suggests that severe RSV in infancy is linked with recurrent wheeze and development of asthma later in life [225, 226], however, the causality of this association remains unclear. The SHIVERS study in combination with linked national administrative datasets provides a valuable platform to follow-up children who have experienced severe RSV disease and investigate such outcomes. It will also enable estimation of the long-term economic burden of RSV infections, which can then be accounted for in modelling and cost-effectiveness analyses.

Further develop mathematical models to assess potential RSV vaccines and mAbs

The mathematical model presented in this thesis provides valuable information on the impact of potential RSV preventative strategies. Models should be further developed as more data on RSV disease burden, immunity, and preventative strategies become available. For example, a model that stratifies individuals by age group and risk of severe disease due to comorbidities could inform targeted vaccine/mAb approaches. Likewise, a model that stratifies individuals by age group and ethnicity while accounting for heterogeneities in contact rates and housing density could be used to assess the impact of future RSV preventative strategies on health inequities. Finally, as RSV vaccines are being developed for other target groups in addition to pregnant women and infants, models that assess the impact of combined interventions will also be important.

Carry out cost-effectiveness analysis to inform implementation of RSV preventative strategies

As indicated by the findings from the modelling component of this thesis, some RSV preventative strategies can result in similar health impacts, therefore cost-effectiveness analysis of these strategies will be crucial for decision-making and implementation.

9.4 Conclusions

RSV is a leading cause of respiratory illness in young children. It can also cause severe disease in older adults and among those with certain comorbidities. Given the progress in RSV vaccine and immunoprophylaxis development in recent years, better estimates of RSV-associated health and economic burden together with mathematical modelling approaches to understand transmission are critical for assessing and implementing interventions. In this thesis, data from an ARI surveillance project were linked with national administrative datasets to provide comprehensive estimates of RSV disease burden within Auckland, NZ, a socioeconomically and ethnically diverse city. Additionally, a mathematical model was developed and fitted to this data to assess the impact of potential preventative strategies. Findings from this thesis provide a unique contribution to the understanding of RSV epidemiology in NZ and internationally. It also provides a robust framework for future studies in the area.

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Appendices

Appendix 1.1 Performance of hospital assays (clinician ordered tests) in detecting different respiratory viruses

Two major public hospitals, the Auckland City and Middlemore hospitals, serve the central, eastern, and southern Auckland region and were the study sites of the SHIVERS surveillance. The performance of hospital assays from clinician ordered tests were compared to the US CDC's real-time RT-PCR as a gold standard. Only results from assays with a sensitivity greater than 80% and a specificity greater than 95% were included in the SHIVERS study dataset.

Virus type*	Auckland City Hospital assay			Middlemore Hospital assay	
	Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)
Flu	96.49 (94.74–97.67)	99.75 (99.52–99.87)		97.82 (96.43–98.67)	99.50 (99.29–99.65)
RSV	95.74 (93.84–97.08)	99.61 (99.32–99.78)		91.38 (88.95–93.32)	98.18 (97.47–98.69)
RV	94.79 (92.48–96.42)	99.86 (99.58–99.95)		50.0 (15.10 – 85.00)	85.71 (60.06–95.99)
ADV	87.87 (83.45–91.23)	99.65 (99.39–99.80)		69.87 (64.56–74.70)	97.89 (97.14–98.44)
hMPV	97.37 (93.84–97.08)	99.92 (99.55–99.99)		83.73 (78.13–88.12)	99.50 (99.08–99.73)

*Flu; influenza, RSV; respiratory syncytial virus, RV; rhinovirus, ADV; adenovirus, hMPV; human metapneumovirus.

Appendix 2.1 Seasonal incidence rates (IR) and rate ratios (IRR) of all acute respiratory infection (ARI), lab confirmed respiratory syncytial virus (RSV) associated hospitalisations among children aged less than five years in Auckland, New Zealand, 2012–2015 - *not corrected for non-testing*

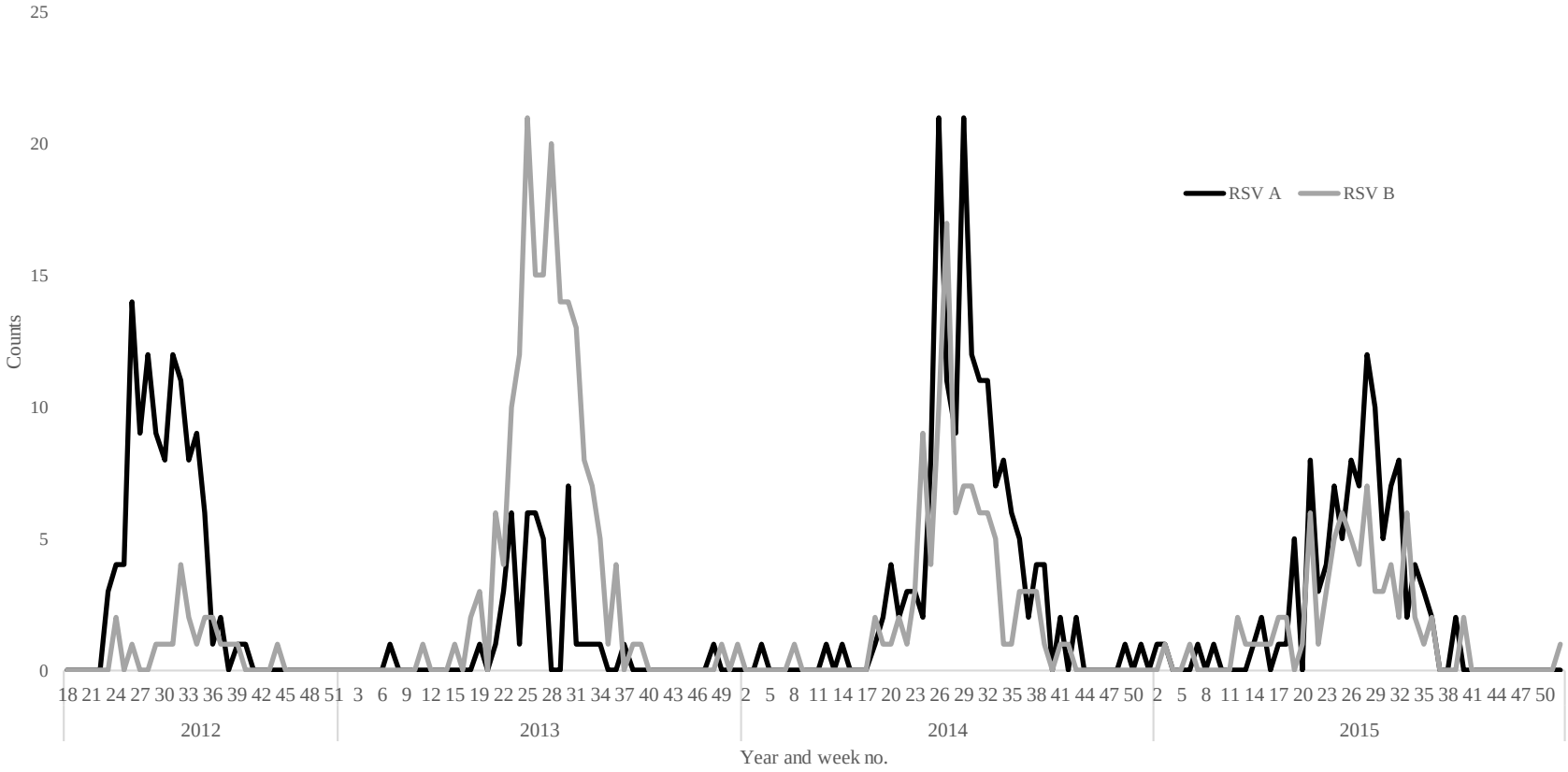
	RSV lab confirmed hospitalisation rates (NOT corrected for non-testing)				
	No.	**Rate per 1,000 child-years at risk**		**Rate per 1,000 children**	
		IR (95% CI)	**IRR (95% CI)**	**IR (95% CI)**	**IRR (95% CI)**
Total	1597	12.2 (11.62–12.86)		4.7 (4.5–5.0)	
Year					
2012	417	12.5 (11.3–13.7)		4.8 (4.4–5.3)	
2013	354	10.7 (9.5–11.8)		4.1 (3.7–4.6)	
2014	442	13.5 (12.2–14.8)		5.2 (4.7–5.7)	
2015	384	11.8 (10.6–13.0)		4.6 (4.1–5.0)	
Sub-region					
Central Auckland	504	9.2 (8.4–10.0)		3.5 (3.2–3.8)	
East, South Auckland	1093	14.4 (13.6–15.3)		5.6 (5.3–6.0)	
Age Group					
0–2 months	450	72.4 (65.7–79.1)	33.7 (30.1–37.6)	27.9 (25.3–30.5)	33.9 (28.3–40.6)
3–5 months	314	48.9 (43.4–54.3)	22.9 (20.1–26.0)	18.9 (16.8–21.0)	23.0 (19.0–27.9)
6 –11 months	363	27.9 (24.9–30.9)	13.1 (11.4–15.0)	10.8 (9.6–11.9)	13.2 (11.0–15.9)
12–23 months	300	11.4 (10.1–12.7)	5.4 (4.6–6.4)	4.4 (3.9–4.9)	5.4 (4.5–6.6)
2–4 years	170	2.1 (1.8–2.4)	Ref	0.8 (0.7–0.9)	Ref

	RSV lab confirmed hospitalisation rates (NOT corrected for non-testing)					
	No.	Rate per 1,000 child-years at risk			Rate per 1,000 children	
		IR (95% CI)	IRR (95% CI)		IR (95% CI)	IRR (95% CI)
SES*						
1 (least deprived)	78	8.9 (6.8–11.0)	Ref		3.5 (2.6–4.3)	Ref
2	133	10.4 (8.5–12.3)	1.2	(0.9–1.6)	4.0 (3.3–4.7)	1.2 (0.9–1.5)
3	123	9.2 (7.6–10.9)	1.0	(0.8–1.4)	3.6 (2.9–4.2)	1.0 (0.8–1.4)
4	219	13.0 (11.2–14.7)	1.5	(1.1–1.9)	5.0 (4.4–5.7)	1.5 (1.1–1.9)
5 (most deprived)	1044	13.3 (12.4–14.2)	1.5	(1.2–1.9)	5.2 (4.8–5.5)	1.5 (1.2–1.9)
Ethnicity						
Māori	509	25.0 (22.7–27.4)	4.7	(3.9–5.6)	9.7 (8.8–10.6)	4.7 (3.9–5.6)
Pacific	720	18.1 (16.6–19.7)	3.4	(2.9–4.0)	7.0 (6.4–7.6)	3.4 (2.8–4.0)
Asian	141	5.0 (4.2–5.9)	0.9	(0.8–1.2)	2.0 (1.6–2.3)	0.9 (0.8–1.2)
European/Other	227	5.3 (4.6–6.1)	Ref		2.1 (1.8–2.4)	Ref

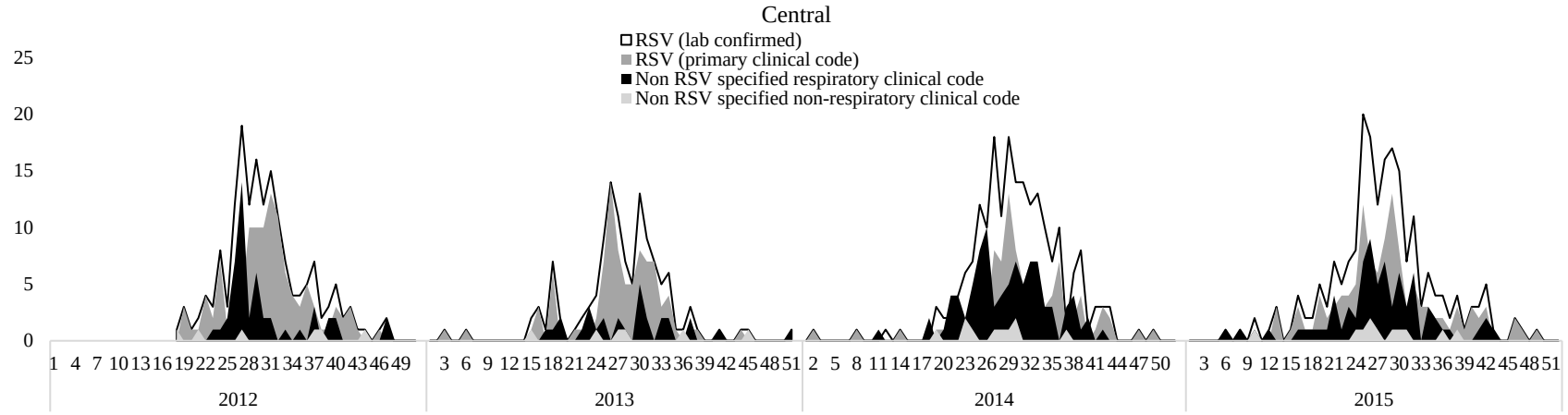
IR; Incidence rate, IRR; incidence rate ratio,

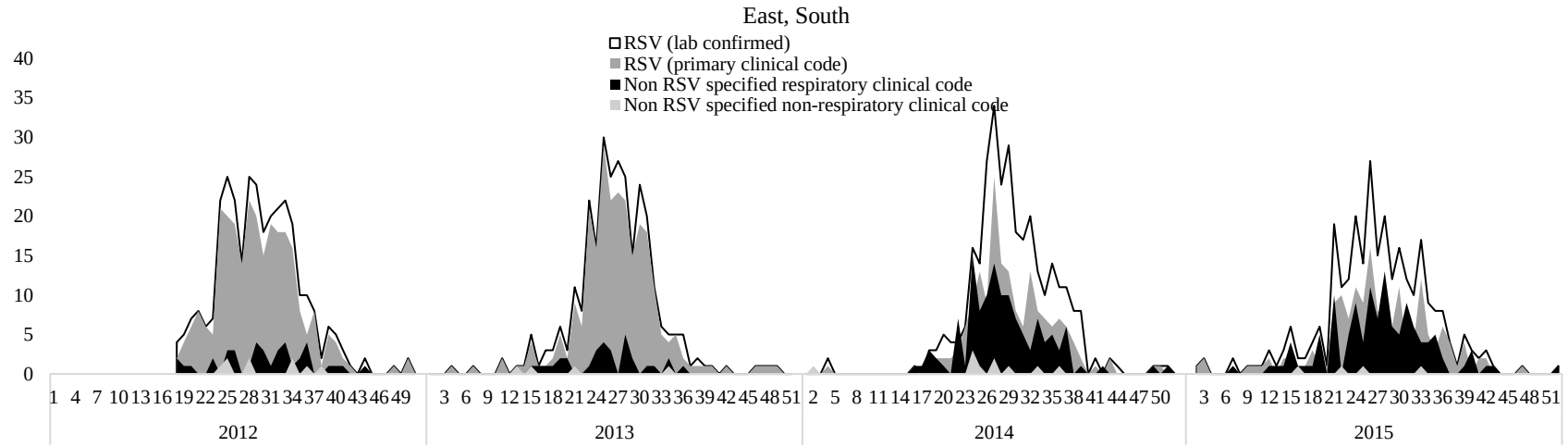
* SES (Socioeconomic status) quantified using a small area level measure of neighbourhood deprivation derived from the national census (NZDep2013) [27]

Appendix 2.2 Weekly counts of RSV laboratory confirmed hospitalisations by respiratory syncytial virus (RSV) subtype (RSV A, RSV B) in Auckland, NZ, 2012–2015

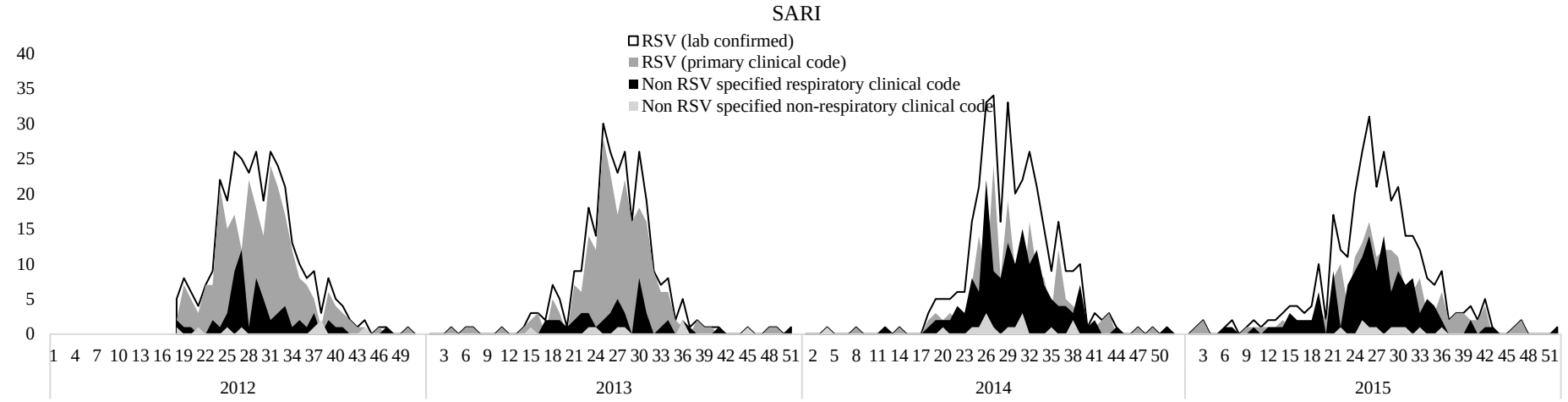


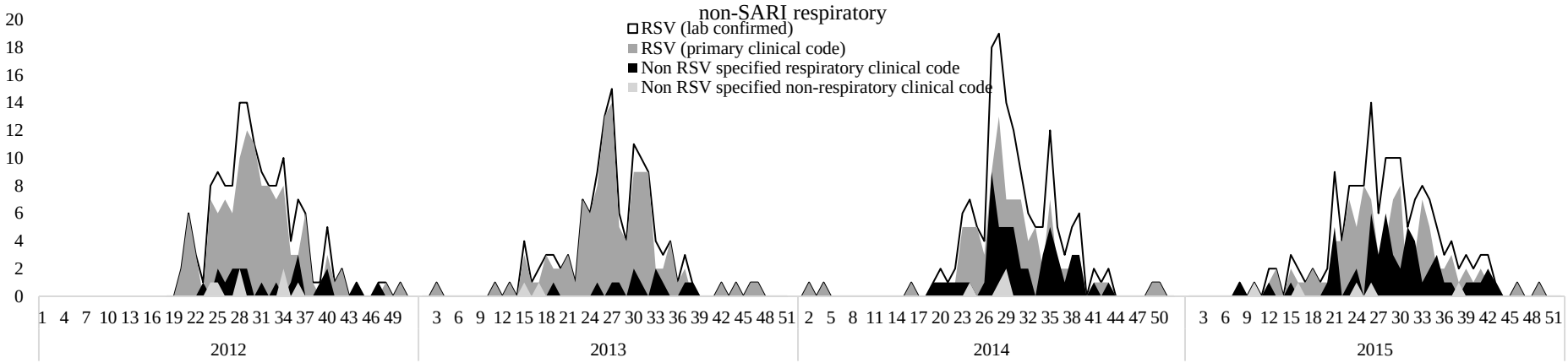
Appendix 2.3 Comparison of counts of respiratory syncytial virus (RSV) lab confirmed events to primary ICD-10 clinical codes by week and year in the central, east and southern Auckland regions, 2012–2015





Appendix 2.4 Comparison of counts of respiratory syncytial virus (RSV) lab confirmed events to primary ICD-10 clinical codes by week and year among severe acute respiratory infection (SARI) and non-SARI respiratory cases, 2012–2015





Appendix 3.1 Comparison of SHIVERS systematic and clinical ordered testing among acute respiratory infection (ARI) hospitalisations in adults aged 18 years or older in Auckland, New Zealand, 2012–2015

	SHIVERS	Col (%)	Clinician	Col (%)	p-value
Total	3220	(100.0)	1371	(100.0)	
Age group (years)					
18–49	1058	(32.9)	307	(22.4)	<0.001
50–64	783	(24.3)	341	(24.9)	0.267
65–79	892	(27.7)	415	(30.3)	0.928
≥80	487	(15.1)	308	(22.5)	<0.001
Sex					
Female	1779	(55.2)	742	(54.1)	0.506
Male	1441	(44.8)	629	(45.9)	0.506
SES*					
1	362	(11.2)	126	(9.2)	0.027
2	482	(15.0)	180	(13.1)	0.313
3	476	(14.8)	181	(13.2)	0.153
4	438	(13.6)	178	(13.0)	0.191
5	1462	(45.4)	706	(51.5)	0.001
Ethnicity					
Māori	609	(18.9)	215	(15.7)	0.009
Pacific	994	(30.9)	457	(33.3)	0.100
Asian	290	(9.0)	150	(10.9)	0.042
European/Other	1327	(41.2)	549	(40.0)	0.462
Case definition					
SARI	2641	(82.0)	399	(29.1)	<0.001
non-SARI respiratory	579	(18.0)	972	(70.9)	<0.001
ICU					
Not admitted	3124	(97.0)	1328	(96.9)	0.779
Admitted	96	(3.0)	43	(3.1)	0.779
Hospital length of stay					
Mean (IQR)	4.1	(2–5)	4.6	(2–6)	0.001
Primary ICD-10 codes (most common)					
Influenza (J10)	356	(11.1)	162	(11.8)	0.224
Viral pneumonia (J12)	71	(2.2)	39	(2.8)	0.338
Pneumonia due to Step pneumonia (J13)	131	(4.1)	50	(3.6)	0.414
Pneumonia unspecified (J18)	603	(18.7)	220	(16.0)	0.078
Unspecified ALRI (J22)	327	(10.2)	154	(11.2)	0.363
COPD (J44)	508	(15.8)	245	(17.9)	0.679
Asthma (J45)	240	(7.5)	109	(8.0)	0.691

*SES quantified using a small area level measure of neighbourhood deprivation derived from the national census (NZDep2013) with SES 1 as least deprived and SES 5 as most deprived

Appendix 4.1 Methods for estimating chronic medical condition (CMC) prevalence at the population level

Datasets used

National Minimum Dataset

The National Minimum Dataset (NMDS), a collection of ICD-10-AM hospital discharge codes obtained primarily from public hospitals throughout NZ, was queried for study participants between June 30, 2011 and July 1, 2016. For each individual, a NMDS CMC status was marked present if a single ICD-10AM code matching the specific CMC was found (Supplement 2) and was considered present for the entire study period**.** Those who had no codes matching the CMC were marked as absent. To reduce the likelihood a CMC status would be incorrectly marked as negative, we searched for ICD-10AM codes from June 30, 2011 to July 1, 2016, rather than limiting this search to the ARI active surveillance period (2012 to 2015).

Pharmaceutical collection

The pharmaceutical collection, a database containing data on prescription medications dispensed by community pharmacies throughout NZ, was used to obtain prescription medication data on study participants from June 30, 2011 to July 1, 2016. If a medication was present in the pharmaceutical collections database less than 10 times, this medication ID was not included in further analysis. As some CMC-related medications may be prescribed to treat temporary, unrelated conditions, we limited inclusion to individuals with two or more prescriptions for any CMC-related medication, thus preventing one-time users without the CMC from weakening a medication's association in the model. We chose to mark medications as present or absent rather than counting the number of prescriptions to prevent very frequent or prolonged use of any given medication from skewing the model. Additionally, we analysed medication class combinations that help discriminate between conditions treated with similar medications (i.e., COPD and asthma) to provide specificity and context to an individual's medication profile. Medication class combinations were marked as present if the rules for that particular combination were met (Supplement 2). Otherwise, the combination was marked as absent.

TestSafe laboratory database

TestSafe database is a repository of laboratory results from specimens collected from patients throughout NZ during routine medical care. We retrieved clinician-selected, CMC-related results from June 30, 2011 to July 1, 2016 on study participants. When multiple laboratory values were available for any specific test, the result indicating the most severe status was analysed with the exception of renal function tests, for which a median value was selected, to attempt to capture those who had long-term impairment. Those individuals with a test result value meeting the cut-off criteria were marked as positive for that test. If they did not meet the criteria, they were marked as negative, and if there was no result for the test, they were marked as missing.

Partial Least Squares model

A predictive Partial Least Squares (PLS) model was created to define each study participant's CMC status by training CMC-related pharmaceutical and laboratory data to NMDS CMC statuses. Relevant medications, medication group combinations, and laboratory test results for each CMC that were included in the model were determined by a three-physician consensus. Variables discriminating between highly related CMC in univariate logistical regression were included as predictors for training in the PLS model. Models were trained on a dataset composed of 100 individuals with at least one hospitalisation between June 30, 2011 and July 1, 2016 randomly selected from age, sex, ethnicity and socioeconomic status strata as

determined by the NZ Index of Deprivation score [1]. Re-sampling and training were completed for a total of 12,000 individuals. By sampling individuals from each sociodemographic stratum equally, we aimed to prevent biased predictions for individuals from uncommon sociodemographic strata. Class imbalance was further addressed with up sampling. Final models were generated using 10-fold cross validation, optimising for ROC area under the curve. The model was tuned over one through five terms. To adjust for the low sensitivity of NMDS CMC statuses (ICD-10AM codes), we applied a cost against false negative classification equal to the ratio of the expected CMC prevalence divided by the NMDS CMC status prevalence. By training the model to distinguish between pharmaceutical and laboratory predictors based on their association with NMDS CMC status, we more accurately captured prevalence of CMCs in the population than those captured with ICD-10AM hospitalisation data alone. The optimal threshold for assigning each PLS-predicted CMC status was determined by randomly sampling 100,000 individuals from the study population and applying the Youden modified optimality criterion[2] using expected CMC prevalence's from available NZ CMC statistics [3–5].

The model was not used to predict CVA and ESRD statuses due to its inability to accurately predict the prevalence of these diseases in comparison with reported estimates. CVA status was assigned using only ICD-10 discharge codes. If a study participant had an ICD-10 code for CVA, the participant was considered to have had a CVA. ESRD status was assigned using a combination of ICD-10 discharge codes and laboratory data. To meet the ESRD status, a resident required either a qualifying ICD-10 discharge code or a qualifying laboratory value.

Case Definition

To compare the PLS-predicted CMC status output with methods more commonly used, an algorithm-based case definition was created for each CMC and applied to the study population. The same data collections periods were used for NMDS, PHARMS and TestSafe databases. To meet the case definition for each CMC, one must have either a single ICD-10AM code, ≥2 pharmaceutical prescriptions, or ≥2 laboratory test results meeting clinician-determined criteria (Appendix 4.2b).

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Appendix 4.2a Variables used in partial least squares model to determine CMC status of adults in the study population

Variables	Congestive Heart Failure	Coronary Artery Disease	Cerebro-vascular accident	Chronic Obstructive Pulmonary Disease	Asthma	Diabetes Mellitus	End Stage Renal Disease
ICD10-AM code	I09.81 I500 I509 I11.0 I30.0 P29.0	I200 I201 I208 I209 I210 I211 I212 I213 I214 I219 I220 I221 I228 I229 I230 I231 I232 I233 I234 I235 I236 I238 I240 I248 I249 I250 I2510 I2511 I2512 I2513 I252 I253 I254 I255 I256 I258 I259 Z951 Z955 Z958 Z959 3530306 3530307 3530400 3530401 3530500 3530501 3530906 3530907 3530908 3530909 3531,000 3531001 3531002 3531003 3531004 3531005 3845619 3849700 3849701 3849702 3849703 3849704	G460 G461 G462 G463 G464 G465 G466 G467 G468 I600 I601 I602 I603 I604 I605 I606 I607 I608 I609 I610 I611 I612 I613 I614 I615 I616 I618 I619 I630 I631 I632 I633 I634 I635 I636 I638 I639 I64 I650 I651 I652 I653 I658 I659 I660 I661 I662 I663 I664 I668 I669 I670 I672 I693 I694 I698	J44 J41 J42 J43	J45 J46 J82	E10 E11 E12 E13 E14 O240 O241 O242 O243	N18.0 Z99.2

Variables	Congestive Heart Failure	Coronary Artery Disease	Cerebro-vascular accident	Chronic Obstructive Pulmonary Disease	Asthma	Diabetes Mellitus	End Stage Renal Disease
		3849705 3849706 3849707 3850000 3850001 3850002 3850003 3850004 3850300 3850301 3850302 3850303 3850304 3850500 3863700 9020100 9020101 9020102 9020103					

Variables	Congestive Heart Failure	Coronary Artery Disease	Cerebro-vascular accident	Chronic Obstructive Pulmonary Disease	Asthma	Diabetes Mellitus	End Stage Renal Disease
Medication	Beta blockers: Carvedilol Bisoprolol Metoprolol tartrate ACE Inhibitors: Captopril Cilazapril Enalapril Lisinopril Perindopril Quinapril Loop diuretics: Furosemide Bumetanide Potassium sparing diuretics: Spironolactone Amiloride Metolazone Loop w potassium sparing diuretics: Amiloride w furosemide Amiloride w HCTZ ACE-I w Diuretics: Cilazapril w HCTZ Quinapril with HCTZ Captopril with HCTZ Enalapril maleate with HCTZ Lisinopril with HCTZ Antiarrhythmic: Digoxin Amiodarone	Beta-blockers: Atenolol Bisoprolol Carvedilol Celiprolol Labetalol Metoprolol succinate Metoprolol tartrate Nadolol Pindolol ACE inhibitors: Captopril Cilazapril Enalapril Lisinopril Perindopril Quinapril ARBs: Candesartan Losartan Nitrates: Glyceryl trinitrate Isosorbide mononitrate Fibrates: Bezafibrate Gemfibrozil Other lipid-modifying agents: Acipimox Nicotinic acid Resins: Cholestyramine Colestipol HMG CoA Reductase Inhibitors Atorvastatin Pravastatin Simvastatin Fluvastatin Selective Cholesterol absorption inhibitors: Ezetimibe Ezetimibe with simvastatin Antiplatelet agents: Aspirin Clopidogrel Dipyridamole Prasugrel Ticagrelor	N/a	SAMA: Ipratropium Bromide, SABA+SAMA: Salbutamol with Ipratropium Bromide LAMA: Tiotropium Bromide Glycopyrronium Umeclidinium IC: Fluticasone Budesonide Beclomethasone LABA: Eformoterol Indacaterol Salmeterol LAMA w LABA: Glycopyrronium w Indacaterol Tiotropium w Olodaterol Umeclidinium w Vilanterol IC w LABA: Budesonide w Eformoterol Fluticasone w Vilanterol Fluticasone w Salmeterol For exacerbation: Salbutamol Terbutaline Dexamethasone Dexamethasone phosphate Methylprednisolone Methylprednisolone sodium succinate Prednisolone Prednisolone sodium phosphate Prednisone	SABA: Salbutamol Terbutaline IC: Fluticasone Beclomethasone Diproprionate Budesonide LABA: Eformoterol Fumarate Salmeterol Indacaterol LABA w IC: Budesonide w/ Eformoterol Fluticasone w/ Salmeterol Fluticasone w vilanterol Leukotriene modifier: Montelukast Mast cell stabilizers: Nedocromil Sodium cromoglycate Methylxanthines: Theophylline Aminophylline SAMA: Ipratropium Bromide LAMA: Tiotropium Bromide For exacerbation: Salbutamol with Ipratropium Bromide Dexamethasone Dexamethasone phosphate Methylprednisolone Methylprednisolone sodium succinate Prednisolone Prednisolone sodium phosphate Prednisone	Insulin- Rapid-, short- and intermediate-acting preparations: Insulin Neutral Insulin zinc suspension Insulin aspart with insulin aspart protamine Insulin isophane Insulin isophane with insulin neutral Insulin lispro with insulin lispro protamine Insulin aspart Insulin glulisine Insulin lispro Insulin- Long-acting preparations: Insulin glargine Alpha glucosidase inhibitors Acarbose Sulfonylureas: Chlorpropamide Glibenclamide Gliclazide Glipizide Tolazamide Tolbutamide Thiazolidinedione: Rosiglitazone Pioglitazone Other oral hypoglycaemic agents: Metformin hydrochloride	N/a

Variables	Congestive Heart Failure	Coronary Artery Disease	Cerebro-vascular accident	Chronic Obstructive Pulmonary Disease	Asthma	Diabetes Mellitus	End Stage Renal Disease
Medication class combinations	BB without CCB BB and CCB ACEI without ARB ACEI and diuretic ACEI and loop diuretic Loop diuretic and Potassium sparing diuretic Loop diuretic without Thiazide diuretic vasodilators and nitrates BB and ACEI BB and ACEI and loop diuretic CCB and ACEI BB and ARB CCB and ARB HMG CoA Reductase Inhibitors and ACEI BB and ACEI and HMG CoA Reductase Inhibitors	BB without CCB BB and CCB ACEI without ARB vasodilators and nitrates BB and ACEI CCB and ACEI BB and ARB CCB and ARB BB and antiplatelet nitrates and antiplatelet HMG CoA Reductase Inhibitors and antiplatelet BB and ACEI and HMG CoA Reductase Inhibitors BB and HMG CoA Reductase Inhibitors and antiplatelet	N/a	SAMA and SABA SABA without SAMA SAMA without SABA SAMA and LABA SABA and LABA SABA without LABA SABA without LAMA SAMA and LAMA SABA and LAMA LABA without SAMA LABA without LAMA IC without LAMA SABA and SAMA without LABA SABA and SAMA without LAMA SABA and IC without LAMA LABA and IC LAMA and LABA SABA and IC SABA and IC and LABA SABA and LABA and IC without LAMA LAMA and IC IC and LABA and LAMA IC and LABA and LAMA Theophylline without SAMA Theophylline without LAMA Theophylline and SAMA Theophylline and LAMA corticosteroids and LAMA corticosteroids and SABA without LAMA corticosteroids and SABA without SAMA corticosteroids and SABA	SAMA and SABA SABA without SAMA SAMA without SABA SAMA and LABA SABA and LABA SABA without LABA SABA without LAMA SAMA and LAMA SABA and LAMA LABA without SAMA LABA without LAMA IC without LAMA SABA and SAMA without LABA SABA and SAMA without LAMA SABA and IC without LAMA LABA and IC LAMA and LABA SABA and IC SABA and IC and LABA SABA and LABA and IC without LAMA LAMA and IC IC and LABA and LAMA IC and LABA and LAMA Theophylline without SAMA Theophylline without LAMA Theophylline and SAMA Theophylline and LAMA corticosteroids and LAMA corticosteroids and SABA without LAMA corticosteroids and SABA without SAMA corticosteroids and SABA	Rapid insulin and long insulin sulfonylurea without Rapid insulin rapid insulin without sulfonylurea Rapid insulin and long insulin and metformin metformin and sulfonylurea sulfonylurea and long insulin	N/a

Variables	Congestive Heart Failure	Coronary Artery Disease	Cerebro-vascular accident	Chronic Obstructive Pulmonary Disease	Asthma	Diabetes Mellitus	End Stage Renal Disease
Laboratory tests and thresholds	BNP: 100 pg/mL or NT-proBNP: 53 pmol/L if less than 50YOA, 106 pmol/L if 50-75YOA, or 212 pmol/L if >75YOA	Troponin I or hs Troponin T: 200 ng/L	N/a	N/a	N/a	HbA1c =50mmol/mol	eGFR: less than 15 mL/min

All models were adjusted for age, ethnicity, and sex.
ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, BB: Beta-receptor blocker, BNP: Brain natriuretic peptide, eGFR: estimated glomerular filtration rate, HbA1c: Haemoglobin A1c, HMG CoA: Beta-Hydroxy Beta-methylglutaryl-CoA, hs Troponin T: High sensitivity Troponin T, IC: inhaled corticosteroids, LABA: long-acting beta-receptor agonist, LAMA: long-acting muscarinic receptor antagonist, NT-proBNP: N-terminal pro-brain natriuretic peptide, SABA: short-acting beta-receptor agonist, SAMA: short-acting muscarinic antagonist

Appendix 4.2b Variables used to create case definitions for adults in the SHIVERS study population against which modelled CMC status incidences were validated

Variables	CHF	CAD	CVA	COPD	Asthma	DM	ESRD
ICD10-AM code	I09.81 I500 I509 I11.0 I30.0 P29.0	I200 I201 I208 I209 I210 I211 I212 I213 I214 I219 I220 I221 I228 I229 I230 I231 I232 I233 I234 I235 I236 I238 I240 I248 I249 I250 I2510 I2511 I2512 I2513 I252 I253 I254 I255 I256 I258 I259 Z951 Z955 Z958 Z959 3530306 3530307 3530400 3530401 3530500 3530501 3530906 3530907 3530908 3530909 3531,000 3531001 3531002 3531003 3531004 3531005 3845619	G460 G461 G462 G463 G464 G465 G466 G467 G468 I600 I601 I602 I603 I604 I605 I606 I607 I608 I609 I610 I611 I612 I613 I614 I615 I616 I618 I619 I630 I631 I632 I633 I634 I635 I636 I638 I639 I64 I650 I651 I652 I653 I658 I659 I660 I661 I662 I663 I664 I668 I669 I670 I672 I693 I694 I698	J44 J41 J42 J43	J45 J46 J82	E10 E11 E12 E13 E14 O240 O241 O242 O243	N18.0 Z99.2

		3849700 3849701 3849702 3849703 3849704 3849705 3849706 3849707 3850000 3850001 3850002 3850003 3850004 3850300 3850301 3850302 3850303 3850304 3850500 3863700 9020100 9020101 9020102 9020103					
Medications	≥2 Rx for one of the following: Loop diuretics: 1544- Furosemide 1171- Bumetanide Potassium sparing diuretics: 2176- Spironolactone 1050- Amiloride 4006- Metolazone Loop w potassium sparing diuretics: 1051- Amiloride w furosemide	≥2 Rx for one of the following Nitrates: 1577 Glyceryl trinitrate 2836 Isosorbide mononitrate Vasodilators: 3975 Nicorandil Calcium Channel blockers: 1949- Perhexiline	N/a	≥2 Rx for one of the following: LAMA SAMA	≥2 Rx for one of the following: LABA IC	≥2 Rx for one of the following Insulin- Rapid-, short- and intermediate-acting preparations: 1648 - Insulin Neutral 1655 - Insulin zinc suspension 3982- Insulin aspart with insulin aspart protamine 1649 - Insulin isophane 6300 - Insulin isophane with insulin neutral 3982- Insulin lispro with insulin lispro protamine 3783 - Insulin aspart 3908- Insulin glulisine 1192 - Insulin lispro Insulin- Long-acting preparations: 3857 - Insulin glargine Alpha glucosidase inhibitors 1247 - Acarbose Sulfonylureas: 1068 - Chlorpropamide	≥2 Rx for the following combinations Epoetin alfa and colecalciferol and phosphate binders OR Calcitriol and colecalciferol and phosphate binders

						1567 - Glibenclamide 1568 - Gliclazide 1569 - Glipizide 2276 - Tolazamide 2277 - Tolbutamide Thiazolidinedione: 3739 - Rosiglitazone 3800 – Pioglitazone	
Laboratory tests and thresholds	BNP: 100 pg/mL or NT-proBNP: 53 pmol/L if less than 50YOA, 106 pmol/L if 50-75YOA, or 212 pmol/L if >75YOA	≥2 troponin or hstroponinT:200 ng/L	N/a	N/a	N/a	≥2 HgbA1c >=50mmol/mol	≥2 eGFR: less than 15 mL/min

***** To meet the case definition for each CMC, one must have either a single ICD-10AM code, ≥2 medication prescriptions, or ≥2 laboratory test results meeting specified threshold

BNP: Brain natriuretic peptide, eGFR: estimated glomerular filtration rate, HbA1c: Haemoglobin A1c, hs Troponin T: High sensitivity Troponin T, IC: inhaled corticosteroids, LABA: long-acting beta-receptor agonist, LAMA: long-acting muscarinic receptor antagonist, NT-proBNP: N-terminal pro-brain natriuretic peptide, SAMA: short-acting muscarinic antagonist.

Appendix 4.3 Associations of chronic medical conditions with age group and ethnicity in the SHIVERS study population, Auckland, NZ, 2012–2015

Demographic variables	Chronic Medical Condition*											
	COPD			Asthma			CHF			CAD		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age Group (years)												
18–49	†			Ref			Ref			Ref		
50–64	Ref			1.45	1.43–1.48	0.000	9.34	8.87–9.83	0.000	11.63	11.3–11.97	0.000
65–80	2.62	2.55–2.68	0.000	1.98	1.95–2.02	0.000	56.46	53.83–59.23	0.000	47.90	46.54–49.29	0.000
Ethnic Group												
Māori	4.49	4.32–4.66	0.000	1.65	1.62–1.69	0.000	3.23	3.1–3.37	0.000	2.21	2.15–2.29	0.000
Pacific	1.77	1.71–1.84	0.000	0.95	0.93–0.97	0.000	1.99	1.92–2.06	0.000	1.90	1.86–1.95	0.000
Asian	0.33	0.31–0.34	0.000	0.57	0.56–0.58	0.000	0.60	0.58–0.63	0.000	1.01	0.99–1.04	0.279
European/Other	Ref			Ref			Ref			Ref		

Demographic variables	Chronic Medical Condition*								
	CVA			DM			ESRD		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age Group (years)									
18–49	†			Ref			†		
50–64	Ref			6.55	6.42–6.68	0.000	Ref		
65–80	3.87	3.64–4.12	0.000	11.99	11.73–12.26	0.000	2.32	2.11–2.54	0.000
Ethnic group									
Māori	2.06	1.87–2.27	0.000	3.88	3.77–3.99	0.000	9.16	7.91–10.61	0.000
Pacific	1.44	1.52–1.78	0.000	6.35	6.21–6.49	0.000	10.47	9.26–11.83	0.000
Asian	1.03	0.77–0.91	0.336	3.08	3.02–3.15	0.000	1.97	1.67–2.30	0.000
European/Other	Ref			Ref			Ref		

*COPD; Chronic obstructive pulmonary disease, CHF; congestive heart failure, CAD; coronary artery disease, CVA; cerebrovascular accident, DM; diabetes mellitus, ESRD; end–stage renal disease

† Modelled COPD, CVA, and ESRD data was not included for adults aged 18–49 years

Appendix 4.4 Proportion positive for respiratory syncytial virus (RSV) by severe acute respiratory infection (SARI) case definition for each chronic medical condition and age group, Auckland, NZ, 2012–2015

	COPD			Asthma		
Total Population RSV positive/Tested hospitalisations	SARI 81/933 (8.7)	non-SARI 56/609 (9.2)	p-value* 0.729	SARI 101/1399 (7.2)	non-SARI 72/839 (8.6)	p-value* 0.243
By Age Group						
18–49 years RSV positive/Tested hospitalisations	†	†		16/411 (3.9)	14/210 (6.7)	0.127
50–64 years RSV positive/Tested hospitalisations	27/379 (7.1)	23/230 (10.0)	0.210	33/438 (7.5)	24/250 (9.6)	0.344
65–80 years RSV positive/Tested hospitalisations	54/554 (9.7)	33/379 (8.7)	0.592	52/550 (9.5)	34/379 (9.0)	0.803

	CHF			CAD		
Total Population RSV positive/Tested hospitalisations	SARI 32/430 (7.4)	non-SARI 18/241 (7.5)	p-value* 0.990	SARI 59/692 (8.5)	non-SARI 24/354 (6.8)	p-value* 0.323
By Age Group						
18–49 years RSV positive/Tested hospitalisations	3/40 (7.5)	3/23 (13.0)	0.471	6/60 (10.0)	0/20 (0.0)	0.141
50–64 years RSV positive/Tested hospitalisations	9/124 (7.3)	3/70 (4.3)	0.409	19/235 (8.1)	11/102 (10.8)	0.424
65–80 years RSV positive/Tested hospitalisations	20/266 (7.5)	12/166 (7.2)	0.911	34/397 (8.6)	13/232 (5.6)	0.173

	CVA					DM				
Total Population	SARI		non-SARI		p-value*	SARI		non-SARI		p-value*
RSV positive/Tested hospitalisations	6/94	(6.4)	3/40	(7.5)	0.813	67/734	(9.1)	25/348	(7.2)	0.284
By Age Group										
18–49 years RSV positive/Tested hospitalisations	†		†			12/128	(9.4)	4/43	(9.3)	0.989
50–64 years RSV positive/Tested hospitalisations	2/28	(7.1)	0/8	(0.0)	0.437	21/289	(7.3)	5/125	(4.0)	0.209
65–80 years RSV positive/Tested hospitalisations	3/28	(10.7)	3/55	(5.5)	0.382	34/317	(10.7)	16/180	(8.9)	0.513

	ESRD				
Total Population	SARI		non-SARI		p-value*
RSV positive/Tested hospitalisations	7/123	(5.7)	2/57	(3.5)	0.532
By Age Group					
18–49 years RSV positive/Tested hospitalisations	†		†		
50–64 years RSV positive/Tested hospitalisations	5/57	(8.8)	1/20	(5.0)	0.588
65–80 years RSV positive/Tested hospitalisations	1/39	(2.6)	1/27	(3.7)	0.791

COPD; Chronic obstructive pulmonary disease, CHF; congestive heart failure, CAD; coronary artery disease, CVA; cerebrovascular accident, DM; diabetes mellitus, ESRD end-stage renal disease.

* Proportion positive for RSV was not significantly different by SARI case definition for any CMC overall or by age group.

† Modelled COPD, CVA, and ESRD data was not included for adults aged 18–49 years

Appendix 4.5 R code for deterministic, age structured RSV transmission model, including code evaluating RSV preventative strategies.

a. Base model (without intervention) and fitting with maximum likelihood estimation

```
# TIME #
# simulation times
maxtime <- 15 * 52 # number of weeks that the model runs for.
dt <- 1
T0 <- 0

# PARAMETERS #
# Disease parameters
beta0 <- 0.03212573 # transmission rate
beta1 <- 0.19111865 # seasonality - kept same for both child and adults as same seasonality/climatic factors
phi <- -0.70760872 # phase shift
sigma <- 1/0.57 # loss of latency rate (weekly)
gamma <- 1/1.4 # loss of infectiousness rate (weekly)
v <- 1/28.5 # loss of immunity (weekly)
alpha1 <- 0.32956471 #reduced susceptibility in age group 1 (<2m)
alpha3 <- 0.91862882 #reduced susceptibility in age group 3 (6-23m)
alpha4 <- 0.34550328 #reduced susceptibility in age group 4 (24m +)

# Population and ageing parameters
live_births = 279 # weekly life births in Auckland
mu1 = 1/(3*4.34524) # ageing out rate from age group 1 to age group 2
mu2 = 1/(3*4.34524) # ageing out rate from age group 2 to age group 3
mu3 = 1/(18*4.34524) # ageing out rate from age group 3 to age group 4
mu4 = 1/(78*52)# ageing out/death rate from age group 4
auck_pop = 1e6 # total Auckland population size
rel_sizes = c(0.005, 0.005, 0.028, 0.962) # relative size of each age class
nage = length(rel_sizes) # number of age classes
age.names = c("under3m","3–5m", "6-23m", "24m+") # age-class names

# Import mixing matrix
K <- as.matrix(read.csv("mixing_matrix_4ageclass_weekly.csv", header = FALSE), header = FALSE)
colnames(K) = paste( "i_",age.names,sep="")
rownames(K) = paste( "j_",age.names,sep="")
K <- as.vector(K)

# Initial conditions
I0 = rel_sizes * auck_pop * 0.01
S0 = rel_sizes * auck_pop * 0.98
E0 = rel_sizes * auck_pop * 0.01
R0 = rel_sizes * auck_pop * 0.00
N = S0+E0+I0+R0
Incidence0 <- R0
# Set up inputs for ODE solver
parameters = c(v=v, sigma=sigma,gamma=gamma,beta0=beta0,beta1=beta1, K=K, phi=phi, live_births=live_births,
mu1=mu1, mu2=mu2, mu3=mu3, mu4=mu4, alpha1=alpha1, alpha3=alpha3, alpha4=alpha4)
initial.conds = c(S=S0,E=E0,I=I0,R=R0, Incidence=Incidence0)
times <- seq(0, maxtime, by = dt)
```

```
# MODEL FUNCTION
seirs.rsv.model <- function(time, initial.conds, parameters) {
  with(as.list(c(initial.conds, parameters)), {
    K <- matrix(as.vector(K), nrow=4, ncol=4)
    #  make vector for reduced infectiousness
    alpha_vect <- matrix(1, 1, nage)
    alpha_vect[1] <- alpha1
    alpha_vect[3] <- alpha3
    alpha_vect[4] <- alpha4
    alpha_vect <- as.vector(alpha_vect)
    S <- matrix(initial.conds[1:nage], nrow = nage, ncol=1)
    E <- matrix(initial.conds[(nage+1):(2*nage)], nrow = nage, ncol=1)
    I <- matrix(initial.conds[(2*nage+1):(3*nage)], nrow = nage, ncol=1)
    R <- matrix(initial.conds[(3*nage+1):(4*nage)], nrow = nage, ncol=1)
    N <- S + E + I + R
    lambda <- beta0 * (1 + beta1 * cos(2 * pi * time / 52 + phi)) * (K %*% (as.vector(I) / as.vector(N)))
    infect <- lambda * alpha_vect* as.vector(S)

    # differential equations
    dS1 <- live_births - infect[1] + v * R[1] - mu1*S[1]
    dE1 <- infect[1] - sigma * E[1] - mu1*E[1]
    dI1 <- sigma*E[1] - gamma * I[1] - mu1*I[1]
    dR1 <- gamma * I[1] - v * R[1] - mu1*R[1]

    dS2 <- mu1*S[1] -infect[2] + v * R[2] - mu2*S[2]
    dE2 <- mu1*E[1] + infect[2] - sigma * E[2] - mu2*E[2]
    dI2 <- mu1*I[1] + sigma*E[2] - gamma * I[2] - mu2*I[2]
    dR2 <- mu1*R[1] + gamma * I[2] - v * R[2] - mu2*R[2]

    dS3 <- mu2*S[2] -infect[3] + v * R[3] - mu3*S[3]
    dE3 <- mu2*E[2] + infect[3] - sigma * E[3] - mu3*E[3]
    dI3 <- mu2*I[2] + sigma*E[3] - gamma * I[3] - mu3*I[3]
    dR3 <- mu2*R[2] + gamma * I[3] - v * R[3] - mu3*R[3]

    dS4 <- mu3*S[3] -infect[4] + v * R[4] - mu4*S[4]
    dE4 <- mu3*E[3] + infect[4] - sigma * E[4] - mu4*E[4]
    dI4 <- mu3*I[3] + sigma*E[4] - gamma * I[4] - mu4*I[4]
    dR4 <- mu3*R[3] + gamma * I[4] - v * R[4] - mu4*R[4]

    dIncidence1 <- infect[1]
    dIncidence2 <- infect[2]
    dIncidence3 <- infect[3]
    dIncidence4 <- infect[4]

    out = c(dS1, dS2, dS3, dS4,dE1, dE2,dE3, dE4, dI1, dI2, dI3, dI4,dR1, dR2,dR3, dR4, dIncidence1, dIncidence2,
dIncidence3, dIncidence4)
    list (out)
  })
}

# OUTPUT
pop_out <-as.data.frame(lsoda(y = initial.conds,times = times,func = seirs.rsv.model,parms = parameters))
pop_out <- pop_out %>% mutate(total_pop = S1+E1+I1+R1+S2+E2+I2+R2+S3+E3+I3+R3+S4+E4+I4+R4)
# Calculate incidence rate i.e. no. of new cases
pop_out <- pop_out %>% mutate(IR1=lead(Incidence1,n = 1)-Incidence1)
pop_out <- pop_out %>% mutate(IR2=lead(Incidence2,n = 1)-Incidence2)
pop_out <- pop_out %>% mutate(IR3=lead(Incidence3,n = 1)-Incidence3)
pop_out <- pop_out %>% mutate(IR4=lead(Incidence4,n = 1)-Incidence4)
```

```
# IMPORT DATA
obs = read.csv("data_4ageclass.csv")

# Estimation proportion of infected cases that are hospitalised and detected
# First limit modelled incidence to 4 seasons which is how long we have data for
model_out <- subset(pop_out, time>=418 & time<627, select = c(time, IR1, IR2, IR3, IR4))
# Get an estimate of proportion of infected cases that are hospitalised and detected by dividing incidence in data by incidence in model
# Calculate p1 and p2
p1 = (sum(obs$age_grp1))/(sum(model_out$IR1))
p2 = (sum(obs$age_grp2))/(sum(model_out$IR2))
p3 = (sum(obs$age_grp3))/(sum(model_out$IR3))
p4 = (sum(obs$age_grp4))/(sum(model_out$IR4))

# FITTING USING MAXIMUM LIKELIHOOD
# 1 - Assume weekly RSV hospitalisations followed a Poisson distribution. P1 represents sampling efficiency and detectability of hospitalised infections in age class 1.

# Produce an auxiliary function that will return a vector of model predictions over 4 seasons (IR in age class 1) once the model has stabilised
prediction1 <- function(params, times) {
  initial.conds=initial.conds
  epi <- as.data.frame( lsoda(func=seirs.rsv.model, y=initial.conds, times=times, parms=params) )
  epi <- epi %>% mutate(IR1=lead(Incidence1,n = 1)-Incidence1)
  epi <- as.vector(epi$IR1) # Overall incidence rate in age class 1
  epi # Overall incidence rate in age class 1
}

# Produce an auxiliary function that will return a vector of model predictions over 4 seasons (IR in age class 2) once the model has stabilised
prediction2 <- function(params, times) {
  initial.conds=initial.conds
  epi2 <- as.data.frame( lsoda(func=seirs.rsv.model, y=initial.conds, times=times, parms=params) )
  epi2 <- epi2 %>% mutate(IR2=lead(Incidence2,n = 1)-Incidence2)
  epi2 <- as.vector(epi2$IR2) # Overall incidence rate in age class 2
  epi2 # Overall incidence rate in age class 2
}

# Produce an auxiliary function that will return a vector of model predictions over 4 seasons (IR in age class 3) once the model has stabilised
prediction3 <- function(params, times) {
  initial.conds=initial.conds
  epi3 <- as.data.frame( lsoda(func=seirs.rsv.model, y=initial.conds, times=times, parms=params) )
  epi3 <- epi3 %>% mutate(IR3=lead(Incidence3,n = 1)-Incidence3)
  epi3 <- as.vector(epi3$IR3) # Overall incidence rate in age class 3
  epi3 # Overall incidence rate in age class 3
}

# Produce an auxiliary function that will return a vector of model predictions over 4 seasons (IR in age class 4) once the model has stabilised
prediction4 <- function(params, times) {
  initial.conds=initial.conds
  epi4 <- as.data.frame( lsoda(func=seirs.rsv.model, y=initial.conds, times=times, parms=params) )
  epi4 <- epi4 %>% mutate(IR4=lead(Incidence4,n = 1)-Incidence4)
  epi4 <- as.vector(epi4$IR4) # Overall incidence rate in age class 4
  epi4 # Overall incidence rate in age class 4
}
```

```
# Poisson loglikelihood function
poisson.loglik <- function (params, data) {
  offset_week = data$week + 400
  times <- c(0, offset_week, offset_week[length(offset_week)]+1)

  pred1 <- prediction1(params,times)
  pred1 = pred1[2:(length(pred1)-1)]

  pred2 <- prediction2(params,times)
  pred2 = pred2[2:(length(pred2)-1)]

  pred3 <- prediction3(params,times)
  pred3 = pred3[2:(length(pred3)-1)]

  pred4 <- prediction4(params,times)
  pred4 = pred4[2:(length(pred4)-1)]

  llik1 = sum(dpois(x=data$age_grp1,lambda=params["p1"]*pred1,log=TRUE))
  llik2 = sum(dpois(x=data$age_grp2,lambda=params["p2"]*pred2,log=TRUE))
  llik3 = sum(dpois(x=data$age_grp3,lambda=params["p3"]*pred3,log=TRUE))
  llik4 = sum(dpois(x=data$age_grp4,lambda=params["p4"]*pred4,log=TRUE))

  sum(llik1 +llik2 + llik3+ llik4)

}

# Add constraints to beta1 to make sure it's between 0-1
logit.beta1 <- function (beta1) log(beta1/(1-beta1)) # logit transform
# Add constraints to alpha3 & alpha4 to make sure it's between 0-1
logit.alpha1 <- function (alpha1) log(alpha1/(1-alpha1)) # logit transform
logit.alpha4 <- function (alpha4) log(alpha4/(1-alpha4)) # logit transform
# Inverse logit for bank transformation
ilogit <- function (x) 1/(1+exp(-x))

# log beta0 so it's always >0
f <- function (log.beta0, logit.beta1, phi, logit.alpha1, alpha3, logit.alpha4) {
  par <- params
  par[c( "beta0", "beta1", "phi", "alpha1", "alpha3","alpha4")] <- c(exp(log.beta0), ilogit(logit.beta1), phi,
ilogit(logit.alpha1), alpha3, ilogit(logit.alpha4))
  -poisson.loglik(par,dat)
}

dat <- obs
params <- c(v=v, sigma=sigma,gamma=gamma,beta0=NA,beta1=NA, K=K, phi=NA, live_births=live_births,
mu1=mu1, mu2=mu2, mu3=mu3, mu4=mu4, p1=p1, p2=p2,p3=p3, p4=p4, alpha1=NA, alpha3=NA, alpha4=NA)
# OPTIMISE LIKELIHOOD
guess <- list(log.beta0=log(beta0), logit.beta1=-1.44, phi=-1.5, logit.alpha1=-0.71, alpha3=0.9, logit.alpha4=0)
fit <- mle2(f, start=guess); fit
mle <- with(as.list(coef(fit)),c(beta0=exp(log.beta0), beta1=ilogit(logit.beta1), phi=phi, alpha1=ilogit(logit.alpha1),
alpha3=alpha3, alpha4=ilogit(logit.alpha4)))

# CIs for fitted parameter values. NOTE: Takes a long time
p0 <- profile(fit)
ci <- confint (fit, method = "quad")
mle_results <- cbind(as.data.frame(fit@fullcoef), as.data.frame(ci))
```

b. Model with maternal vaccination

```
# Vaccination parameters - NOTE default values here
pv=0.5 # proportion vaccinated
ve1 <- 0.6 #reduced susceptibility in age group 1 due to maternal vaccination
ve2 <- 0.8 #reduced susceptibility in age group 2 due to maternal vaccination

# VACCINATION MODEL FUNCTION

seirs.rsv.v.model <- function(time, initial.conds, parameters) {
  with(as.list(c(initial.conds, parameters)), {
    K <- matrix(as.vector(K), nrow=4, ncol=4)

    S <- matrix(initial.conds[1:nage], nrow = nage, ncol=1)
    E <- matrix(initial.conds[(nage+1):(2*nage)], nrow = nage, ncol=1)
    I <- matrix(initial.conds[(2*nage+1):(3*nage)], nrow = nage, ncol=1)
    R <- matrix(initial.conds[(3*nage+1):(4*nage)], nrow = nage, ncol=1)
    V <- matrix(initial.conds[(4*nage+1):(5*nage)], nrow = nage, ncol=1)
    N <- S + E + I + R + V

    #  Make vector for reduced susceptibility due to maternal antibody in age class 1 and age/immunity in age class
3,4. Age class 2 is 100% susceptible
    alpha_vect <- matrix(1, 1, nage)
    alpha_vect[1] <- alpha1
    alpha_vect[3] <- alpha3
    alpha_vect[4] <- alpha4
    alpha_vect <- as.vector(alpha_vect)

    #  Make vector for reduced susceptibility in vaccinated (V) group. Multiplying baseline immunity with vaccine
induced immunity
    ve_vect <- matrix(1, 1, nage)
    ve_vect[1] <- alpha1*ve1
    ve_vect[2] <- ve2
    ve_vect[3] <- alpha3
    ve_vect[4] <- alpha4
    ve_vect <- as.vector(ve_vect)

    lambda <- beta0 * (1 + beta1 * cos(2 * pi * time / 52 + phi)) * (K %*% (as.vector(I) / as.vector(N)))
    infect_s <- lambda * alpha_vect* as.vector(S)
    infect_v <- lambda * ve_vect* as.vector(V) # Vaccination reduces susceptibility further

    # Differential equations
    dS1 <- (1-pv)*live_births - infect_s[1] + delta * R[1] - mu1*S[1]
    dE1 <- infect_s[1] + infect_v[1] - sigma * E[1] - mu1*E[1]
    dI1 <- sigma*E[1] - gamma * I[1] - mu1*I[1]
    dR1 <- gamma * I[1] - delta * R[1] - mu1*R[1]
    dV1 <- pv*live_births - infect_v[1]  - mu1*V[1]

    dS2 <- mu1*S[1] - infect_s[2] + delta * R[2] - mu2*S[2]
    dE2 <- mu1*E[1] + infect_s[2]+ infect_v[2] - sigma * E[2] - mu2*E[2]
    dI2 <- mu1*I[1] + sigma*E[2] - gamma * I[2] - mu2*I[2]
    dR2 <- mu1*R[1] + gamma * I[2] - delta * R[2] - mu2*R[2]
    dV2 <- mu1*V[1] - infect_v[2] - mu2*V[2]

    dS3 <- mu2*S[2] - infect_s[3] + delta * R[3] - mu3*S[3]
    dE3 <- mu2*E[2] + infect_s[3]+ infect_v[3] - sigma * E[3] - mu3*E[3]
    dI3 <- mu2*I[2] + sigma*E[3] - gamma * I[3] - mu3*I[3]
    dR3 <- mu2*R[2] + gamma * I[3] - delta * R[3] - mu3*R[3]
    dV3 <- mu2*V[2] - infect_v[3] - mu3*V[3]
```

```
    dS4 <- mu3*S[3] -infect_s[4] + delta * R[4] - mu4*S[4]
    dE4 <- mu3*E[3] + infect_s[4]+ infect_v[4] - sigma * E[4] - mu4*E[4]
    dI4 <- mu3*I[3] + sigma*E[4] - gamma * I[4] - mu4*I[4]
    dR4 <- mu3*R[3] + gamma * I[4] - delta * R[4] - mu4*R[4]
    dV4 <- mu3*V[3] -infect_v[4] - mu4*V[4]

    dCumltv_inc1 <- infect_s[1] +infect_v[1]
    dCumltv_inc2 <- infect_s[2] +infect_v[2]
    dCumltv_inc3 <- infect_s[3] +infect_v[3]
    dCumltv_inc4 <- infect_s[4] +infect_v[4]

    out = c(dS1, dS2, dS3, dS4,dE1, dE2,dE3, dE4, dI1, dI2, dI3, dI4,dR1, dR2,dR3, dR4, dV1, dV2, dV3, dV4,
dCumltv_inc1, dCumltv_inc2, dCumltv_inc3, dCumltv_inc4)
    list (out)
  })
}
```

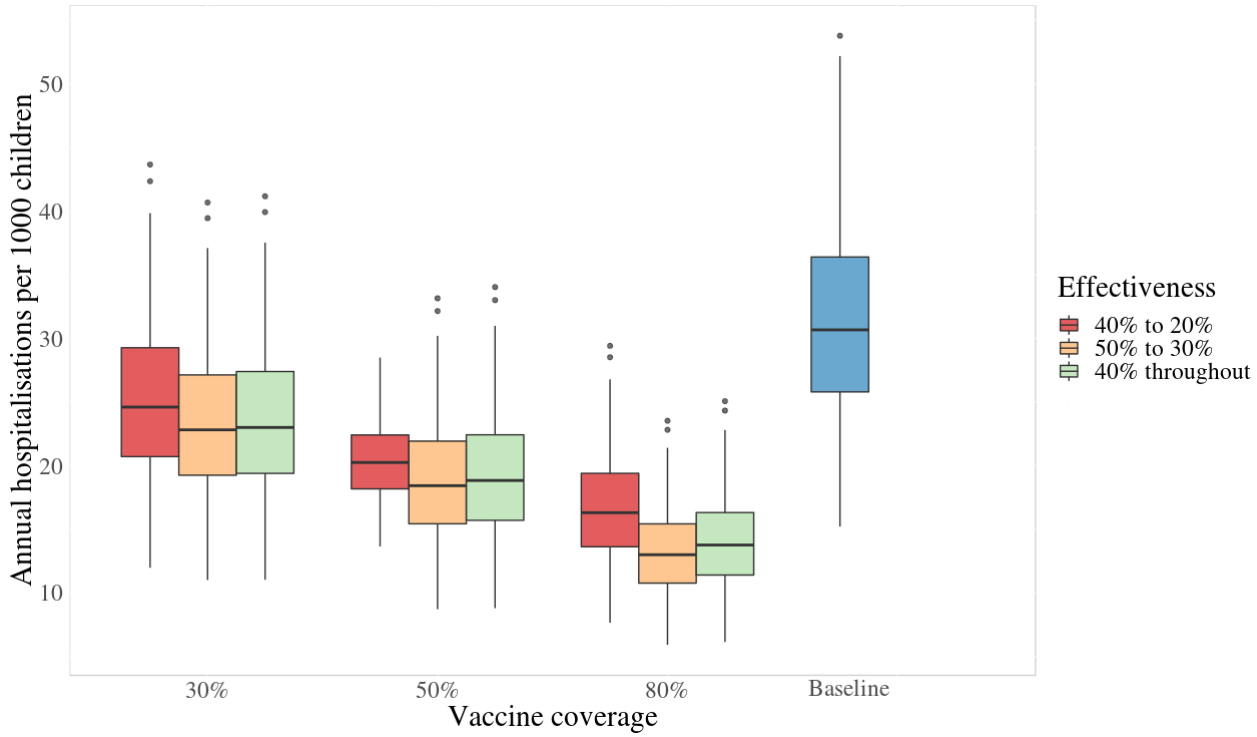
c. Model with seasonal mAb

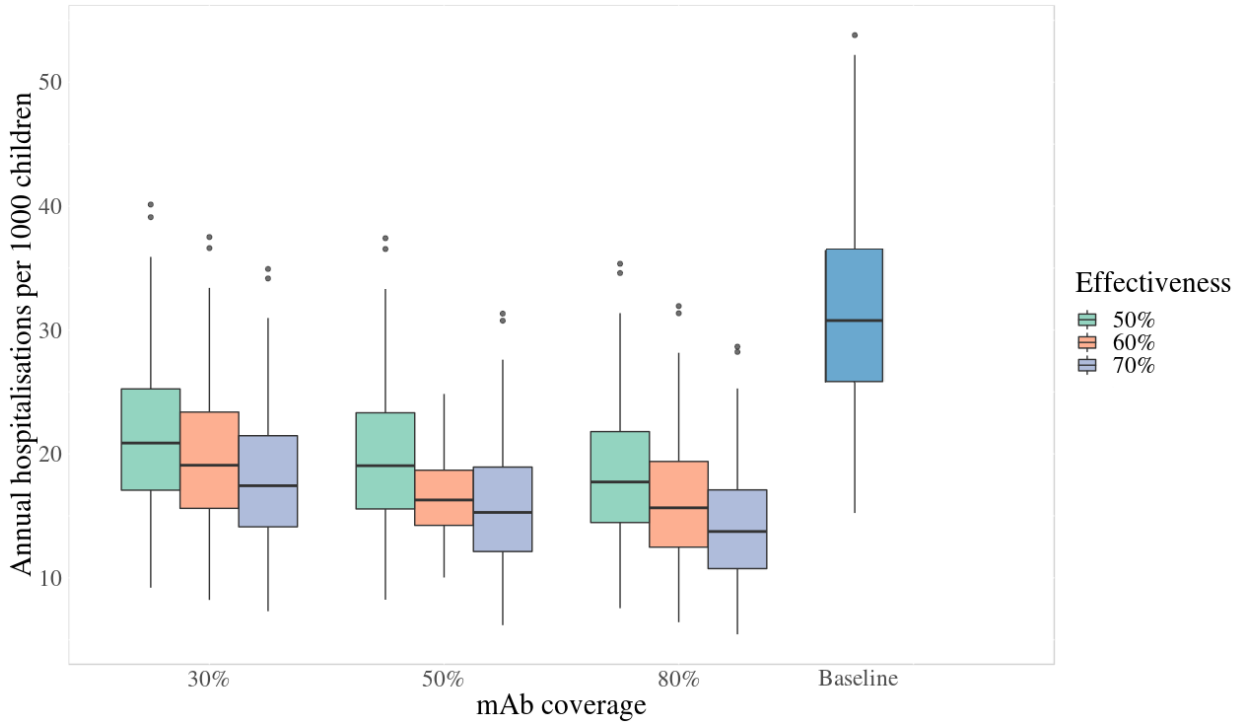
```
# mAb parameters - NOTE default values here
pv=0.5 # proportion immunised
ve1 <- 0.4 #reduced susceptibility in age group 1 due to mAb
ve2 <- 0.4 #reduced susceptibility in age group 2 due to mAb
ve3 <- 0.4 #reduced susceptibility in age group 3 due to mAb
# Loss of mAb induced immunity from immunised group in age class 2/3 if they were immunised in earlier age group, as mAb protection is only for 150 days
ve_loss = 1/(21.4286)


# SEASONAL mAb MODEL FUNCTION
seirs.rsv.mab.model <- function(time, initial.conds, parameters) {

  with(as.list(c(initial.conds, parameters)), {

# Conditional that children are only immunised 1 month before or during RSV season in NZ
    if (time >=14 & time <=39|time >=66 & time <=91|time >=118 & time <=143|time >=170 & time <=195|time >=222 & time <=247|
        time >=274 & time <=299|time >=326 & time <=351|time >=378 & time <=403|time >=430 & time <=455|time >=482 & time <=507) {
      pv=pv
    } else {
      pv=0
    }

    K <- matrix(as.vector(K), nrow=4, ncol=4)

    S <- matrix(initial.conds[1:nage], nrow = nage, ncol=1)
    E <- matrix(initial.conds[(nage+1):(2*nage)], nrow = nage, ncol=1)
    I <- matrix(initial.conds[(2*nage+1):(3*nage)], nrow = nage, ncol=1)
    R <- matrix(initial.conds[(3*nage+1):(4*nage)], nrow = nage, ncol=1)
    V <- matrix(initial.conds[(4*nage+1):(5*nage)], nrow = nage, ncol=1)
    N <- S + E + I + R + V

    #  Make vector for reduced susceptibility due to maternal antibody in age class 1 and age/immunity in age class 3,4. Age class 2 is 100% susceptible
    alpha_vect <- matrix(1, 1, nage)
    alpha_vect[1] <- alpha1
    alpha_vect[3] <- alpha3
    alpha_vect[4] <- alpha4
    alpha_vect <- as.vector(alpha_vect)

    #  Make vector for reduced susceptibility in immunised (V) group. Multiplying baseline immunity with mAb induced immunity
    ve_vect <- matrix(1, 1, nage)
    ve_vect[1] <- alpha1*ve1
    ve_vect[2] <- ve2
    ve_vect[3] <- alpha3*ve3
    ve_vect[4] <- alpha4
    ve_vect <- as.vector(ve_vect)

    lambda <- beta0 * (1 + beta1 * cos(2 * pi * time / 52 + phi)) * (K %*% (as.vector(I) / as.vector(N)))
    infect_s <- lambda * alpha_vect* as.vector(S)
    infect_v <- lambda * ve_vect* as.vector(V) # mAb reduces susceptibility further
```

```
 # Differential equations
    dS1 <- live_births - infect_s[1] + delta*R[1] - mu1*S[1]- pv*S[1] + ve_loss*V[1]
    dE1 <- infect_s[1] + infect_v[1] - sigma * E[1] - mu1*E[1]
    dI1 <- sigma*E[1] - gamma * I[1] - mu1*I[1]
    dR1 <- gamma * I[1] - delta * R[1] - mu1*R[1]
    dV1 <- pv*S[1] - infect_v[1]  - mu1*V[1] - ve_loss*V[1]

    dS2 <- mu1*S[1] -infect_s[2] + delta*R[2] - mu2*S[2] -pv*S[2] + ve_loss*V[2]
    dE2 <- mu1*E[1] + infect_s[2]+ infect_v[2] - sigma * E[2] - mu2*E[2]
    dI2 <- mu1*I[1] + sigma*E[2] - gamma * I[2] - mu2*I[2]
    dR2 <- mu1*R[1] + gamma * I[2] - delta * R[2] - mu2*R[2]
    dV2 <- pv*S[2] + mu1*V[1] -infect_v[2] - ve_loss*V[2] - mu2*V[2]

    dS3 <- mu2*S[2] - infect_s[3] + delta * R[3] + ve_loss*V[3] - mu3*S[3]
    dE3 <- mu2*E[2] + infect_s[3]+ infect_v[3] - sigma * E[3] - mu3*E[3]
    dI3 <- mu2*I[2] + sigma*E[3] - gamma * I[3] - mu3*I[3]
    dR3 <- mu2*R[2] + gamma * I[3] - delta * R[3] - mu3*R[3]
    dV3 <- mu2*V[2] - infect_v[3] - ve_loss*V[3] - mu3*V[3]

    dS4 <- mu3*S[3] -infect_s[4] + delta * R[4] - mu4*S[4] + ve_loss*V[4]
    dE4 <- mu3*E[3] + infect_s[4]+ infect_v[4] - sigma * E[4] - mu4*E[4]
    dI4 <- mu3*I[3] + sigma*E[4] - gamma * I[4] - mu4*I[4]
    dR4 <- mu3*R[3] + gamma * I[4] - delta * R[4] - mu4*R[4]
    dV4 <- mu3*V[3] -infect_v[4] - mu4*V[4] -ve_loss*V[4]

    dCumltv_inc1 <- infect_s[1] +infect_v[1]
    dCumltv_inc2 <- infect_s[2] +infect_v[2]
    dCumltv_inc3 <- infect_s[3] +infect_v[3]
    dCumltv_inc4 <- infect_s[4] +infect_v[4]

    out = c(dS1, dS2, dS3, dS4,dE1, dE2,dE3, dE4, dI1, dI2, dI3, dI4,dR1, dR2,dR3, dR4, dV1, dV2, dV3, dV4,
dCumltv_inc1, dCumltv_inc2, dCumltv_inc3, dCumltv_inc4)
    list (out)
  })
}
```

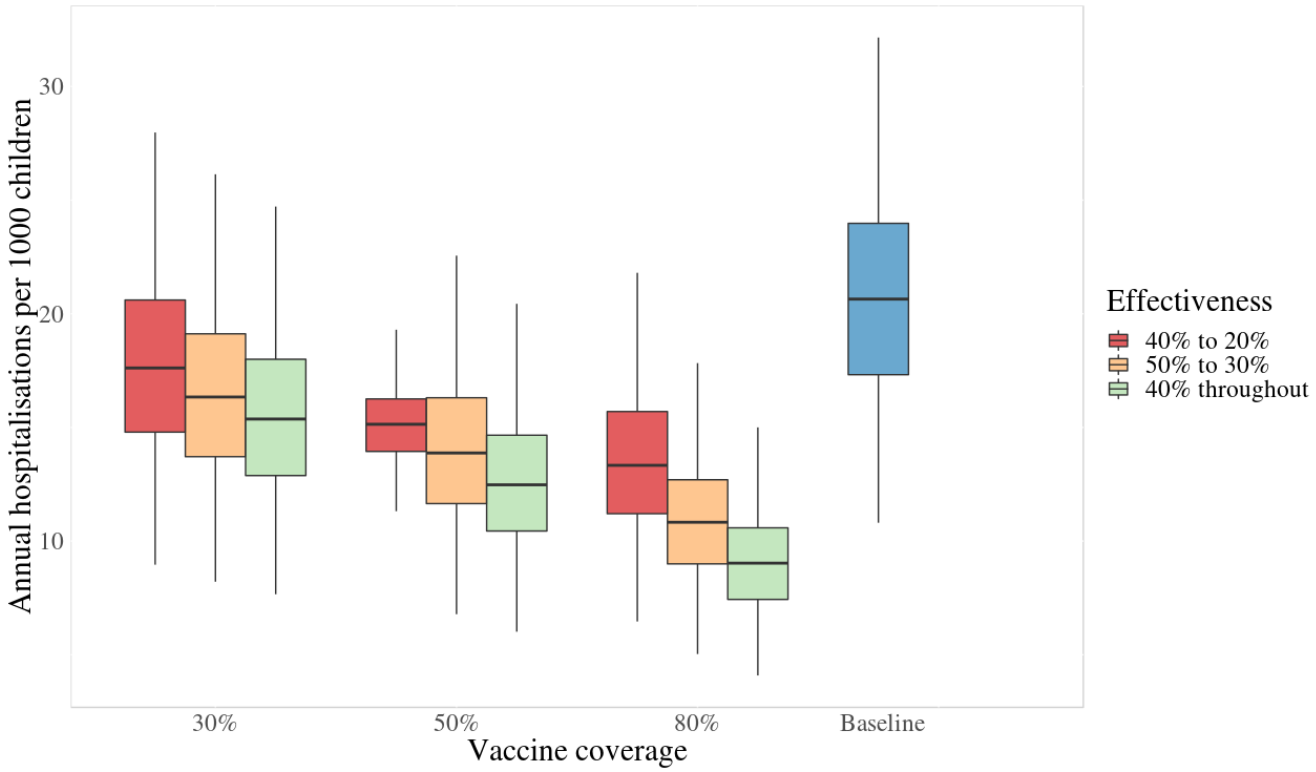
Appendix 4.6 Estimated annual RSV hospitalisations per 1,000 children aged less than two years (by age groups) for baseline and different vaccination and seasonal monoclonal antibody (mAb) effectiveness and coverage scenarios

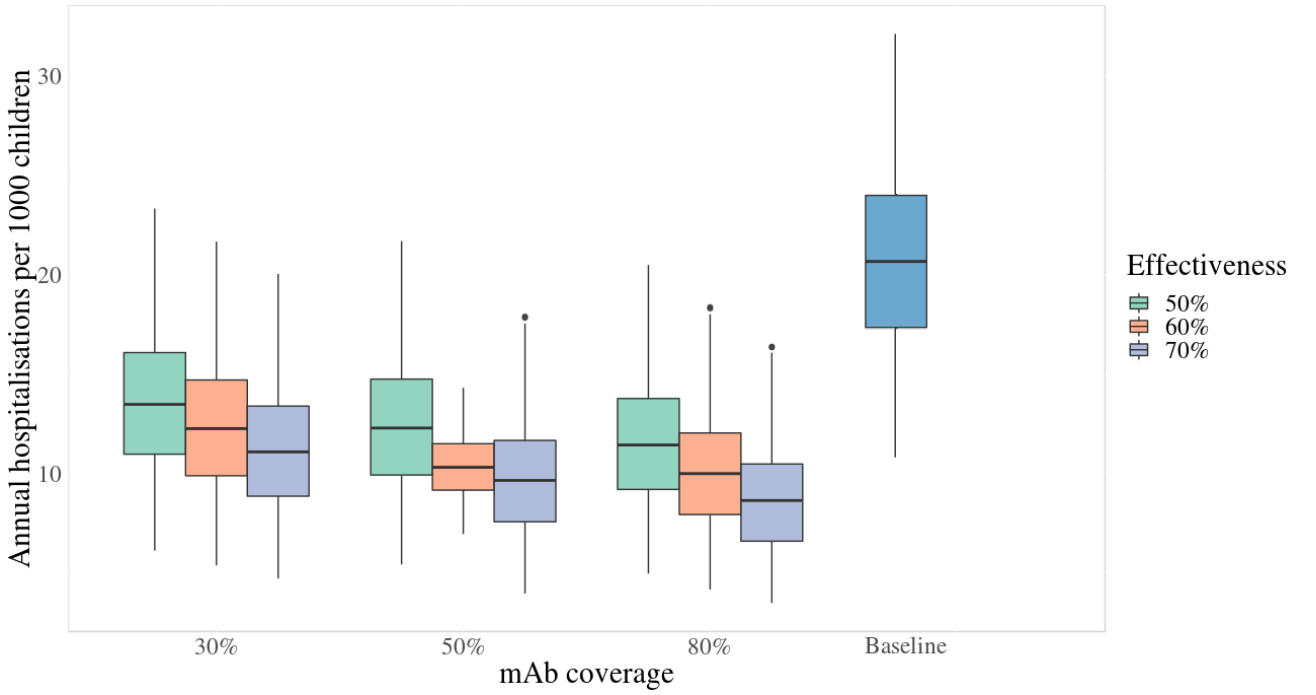
a. Children aged 0–2 months



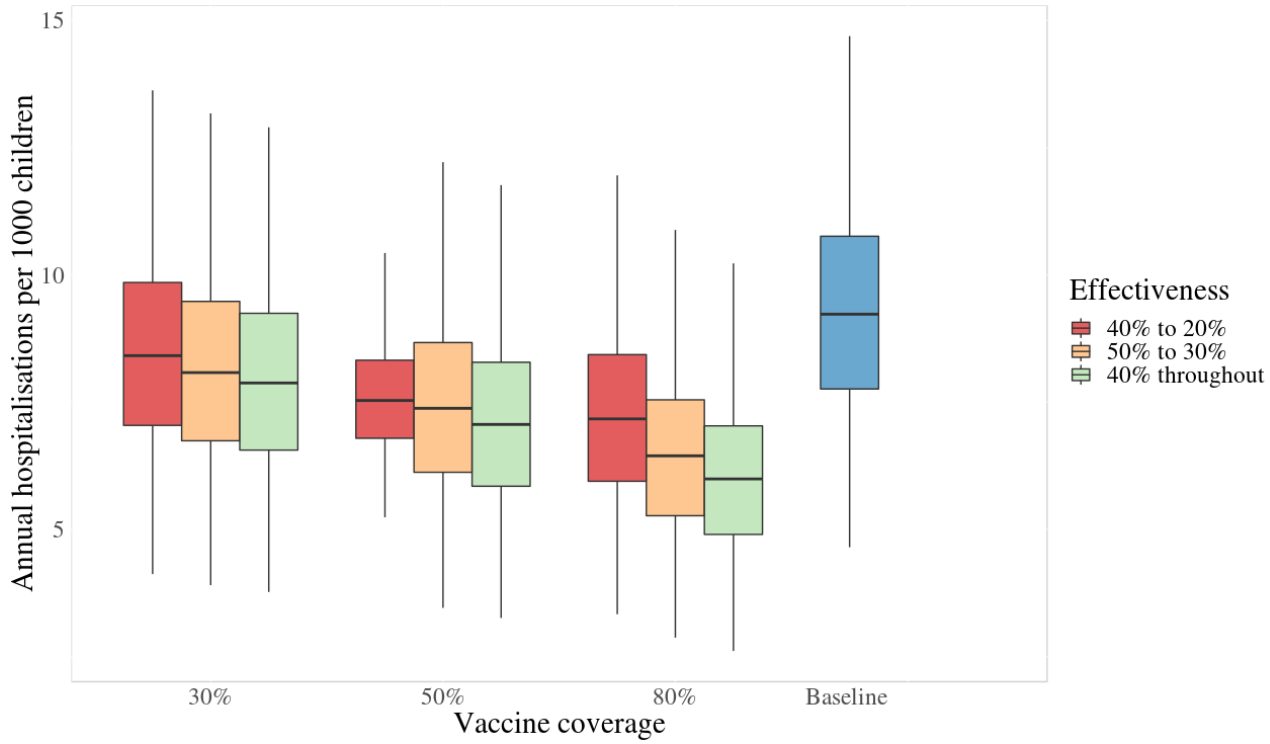


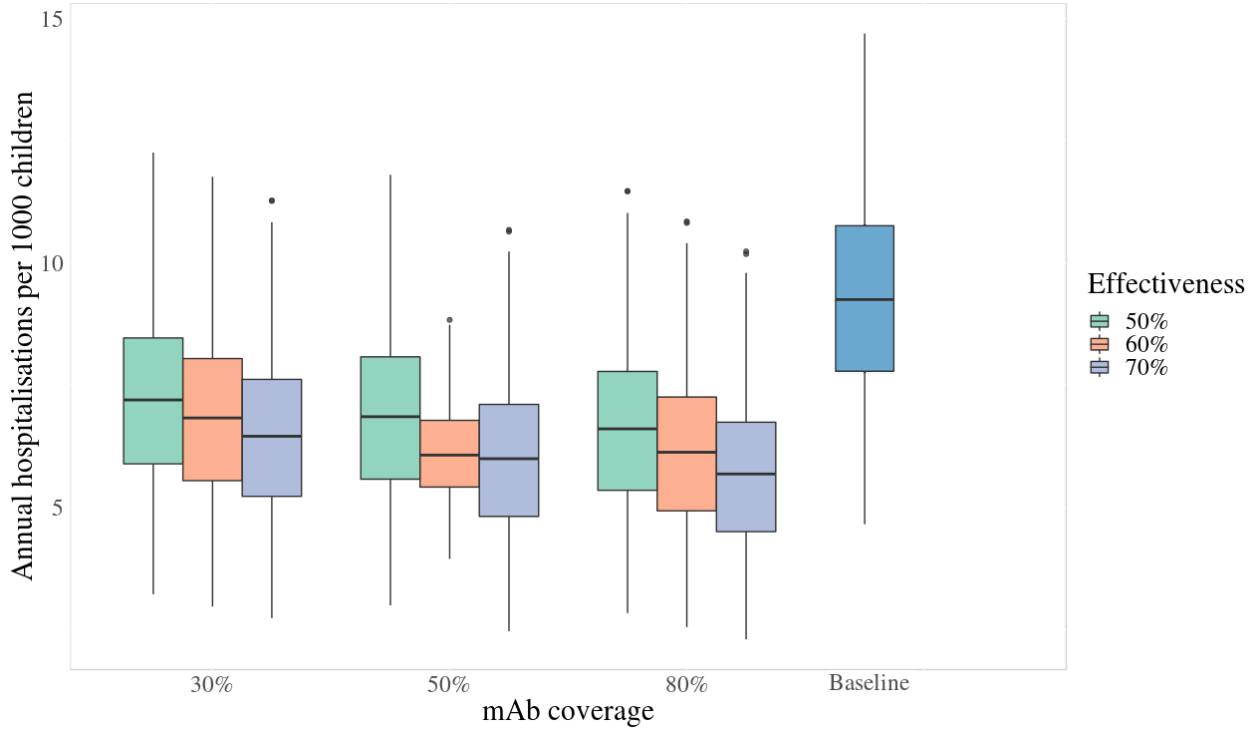
b. Children aged 3–5 months





c. Children aged 6-23 months





Distribution (2.5%, 25%, 75%, and 97.5% quantile and median) of each modelled scenario by age group, which were estimated from the distribution of 500 model simulations. Each simulation used a different combination of parameter values sampling from the fitted parameter uncertainty from maximum likelihood estimation, as shown in Table 8.1.

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Nature of contribution by PhD candidate	Conceptualization, data management, data analysis, drafted the initial manuscript/chapter, revised and approved final manuscript/chapter.
Extent of contribution by PhD candidate (%)	70%

CO-AUTHORS

Name	Nature of Contribution
E.Claire Newbern	Conceptualization, data management, advised on data analysis, revised and approved final manuscript
Adrian A Trenholme	Conceptualization, data acquisition, revised and approved final manuscript
Tim Wood	Data management, data acquistion, advised on data analysis, revised and approved final manuscript
Mark G Thompson	Conceptualization, data acquisiton, advised on data analysis, revised and approved final manuscript
Nayyereh Aminisani	Data management, advised on data analysis, revised and approved final manuscript
Q. Sue Huang & Cameron C Grant	Conceptualization, data acquisition, revised and approved final manuscript

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The undersigned hereby certify that:

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- that the candidate wrote all or the majority of the text.

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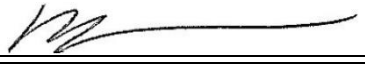
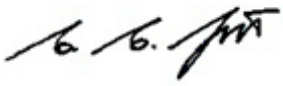
Adrian A Trenholme		22/06/2020
Tim Wood		19/06/2020

Mark G Thompson	Mark Thompson -S Digitally signed by Mark Thompson -S Date: 2020.06.15 09:00:52 -04'00'	15/06/2020
Nayyereh Aminisani		13/06/2020
Q. Sue Huang		12/06/2020
Cameron C Grant		19/06/2020

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Nature of contribution by PhD candidate	Conceptualization, data management, data analysis, drafted the initial manuscript/chapter, revised and approved final manuscript/chapter.
Extent of contribution by PhD candidate (%)	70%

CO-AUTHORS

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Adrian A Trenholme	Conceptualization, data acquisition, advised on data analysis, revised and approved final manuscript
Q. Sue Huang	Data acquisition, revised and approved final manuscript
Jazmin Duque	Conceptualization, advised on data analysis, revised and approved final manuscript
Cameron C Grant	Conceptualization, data acquisition, advised on data ananlysis, revised and approved final manuscript
E. Claire Newbern	Conceptualization, data management, advised on data analysis, revised and approved final manuscript

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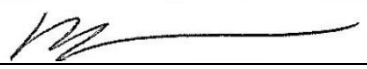
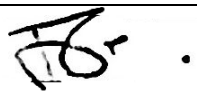
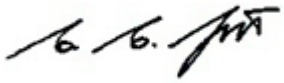
Adrian A Trenholme		22/06/2020
Q. Sue Huang		12/06/2020
Jazmin Duque		14/07/2020

Cameron C Grant		19/06/2020
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Adrian A Trenholme	Conceptualization, data acquisition, revised and approved final manuscript
Mark G Thompson, Lauren Jelley	Data acquisiton, revised and approved final manuscript
Colin McArthur, Conroy A Wong	Data acquisiton, revised and approved final manuscript
Nayyereh Aminisani	Data management, advised on data analysis, revised and approved final manuscript
Q. Sue Huang & Cameron C Grant	Conceptualization, data acquisition, revised and approved final manuscript

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- that the candidate wrote all or the majority of the text.

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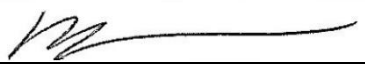
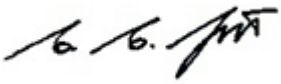
E. Claire Newbern		17/06/2020
Adrian A Trenholme		22/06/2020
Mark G Thompson	Mark Thompson -S Digitally signed by Mark Thompson -S Date: 2020.06.15 09:00:52 -04'00'	15/06/2020

Colin McArthur		12/06/2020
Conroy A Wong		14/06/2020
Nayyereh Aminisani		13/06/2020
Lauren Jelley		12/06/2020
Q. Sue Huang		12/06/2020
Cameron C Grant		19/06/2020

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Co-Authorship Form

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Thesis Chapter : 7 Title: RSV-associated hospitalisations among adults with chronic medical conditions Publication : Prasad N, Walker TA, Waite B, Wood T, Trenholme AA, Baker MG, McArthur CM, Wong CA, Grant CC, Huang QS, Newbern EC. Respiratory syncytial virus associated hospitalisations among adults with chronic medical conditions, Clinical Infectious Diseases; 2020. In Press

Nature of contribution by PhD candidate	Data management, data analysis, drafted the initial manuscript/chapter, revised and approved final manuscript/chapter.
Extent of contribution by PhD candidate (%)	66%

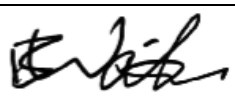
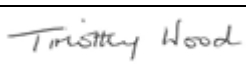
CO-AUTHORS

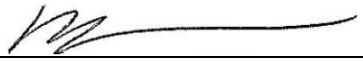
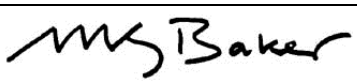
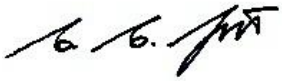
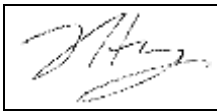
Name	Nature of Contribution
Tiffany A. Walker, Ben Waite	Conceptualization, data management, carried out data analysis (population level comorbidity data), revised and approved final manuscript
Tim Wood	Data management, advised on data analysis, revised and approved final manuscript
Adrian A Trenholme, Cameron C Grant	Data acquisiton, revised and approved final manuscript
Michael G Baker, Colin McArthur, Conroy A Wong	Conceptualization, data acquisition, revised and approved final manuscript
Q. Sue Huang	Conceptualization, data acquisition, revised and approved final manuscript
E. Claire Newbern	Conceptualization, data management, advised on data analysis, revised and approved final manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Tiffany A. Walker		16/06/2020
Ben Waite		17/06/2020
Tim Wood		19/06/2020

Adrian A Trenholme		22/06/2020
Michael G Baker		7/07/2020
Colin McArthur		12/06/2020
Conroy A Wong		14/06/2020
Cameron C Grant		19/06/2020
Q. Sue Huang		12/06/2020
E. Claire Newbern		17/06/2020

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Thesis Chapter : 8 Chapter title: Modelling the impact of respiratory syncytial virus vaccine and immunoprophylaxis strategies in New Zealand Publication: Prasad N, Read J.M, Jewell C, Waite B, Trenholme AA, Grant CC, Huang QS, Newbern EC, Hogan AB. Modelling the impact of respiratory syncytial virus (RSV) vaccine and immunoprophylaxis strategies in New Zealand, Under review		
Nature of contribution by PhD candidate	Conceptualization, data management, data analysis and coding, drafted the initial manuscript/chapter, revised and approved final manuscript/chapter.	
Extent of contribution by PhD candidate (%)	75%	

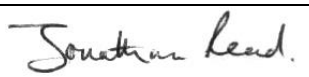
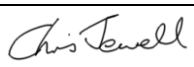
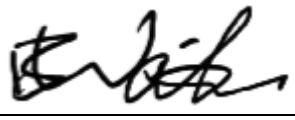
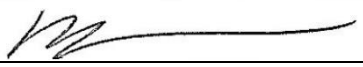
CO-AUTHORS

Name	Nature of Contribution
Jonathan Read, Christopher Jewell	Conceptualization, advised on data analysis and model code, revised and approved final manuscript
Ben Waite	Data acquisition, data mangement, revised and approved final manuscript
Adrian A Trenholme	Conceptualization, data acquisition, revised and approved final manuscript
Cameron C Grant	Conceptualization, data acquisition, revised and approved final manuscript
Q. Sue Huang, E. Claire Newbern	Conceptualization, data acquisition, revised and approved final manuscript
Alexandra B Hogan	Conceptualization, advised on data analysis and model code, revised and approved final manuscript

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Jonathan Read		12/06/2020
Christopher Jewell		10/07/2020
Ben Waite		15/06/2020
Adrian A Trenholme		22/06/2020

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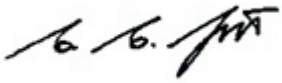
Cameron C Grant		19/06/2020
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Alexandra B Hogan		17/06/2020