Modelling the impact of respiratory syncytial virus (RSV) vaccine and immunoprophylaxis strategies in New Zealand

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Abstract

Background

Mathematical models of respiratory syncytial virus (RSV) transmission can help describe seasonal epidemics and assess the impact of potential vaccines and immunoprophylaxis with monoclonal antibodies (mAb).

Methods

We developed a deterministic, compartmental model for RSV transmission, which was fitted to population-based RSV hospital surveillance data from Auckland, New Zealand. The model simulated the introduction of either a maternal vaccine or a seasonal mAb among infants aged less than 6 months and estimated the reduction in RSV hospitalizations for a range of effectiveness and coverage values.

Results

The model accurately reproduced the annual seasonality of RSV epidemics in Auckland. We found that a maternal vaccine with effectiveness of 30–40% in the first 90 days and 15–20% for the next 90 days could reduce RSV hospitalizations by 18–24% in children younger than 3 months, by 11–14% in children aged 3–5 months, and by 2–3% in children aged 6–23 months. A seasonal infant mAb with 40–60% effectiveness for 150 days could reduce RSV hospitalizations by 30–43%, 34–48% and by 14–21% in children aged 0–2 months, 3–5 months and 6–23 months, respectively.

Conclusions

Our results suggest that either a maternal RSV vaccine or mAb would effectively reduce RSV hospitalization disease burden in New Zealand. Overall, a seasonal mAb resulted in a larger disease prevention impact than a maternal vaccine.

Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute respiratory tract infections (ARI) in children worldwide [1]. Almost all children have an RSV infection by two years of age [2], with infants aged less than six months experiencing the greatest burden of severe disease [1]. The 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 [3] and is rarely used in New Zealand (NZ) [4].

Several RSV vaccines and mAbs are in clinical development [5]. The RSV F nanoparticle maternal vaccine is currently the most advanced vaccine candidate. In a Phase 3 trial, the vaccine did not meet its primary endpoint of reducing RSV lower respiratory tract infections (LRTI), despite an overall efficacy of 39.4% (95% confidence interval [CI], 5.3–61.2) against RSV LRTI for 90 days after vaccination. However, the vaccine did meet secondary objectives of reducing RSV LRTI hospitalizations and severe hypoxemia with benefits through to 180 days after vaccination [6]. Consequently, the vaccine is being assessed in an ongoing Phase 3 trial. In terms of new immunoprophylaxis through mAbs, the candidate Nirsevimab, which is administered once seasonally, demonstrated a 70.1% (95% CI 52.3–81.2) efficacy in reducing RSV LRTI in healthy pre-term infants over the 150 day follow-up period [7]. Nirsevimab is currently being trialled for use in all infants.

Several mathematical modelling studies assessing the impact of potential RSV vaccination and mAbs have been published. In particular, Cromer et al. [8] and Rainisch et al. [9] compared the impact of RSV mAbs and maternal vaccination, using a cohort model and decision tree model respectively. While informative, these studies assumed effectiveness values that were higher than those reported from recent clinical trials, limiting their application. Additionally, differences in

climate, demographics, and contact patterns can impact RSV transmission [10], emphasising the need to develop and fit RSV models to specific regions. Moreover, as RSV is not a notifiable disease, the quality of surveillance methods and RSV burden data varies considerably by location [1].

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

Methods

Setting and population-based data

Data for this study were sourced from the Southern Hemisphere Influenza Vaccine Effectiveness Research and Surveillance (SHIVERS) project [11]. 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. These regions have a combined population of approximately one million, including 36,000 children aged less than two years [12], and are predominantly urban with a sub-tropical climate. The SHIVERS hospital sites provide all respiratory inpatient services for the population residing in these regions. 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 a suspected ARI. All patients meeting the World Health Organization severe acute respiratory infection (SARI) case definition (cough and fever within the last 7 days in 2012 and within 10 days from 2013 onwards) were included [13]. Nurses obtained consent and collected

nasopharyngeal swabs/aspirates from patients. To provide an understanding of the respiratory virus burden among patients with an ARI that did not meet the SARI definition (cough and/or fever but not both within last 10 days), study nurses enrolled a sample of non-SARI respiratory patients from 2013 to 2015. Sampling of non-SARI respiratory patients in 2013 was during the peak winter/spring period (mid-August to October) and included weekly selection of two paediatric and two adult inpatients at each hospital. During 2014 and 2015, this surveillance was extended to enrol approximately six paediatric and six adult non-SARI respiratory patients weekly between April and September at each hospital.

In addition to the SHIVERS testing protocol, hospital laboratories provided results from clinical-ordered tests performed on patients hospitalized with an ARI. These results were included after validation of the hospital PCR assay performance. Collected specimens were tested for RSV using the United States Centers for Disease Control and Prevention real-time reverse transcription (RT)-PCR protocol at the Institute of Environmental Science and Research or using the AusDiagnostic PCR protocol and real-time PCR assays at hospital laboratories [11].

To account for changes in testing criteria and to correct for non-testing, 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.

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 Hogan et al [14]. The model divided the population into four age groups: children aged 0–2 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). Schematic representations of the models are presented in Figure 1 and all equations are provided in Supplementary Material S1. The transmission function $\lambda_i(t)$, representing the force of infection on age group *i* over time t, with indices *i* and *j* representing the four age cohorts, was calculated as:

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

where β_0 is the transmission coefficient. The seasonal fluctuations in RSV transmission observed in temperate/sub-tropical climates including NZ [15], were captured through a cosine function [10]. The parameter 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*.

Mixing between age groups was based on NZ-specific contact rates as reported by Prem et al. [16]. We adapted the contact matrix to match the age structure used in our model and converted daily values to weekly (Supplementary Material S2). As these rates were in five-year age groups, we also assessed the impact on model outcomes when using more finely stratified contact data from the United Kingdom as reported by Fumanelli et al.[17].

There are on average 279 live births per week in Auckland [18], informing the birth rate in the model. The average life expectancy for an Auckland resident is 81 years [19]. We assumed that deaths only took place in the older age group, thus the weekly ageing/death rate in age group 4 (η_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. 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, a duration of infectiousness ($1/\gamma$) of ten days, and immunity following infection ($1/\nu$) of 230 days [14, 20, 21].

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 [22]. Based on data from serological studies of RSV specific antibodies [23, 24], we initially reduced susceptibility to infection by 33% in infants younger than three months ($\alpha_{1=}$ 0.66) and included this as a fitted parameter. As this parameter is derived from limited observations, we also assessed the impact on fitted parameters and model outputs when assuming no natural maternally derived immunity in the model.

Model fitting

Our model output represents the total number of RSV infections in the population while our data are RSV hospitalizations. 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 class that are hospitalized and detected with RSV. 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, the SHIVERS surveillance time period.

We estimated parameters β_0, β_1, φ and $\alpha_1$by fitting the model to weekly hospitalizations for the four age groups in our model. We fitted the model in R software by maximum likelihood estimation using the bbmle package [25]. We assumed that the number of RSV hospitalizations each week represented Poisson samples with expectation pI, where p is probability of a case

being hospitalized and RSV detected, 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 [25].

Model with vaccination or immunoprophylaxis

We considered two RSV preventative strategies: first, a maternal vaccination where infants are born with 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. Recent Phase 3 trials for RSV maternal vaccines and mAbs have assessed efficacy against medically significant LRTI. As the majority of infants are reported to have symptomatic RSV infections [26], we assumed in our analysis that the effectiveness of maternal vaccines or mAbs against all RSV infections in infants could be similar.

For 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 [6]. Immunized infants were born into a P_i group and had susceptibility to infection reduced by factor $1 - ve$, where ve is a proxy for vaccine effectiveness. While the RSV-F maternal vaccine phase 3 trial did not meet its primary endpoint [6], it is possible that the newer maternal vaccine products, which utilise the more antigenic pre-fusion F protein, may lead to higher neutralizing titres in mothers and greater protection for the infant [27]. Moreover, considering the stated minimal criteria for an RSV maternal vaccine efficacy against RSV-associated LRTI was 60% [28], we tested a default scenario where effectiveness against infection waned over time starting at 40% and halved after 90 days. However, we also tested scenarios where vaccine effectiveness was initially 30% and then waned to 15% 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 two months prior to or during the NZ winter season. The duration of protection from RSV mAb was 150 days, which was the duration of follow-up used to assess efficacy in the recent Nirsevimab trial [7]. Like maternal vaccination, immunized infants had susceptibility to infection reduced by factor $1 - ve$, based on mAb effectiveness. Informed by the Phase 3 Nirsevimab trial, which showed a 70.1% efficacy against medically attended LRTI among pre-term infants, who have a greater risk of severe RSV-associated outcomes [29], we tested a default scenario of 50% effectiveness against infection among all infants. We also tested scenarios where mAb effectiveness against infection was 40% and 60%.

For both preventative strategies, the default coverage was set at 50%, informed by recent maternal vaccination coverage data from NZ [30], however we also tested scenarios of 30% and 80% coverage. Model equations with maternal vaccination or seasonal mAb are provided in Supplementary Material S1.

Model outputs

The number and proportion of hospitalizations averted in children aged less than two years was estimated, stratified by age group, for each of the 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, each using a different combination of parameter values based on the fitted parameter uncertainty from maximum likelihood estimation (Table 1).

Results

Model fit

Figure 2 shows the model fitted to RSV hospitalizations for children younger than two years by age group. When testing the assumption of no natural maternally derived protection, we found that our model was unable to fit to the data. Additionally, we found model outcomes were not markedly different when using more finely age-stratified contact data (Supplementary Material S3), and as such, we chose to present results using NZ-specific contact rates. Both the base and intervention model outputs demonstrated a seasonal pattern of RSV infections (Figure 3). Fitted parameter values with 95% confidence intervals (CIs) are shown in Table 1.

Averted hospitalizations

Both RSV preventative strategies modelled reduced the number of hospitalizations compared to baseline among children less than two years of age (Table 2). At default values, the RSV maternal vaccine had a reduced impact in the first year following implementation. By the second year, the vaccine showed a consistent reduction in hospitalizations compared to baseline among children aged less than six months. It also showed a small impact among children aged 6-23 months (Figure 3). A seasonal RSV mAb at default values had a small impact on hospitalizations among children aged less than two years in the first year but had a larger impact in the second year following implementation (Figure 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 24% reduction in hospitalizations per 1000 children aged 0–2 months, a 14% reduction among children aged 3–5 months, and a 3% 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 14%, 9%, and 3% reduction in hospitalizations among children aged 0–2 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 in which it was assumed there was no waning vaccine effectiveness, where the impact was similar in both children aged 0–2 months and 3–5 months (Table 2, Supplementary Material S4).

A seasonal mAb among infants aged less than six months at default values of 50% coverage and 50% effectiveness for 150 days, resulted in a 37% reduction in hospitalizations per 1000 children aged 0–2 months, a 41% reduction among children aged 3–5 months, and a 17% reduction among children aged 6–23 months, compared to baseline. If coverage of a mAb with 50% effectiveness was increased from 50% to 80%, there was an additional 3%, 3%, and 2% reduction in hospitalizations 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 hospitalizations was greatest in children aged 3–5 months for all scenarios.

Discussion

We report the potential impact of an RSV maternal vaccine or a seasonal infant RSV mAb on RSV hospitalizations, given a range of coverage and effectiveness measures and 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 hospitalizations 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 hospitalizations by 24%, 14%, and 3% in children aged 0–2 months, 3–5 months, and 6–23 months, respectively. In contrast, a seasonal mAb administered to infants aged less than six months with 50% effectiveness could reduce RSV hospitalizations by 37%, 41%, and 18% in the same age groups. 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, although this finding should be interpreted within the context of our assumptions about the effectiveness and durability of the two interventions modelled.

RSV is the leading cause of ARI hospitalizations in young children, highlighting the need for new pharmaceutical interventions to reduce health system burden and cost. Given the challenges of active immunization in early infancy, either an RSV maternal vaccination or an infant RSV 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 [4], the previous success of licensed immunoprophylaxis for RSV (Palvizumab) may aid in the licensure and acceptability of a new candidate. Moreover, producers of Nirsevimab expect the product to have vaccine-like pricing [31]. As the modelled health impacts from both strategies in our study were not substantially 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 a small impact in terms of averted hospitalizations among children aged 6–23 months, suggesting some indirect effects. This contrasts with a related mathematical modelling study from Western Australia that found the effect of an RSV maternal vaccine to be negligible for children 6–23 months of age [14]. It is possible that this impact may be due to our adaptation of contact rates from 0-4-year old children to infants, however, in a sensitivity analyses using more finely age-stratified contact data, we still observed a small indirect effect of maternal vaccination. Another possible explanation is that our inclusion of RSV ARI hospitalization data among all ages 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, whereas we applied continuous ageing, which due to the exponential distribution of the duration of each compartment, could result in a larger modelled indirect effect.

Previous studies comparing RSV vaccines and/or mAbs have assumed effectiveness values higher than recent clinical trial results. In terms of the relative impact of RSV mAb and maternal vaccinations on hospitalizations, 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 hospitalizations than a maternal vaccine among infants aged less than six months [8, 9]. In our study, if assuming 100% uptake at the default effectiveness values for each candidate, a seasonal mAb prevented 1.1 times more hospitalizations than a maternal vaccine among infants aged less than six months. The greater impact of maternal vaccination in our study is likely due to our longer assumed duration of protection, informed by recent clinical trial results. Additionally, we noted a greater impact on hospitalizations 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. We found our model was unable to fit to data if we assumed no such immunity and our fitted values aligned closely with previous seroprevalence and modelling studies [14, 23, 24]. Secondly, we utilized scaling parameters to fit the modelled incidence to the number of RSV hospitalizations reported in our data. Due to limited information on the proportion of RSV infections that are hospitalized by age, validation of these parameters was challenging. Examination of emergency care presentation and hospitalization rates due to RSV in NZ show that infants aged 0–2 months are three times as likely to be hospitalized than those aged 6–11 months [32], which supports our assumptions. Nevertheless, better data on RSV disease burden in the community and hospitalization risk will be valuable for future RSV modelling and are needed to assess the potential benefit of pharmaceutical interventions more comprehensively. Finally, our modelling relied on hospitalization data, thus did not assess the health impact of preventive strategies in other settings. Furthermore, an 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 [33]. 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) [6]. 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.

Our study suggests that both an RSV maternal vaccination and a seasonal mAb could effectively reduce RSV hospitalization burden in young children. 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 a small indirect effect among children aged 6–23 months and had greater impact with increased coverage. Additional data on the burden of RSV in the community and in other health care settings together with cost-effectiveness analyses will be vital for assessing the impact of future possible implementation of these interventions. 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 important.

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Table 1: Model parameter values

Parameter	Definition	Fixed/Fitted	Value(s)	Reference
$1/\sigma$	Latent period (days)	Fixed	4	[21]
$1/\gamma$	Infectious period (days)	Fixed	10	[20, 21]
$1/\nu$	Duration of immunity following infection (days)	Fixed	230	[14, 21]
β_0	Transmission coefficient	Fitted	0.054 (0.053 – 0.056)	
β_1	Amplitude of seasonal forcing	Fitted	0.451 (0.431 – 0.471)	
φ	Phase of seasonal forcing	Fitted	-1.546 (-1.595 – -1.497)	
α_1	Reduced susceptibility in 0–2 months age group due to RSV-natural maternal antibodies	Fitted	0.684 (0.614 – 0.747)	[23, 24]
P_1	Proportion of infected that are hospitalized and detected in age group 0–2 months		0.55	
P_2	Proportion of infected that are hospitalized and detected in age group 3–5 months		0.29	
P_3	Proportion of infected that are hospitalized and detected in age group 6–23 months		0.03	
P_4	Proportion of infected that are hospitalized and detected in age group ≥24 months		0.0002	
pv	Vaccine/mAb coverage	Fixed	50%[a]	[30]
$1/\omega$	Duration of mAb [b] induced protection (days)	Fixed	150	[6, 7]
	Duration of vaccine induced protection (days)	Fixed	180	[6,7]
ve	Vaccine effectiveness mAb [b] effectiveness	Fixed	40% – 20%[a] 50%[a]	[6, 7]

[a] Default values, [b] mAb; monoclonal antibody. 95% Confidence intervals are for fitted parameters

Table 2: Annual hospitalizations in terms of cases per 1,000 children and percentage reduction in hospitalizations for each age group compared to baseline (no intervention) for a range of scenarios among children aged less than two years.

	Annual hospitalizations					
	Infants aged 0–2 months		Infants aged 3–5 months		Children aged 6–23 months	
	Cases per 1,000	(%)	Cases per 1,000	(%)	Cases per 1,000	(%)
Baseline	30.0 (26.3-34.1)		22.9 (21.3-24.5)		10.1 (9.6-10.7)	
Maternal vaccine impact with protection of 180 days						
Expected coverage (50%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	22.8 (20.0-25.8)	(24.1)	19.6 (18.3-20.9)	(14.3)	9.8 (9.2-10.3)	(3.4)
Lower effectiveness (30% first 90 days, 15% next 90 days)	24.6 (21.6-27.9)	(17.9)	20.5 (19.1-21.9)	(10.5)	9.9 (9.4-10.4)	(2.1)
Sustained protection (40% for 180 days)	22.1 (19.5-25.1)	(26.2)	17.0 (15.8-18.1)	(25.7)	9.6 (9.1-10.1)	(5.4)
Higher coverage (80%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	18.6 (16.4-21)	(38.0)	17.6 (16.4-18.7)	(23.1)	9.5 (9-9.9)	(6.5)
Lower effectiveness (30% first 90 days, 15% next 90 days)	21.4 (18.8-24.2)	(28.8)	18.9 (17.7-20.2)	(17.2)	9.7 (9.2-10.2)	(4.4)
Sustained protection (40% for 180 days)	17.8 (15.7-20.1)	(40.6)	13.7 (12.8-14.6)	(40.1)	9.2 (8.7-9.6)	(9.6)
Lower coverage (30%)						
Default effectiveness (40% first 90 days, 20% next 90 days)	25.7 (22.6-29.2)	(14.2)	21.0 (19.6-22.5)	(8.1)	10.0 (9.4-10.5)	(1.4)
Lower effectiveness (30% first 90 days, 15% next 90 days)	26.9 (23.6-30.5)	(10.4)	21.6 (20.1-23.1)	(5.7)	10.1 (9.5-10.6)	(0.6)
Sustained protection (40% for 180 days)	25.3 (22.2-28.7)	(15.6)	19.4 (18-20.7)	(15.3)	9.9 (9.3-10.4)	(2.6)

Seasonal mAb‡ impact with duration of protection of 150 days						
Expected coverage (50%)						
Default effectiveness (50%)	18.9 (16.7-21.4)	(36.9)	13.5 (12.6-14.4)	(41.0)	8.3 (7.9-8.8)	(17.7)
Lower effectiveness (40%)	20.9 (18.4-23.6)	(30.3)	15.2 (14.2-16.2)	(33.6)	8.7 (8.2-9.2)	(13.9)
Higher effectiveness (60%)	17.1 (15.1-19.3)	(43.0)	11.9 (11.2-12.7)	(47.9)	8.0 (7.5-8.4)	(21.4)
Higher coverage (80%)						
Default effectiveness (50%)	17.9 (15.8-20.2)	(40.2)	12.8 (12-13.7)	(43.9)	8.2 (7.7-8.6)	(19.2)
Lower effectiveness (40%)	20.0 (17.7-22.7)	(33.2)	14.6 (13.6-15.6)	(36.1)	8.6 (8.1-9.0)	(15.1)
Higher effectiveness (60%)	16.0 (14.1-18.0)	(46.6)	11.2 (10.5-11.9)	(51.0)	7.8 (7.4-8.2)	(23.1)
Lower coverage (30%)						
Default effectiveness (50%)	20.3 (17.9-23)	(32.2)	14.5 (13.5-15.5)	(36.6)	8.6 (8.1-9.0)	(15.5)
Lower effectiveness (40%)	22.1 (19.5-25.1)	(26.2)	16.1 (15-17.1)	(29.8)	8.9 (8.4-9.4)	(12.1)
Higher effectiveness (60%)	18.7 (16.5-21.1)	(37.7)	13.1 (12.2-13.9)	(43.0)	8.2 (7.8-8.6)	(18.8)

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

Figure headings and captions

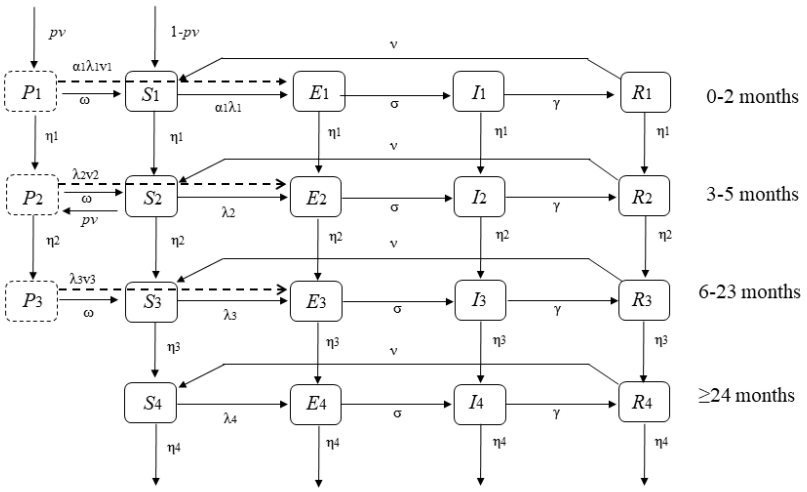

Figure 1. Schematic diagram for model assessing impact of a maternal RSV vaccine and a seasonal newborn monoclonal antibody (mAb).

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 is represented by α_1. Vertical lines represent births and ageing. The parameter *pv* represents the proportion vaccinated or administered a mAb. Infants protected by immunization or mAb have susceptibility to infection reduced by factor 1 – *ve*. A seasonal mAb was given to all infants aged less than 6 months and had a duration of protection of 150 days (with the waning mAb protection rate represented by ω). All model equations are presented in the Supplementary Material S1.

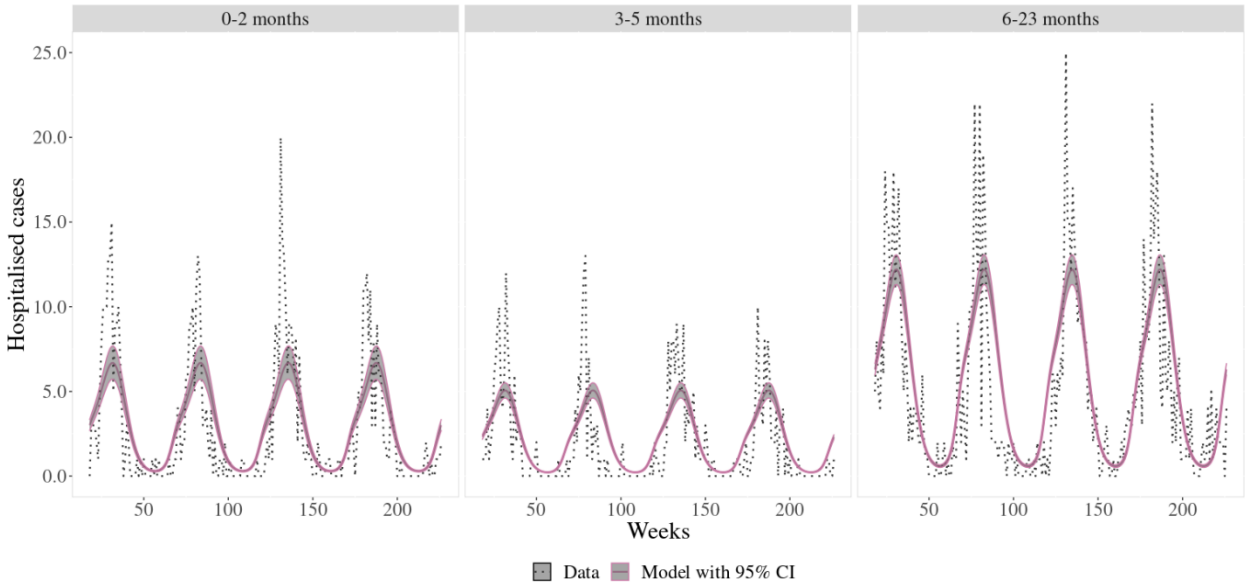

Figure 2: Model output with 95% Confidence Intervals against RSV hospitalization data (dots) for each age group.

The shaded area represents 95% confidence intervals for model outputs which were estimated from the distribution of 500 model simulations, each using a different combination of parameter values based on the fitted parameter uncertainty from maximum likelihood estimation, as shown in Table 1.

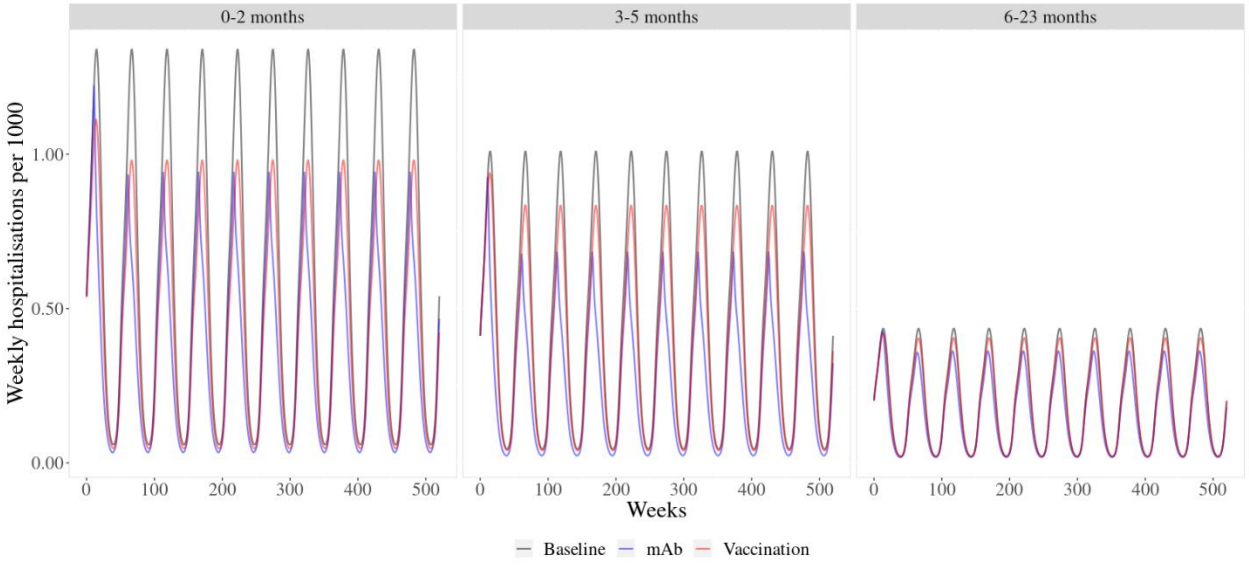

Figure 3: Weekly RSV hospitalizations per 1000 children by age group for baseline, default maternal vaccine, and default seasonal infant monoclonal antibody (mAb) scenarios for five years following implementation.

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

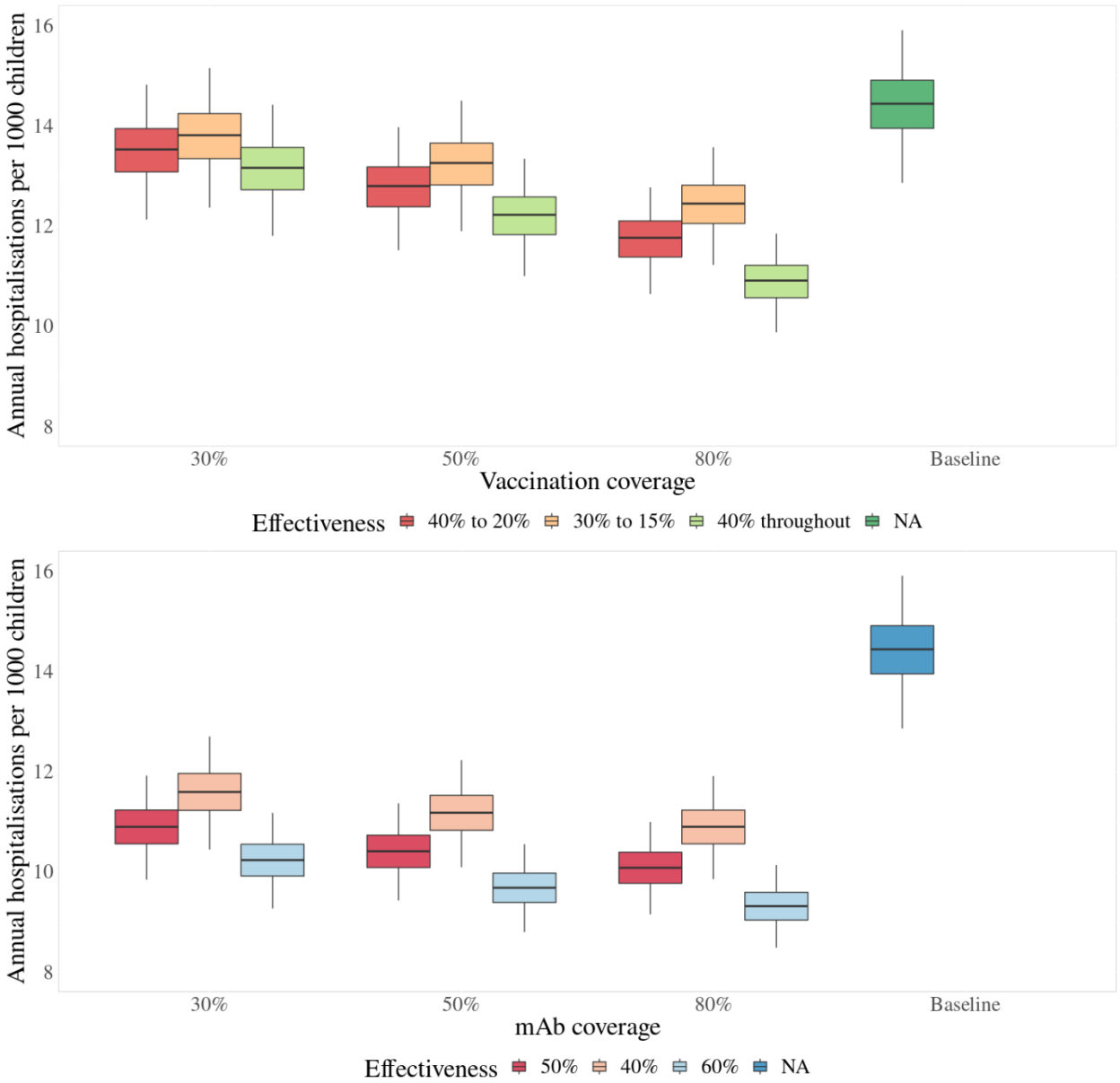

Figure 4: Estimated annual RSV hospitalizations per 1000 children aged less than two years for baseline and different vaccination and seasonal monoclonal antibody (mAb) effectiveness and coverage scenarios.

Distribution (2.5%, 25%, 75%, and 97.5% quantile and median) of each modelled scenario, which were estimated from the distribution of 500 model simulations, each using a different combination of parameter values based on the fitted parameter uncertainty from maximum likelihood estimation, as shown in Table 1. Figures by finer age groups among children aged less than two years are provided in Supplementary Material S4

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