Potential impact of a maternal vaccine for RSV: a mathematical modelling study

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ABSTRACT

Respiratory syncytial virus (RSV) is a major cause of respiratory morbidity and one of the main causes of hospitalisation in young children. While there is currently no licensed vaccine for RSV, a vaccine candidate for pregnant women is undergoing phase 3 trials. We developed a compartmental age-structured model for RSV transmission, validated using linked laboratory-confirmed RSV hospitalisation records for metropolitan Western Australia. We adapted the model to incorporate a maternal RSV vaccine, and estimated the expected reduction in RSV hospitalisations arising from such a program. The introduction of a vaccine was estimated to reduce RSV hospitalisations in Western Australia by 6–37% for 0–2 month old children, and 30–46% for 3–5 month old children, for a range of vaccine effectiveness levels. Our model shows that, provided a vaccine is demonstrated to extend protection against RSV disease beyond the first three months of life, a policy using a maternal RSV vaccine could be effective in reducing RSV hospitalisations in children up to six months of age, meeting the objective of a maternal vaccine in delaying an infant's first RSV infection to an age at which severe disease is less likely.

KEYWORDS

respiratory syncytial virus; RSV; mathematical model; vaccine model; maternal vaccine

INTRODUCTION

Respiratory syncytial virus (RSV) causes respiratory illness in young children and presents a significant global health burden. In 2005, at least 33.8 million episodes of RSV occurred worldwide in children younger than five years [1]. Almost all children experience an RSV infection by the age of two years, and the highest burden is in children between six weeks and six months of age [2].

There is currently no licensed vaccine for RSV, however it is widely recognised that such a vaccine would have a considerable impact on global public health [3]. Distinct target populations have been identified – pregnant women, infants and young children, and the elderly – and several vaccine candidates for each of these groups are undergoing either clinical trials or preclinical development [3–5]. A potential strategy to protect newborn infants against RSV is to vaccinate pregnant women in the third trimester of pregnancy, and a RSV F nanoparticle vaccine for pregnant women is undergoing phase 3 trials (Novavax, NCT02624947) [6,7].

The potential introduction of a novel RSV vaccine prompts the need for mathematical modelling to inform rollout strategies for target population groups. However, few mathematical modelling studies of RSV vaccination have been published to date, and these have largely focused on infant or childhood vaccines [8–14]. A study modelling the use of a maternal RSV vaccine in Kenya found that such a vaccine would likely reduce RSV incidence in very young children, even with sub-optimal coverage [15]. Here, we model the reduction in RSV hospital admissions due to a maternal RSV vaccination in a high-income setting, under varying levels of coverage and effectiveness, using a mathematical model fitted to linked population-based RSV data from Western Australia (WA).

METHODS

Setting and population-based data

47 Data for this study were sourced from a population-based birth cohort data linkage study on

48 the pathogen-specific burden of acute lower respiratory infections (ALRI). The birth cohort

49 comprised all children born in WA between 1996 and 2012, identified from the Midwives'

50 Notification System and the Birth Registry [16]. Hospital admission records and laboratory

51 records were extracted from the Hospital Morbidity Data Collection and the PathWest

52 Laboratory Database and probabilistically linked through the Western Australian Data Linkage

53 System [17]. PathWest is the sole public pathology service in WA and services all but three

54 hospitals that admit paediatric patients. Only hospital records with both admission and

55 separation dates during the study period (January 1996 to December 2012) were included in

56 these analyses. These are henceforth referred to as hospital admissions. We identified all ALRI

57 hospital admission records from children in the birth cohort through a selection of International

58 Classification of Diseases version 10 Australian modification (ICD-10 AM) diagnosis codes

59 as described in previous work [18]. ALRI was defined as pneumonia (J12–J18), acute

60 bronchiolitis (J21), influenza (J09–J10), whooping cough (A37), bronchitis (J20, J40) and

61 unspecified ALRI (J22). Using linked laboratory data, we further restricted these ALRI

62 admissions to those where RSV was detected within 48 hours of the hospital admission. Further

63 details of the linkage of laboratory and hospital admission records can be found elsewhere [19].

64 The residential postcode at the time of the hospital admission was used to restrict analyses to

65 cases in the metropolitan region of WA, which consists of the capital city Perth and its

66 surrounds, with a population of two million [20]. The resultant dataset included 5,898

67 laboratory-confirmed RSV-associated ALRI hospital admissions, herein referred to as RSV

68 hospitalisations.

69 *Model without vaccination*

70   We developed a deterministic compartmental mathematical model for RSV transmission, using

71   the Susceptible–Exposed–Infectious–Recovered–Susceptible form as in prior work [21,22].

72   We included 75 age classes: 60 one-month classes for individuals younger than five years, and

73   five-year age groups thereafter. We set a constant total population size with a uniform age

74   distribution across ages 0–79, and assumed that deaths only take place in the oldest age class,

75   as we were estimating the vaccine impact in infants and young children in a setting where child

76   mortality is very low. To simulate monthly ageing between classes we used cohort ageing.

77   Cohort ageing is a method where, instead of including continuous ageing rates in the ordinary

78   differential equations (ODEs) to simulate movements between age classes, individuals from

79   each compartment are shifted instantaneously at fixed time points [23–25]. The seasonal nature

80   of RSV transmission was simulated using a cosine forcing function, in line with earlier work

81   [21]. Further details of the model equations are in the Supplementary Material (S1).

82   *Parameters*

83   In line with empirical and modelling studies, we assumed a latent period of four days

84   [26,27], an infectious period of nine days [9,27,28], and that immunity following natural

85   infection persisted for 230 days [21]. It is known that there is transplacental transfer of

86   protective RSV-specific antibodies from a pregnant woman to her unborn child, however the

87   level of protection is uncertain [29]. Considering studies from Spain, Brazil, Kenya and Turkey,

88   we assumed that unvaccinated infants have some protection from maternally-derived RSV-

89   specific antibodies for the first three months of life [12,30–33]. Based on the seropositive

90   proportion reported in the Brazilian study, we reduced susceptibility to infection by 92% in the

91   first month of life and 55% in the second and third months.

92   Studies indicate that adults are less infectious than young children, and that RSV is often

93   introduced into a household by an older sibling [34–36]. We therefore introduced a scaling

94   parameter ω that reduced infectiousness in individuals aged ten years and older.

95   Mixing between age groups was based on the POLYMOD study, using all reported contacts

96   (physical and non-physical) for Great Britain [37]. The contact matrix was first made

97   symmetric using the method described by Brisson et al [24]. Then, since the age classes in the

98   POLYMOD matrices are in groups of five years, we adapted the contact matrix to match the

99   age structure in our model, and the daily values were converted to monthly (Supplementary

100   Material S1). We also tested the sensitivity of the model outcome to different assumptions

101   about contact, by simulating the model with a more finely stratified contact matrix in children

102   younger than five years derived by Fumanelli et al [38].

103   *Model fitting*

104   In the first instance, we attempted to fit the model by varying the reduced infectiousness

105   parameter ω and the transmission function parameters b_0 (the transmission coefficient), b_1

106   (the amplitude of seasonal forcing) and ϕ (the phase shift) simultaneously, using a numerical

107   fitting routine. However, we found that the model would fit the data well for a range of starting

108   values for ω. Therefore, we instead adopted a two-fold approach to determine values for these

109   four parameters.

110   We estimated the three transmission function parameters b_0, b_1 and ϕ by fitting the model to

111   monthly RSV hospitalisations for four key age groups (0–2 months, 3–5 months, 6–11 months

112   and 12–23 months) simultaneously. We fitted the model in MATLAB using maximum

113   likelihood estimation with the inbuilt Nelder Mead algorithm function *fminsearch*, and solved

114   the ODEs using the inbuilt differential equation solver *ode45* [39]. In the fitting routine, we

115   included four parameters (h_{0-2}, h_{3-5}, h_{6-11} and h_{12-23}) to scale the modelled incidence to the

116 RSV hospitalisations data for each of the four key age groups. Each parameter h_k represents

117 the proportion of infections that result in a hospitalisation, where a laboratory test is also

118 conducted, for that age group.

119 We ran the fitting routine for a range of starting values for the reduced infectiousness parameter

120 ω. We then extracted from the model the proportion of 0–23 month old children who were

121 infected by an individual 2–14 years of age. In a study of subcohort data extracted from the

122 same birth cohort from which our RSV hospitalisations data were derived, it was estimated that

123 45% of the RSV detections in that subcohort were attributable to infection from an older sibling

124 [40]. We therefore took infections from individuals 2–14 years as a proxy for infections from

125 older siblings, and selected the fitted parameter set where the proportion of infections in

126 children 0–2 years of age who were infected by an individual 2–14 years of age was closest to

127 45%. Details of all parameter values are in Table 1. The fitting method is further described in

128 the Supplementary Material (S2).

129 *Maternal vaccination model*

130 Maternal vaccination was modelled by incorporating an additional compartment V_i that

131 represented infants in age class i with reduced susceptibility to infection derived from their

132 mother's vaccination (Figure 1). This means that rather than explicitly modelling the

133 vaccination of pregnant women, we modelled infants as being born either with or without

134 maternally-derived vaccine protection. The proportion of infants born into the V_i class (the

135 'vaccine coverage parameter') encompassed both vaccine uptake by pregnant women, and the

136 proportion of women that develop protective levels of antibodies. The default value for the

137 vaccine coverage parameter κ was set to 50%, and we tested values between 30% and 70%,

138 informed by recent uptake estimates of 70% and 56% for the maternal pertussis and influenza

139   vaccines in WA, and accounting for assumed imperfect development of protective antibodies

140   in vaccinated pregnant women [41].

141   We assumed that the maternal vaccine would extend the length of natural maternal protection,

142   so that the maximum duration of vaccine-induced protection in infants was six months [42].

143   This duration is approximately equivalent to the estimated duration of protection afforded to

144   an RSV-infected person following recovery, and similar to estimates in other studies, but we

145   also tested values of three and four months [8,15]. Infants in class V_i had susceptibility to

146   infection scaled by a factor $1 - \rho_i$, where ρ_i is a proxy for initial vaccine effectiveness relative

147   to a completely native individual, without naturally-derived maternal antibody protection.

148   Considering the stated minimal criteria for an RSV maternal vaccine efficacy of 60% [43], we

149   tested values between 60% and 90% for vaccine effectiveness, and used a value of 80% for our

150   default scenario. We also considered the scenario where the effectiveness parameter changed

151   over the period of six months to simulate waning effectiveness, with $\rho_1 = \rho_2 = \rho_3 = 0.8, \rho_4 = $

152     $0.6, \rho_5 = 0.4$ and $\rho_6 = 0.2$. The vaccination model equations are provided in the

153   Supplementary Material (S1).

154   [INSERT FIGURE 1]

155   *Model outcomes and sensitivity analysis*

156   We compared the output of the base model to that of the maternal vaccination model for both

157   the number of infections and number of hospitalisations. Outputs were compared for the

158   equilibrium model solutions after a burn in time of 400 years. We estimated the avoided RSV

159   hospitalisations in children younger than 24 months for a range of vaccine coverage,

160   effectiveness and duration scenarios.

161 The relationship between the RSV-specific antibody titre in infants and protection from RSV

162 disease has not been fully elucidated [44]. We therefore analysed scenarios with lower levels

163 of existing maternal protection by varying the parameters relating to reduced susceptibility in

164 the first three months of life. We considered a scenario with lower natural protection by

165 reducing susceptibility to infection by 75% in the first month of life and 35% in the second and

166 third months. We compared this to a scenario with no natural maternal protection by

167 incorporating no reduced susceptibility in the first three months of life.

168 We assessed the sensitivity of the model output to variation in model parameters influencing

169 the age-specific force of infection. We varied the level of reduced infectiousness in older age

170 classes by running our analysis for a range of values of ω between 0.4 and 0.8. We also

171 considered the contact data for children younger than 10 years. A limitation of using the

172 POLYMOD data in this study is that the POLYMOD age groups are in five-year cohorts [37].

173 We investigated whether more finely stratified contact data for children younger than five years

174 would change the model results. We used United Kingdom data from a study that estimated

175 contact frequencies in individuals in one-year age groups to stratify the contact matrix

176 parameters for our age cohorts under five years of age [38], but retained the POLYMOD

177 parameters for the contact rates between individuals older than five years. Finally, we

178 considered the impact of the uniform age distribution in our model. We ran the models for the

179 default parameter set using a non-uniform age distribution, based on age distribution data for

180 Greater Perth in 2014 [20].

181 Ethical approvals for this study were received from the Department of Health WA Human

182 Research Ethics Committee (#2012/56) and The Australian National University Human

183 Research Ethics Committee (Protocol 2015/177).

184 [INSERT TABLE 1]

185   RESULTS

186   *Model outcome and fit*

187   Figure S2 shows the model fitted to RSV hospitalisations for children younger than two years

188   by age group. Fitted parameter values are in Tables 1 and S1. We compared the model outputs

189   with the proportion of infections in young children caused by an older sibling in this dataset,

190   and therefore determined that the infectivity of individuals age ten years and older was 60% of

191   that of younger children (Table S2). The base and maternal vaccination model outputs retain

192   the biennial seasonal infection pattern typically observed in metropolitan WA (Figure S1),

193   therefore we present the avoided RSV hospitalisations over a two-year period to capture both

194   a large and small RSV season.

195   *Reduction in hospitalisations*

196   [INSERT FIGURE 2]

197   The modelled introduction of a maternal RSV vaccine reduced the number of infections and

198   hospitalisations in young children. The range of modelled scenarios showed a 6–51% reduction

199   in RSV hospitalisations in children younger than two months, with a 6% reduction only if

200   vaccine effectiveness was poor (Table 2). Figure 2 shows the base model output compared to

201   the vaccination model for vaccine effectiveness levels in the range 60–90%. The percentage

202   reduction in hospitalisations in children aged 3–5 months was higher than for children aged 0–

203   2 months under most scenarios, except where vaccine protection was assumed to last only three

204   or four months. The default scenario (80% vaccine effectiveness, 50% coverage and a

205   maximum of six months' vaccine-induced immunity) resulted in a 26% reduction in

206   hospitalisations in children younger than two months, and 40% in children aged 3–5 months

207   (Table 2). For all modelled scenarios, the vaccine had a negligible impact on the number of

9

208   RSV hospitalisations in children aged 6–11 months and 12–23 months, as demonstrated in

209   Figure S3.

210   [INSERT TABLE 2]

211   *Sensitivity analysis*

212   As the model parameters capturing maternal immunity in unvaccinated children were based on

213   a single study, we tested alternative assumptions. With a lower level of natural maternally-

214   derived protection, we found that the impact of vaccination in the 0–2 month old age group

215   was larger, with 33% and 41% of hospitalisations avoided for the reduced and no maternal

216   immunity scenarios respectively, compared to 26% for the default scenario (Table 3). The

217   impact on older age groups was minimal. By reducing the natural maternally-derived

218   protection, the hospitalisation scaling factor in the 0–2 month old age group decreased, but the

219   fitted parameters did not greatly change (Table S5).

220   Model outcomes were insensitive to changes in the level of transmission from individuals aged

221   over ten years (Table S3). We also conducted the analysis for the default parameter set using

222   models with a non-uniform age distribution, but found that the proportions of hospitalisations

223   avoided changed only slightly (Figure S4 and Table S4). Finally, we repeated our analysis with

224   the default parameter set, using a more finely stratified contact structure in children younger

225   than five years of age, but the results did not change.

226   [INSERT TABLE 3]

227   DISCUSSION

228   The introduction of a maternal vaccine for RSV, with similar coverage to that for existing

229   maternal vaccination programs in WA, is likely to reduce the RSV hospitalisation burden in

230   children younger than three months of age by 6–37%, and by approximately 30–46% in

children between three and five months of age, for vaccine effectiveness levels between 60%

and 90%. If both vaccine effectiveness and coverage are high, hospitalisations may be reduced

by up to 51% and 63% in these two age groups respectively. For children six months and older,

maternal vaccination had a negligible impact, indicating the herd immunity impact may be

small. In our analysis, the percentage of RSV hospitalisations avoided was lower in the younger

age group, due to natural maternally-derived immunity in the first three months of life. We also

found that a maternal vaccine would be unlikely to change the biennial RSV infection pattern

observed in WA.

An RSV intervention that prevents infection in young children would reduce the health system

burden and cost during the winter months. One Australian study estimated that the median

length of stay for a RSV hospitalisation is three days, and the mean cost of each RSV

hospitalisation episode for children younger than five years is AUD 6350 [45]. Our study was

based on data from a total population birth cohort of children born in WA during 1996–2012,

and restricted to hospital admissions for ALRI. As RSV has also been detected in admissions

without a diagnosis for ALRI [19], these data likely underrepresent the number of RSV

hospitalisations in young children in WA, meaning the findings from our study are a

conservative estimate of the true impact. A maternal vaccine for RSV would also provide

broader health benefits; there is evidence that if an infant's first RSV episode is delayed, the

risk of later respiratory issues such as asthma and wheezing may be reduced [3]. Further, in our

model we did not incorporate a reduction in susceptibility to RSV for women protected by the

maternal vaccine, due to a lack of information on the likely duration or protection mechanism

of the vaccine in adults. With pregnant women forming only a small proportion of the

population spread over a large age range, this assumption is unlikely to have influenced our

findings, but may provide an additional health benefit. In addition, as this study focussed on

255 avoided hospitalisations, the findings reported here do not account for the public health and

256 economic benefit of reduced community-level RSV in young children arising from a vaccine.

257 Previous RSV vaccine mathematical modelling studies have focussed on infant and childhood

258 vaccines in order to evaluate cost-effectiveness [9–11]. Other studies have considered the

259 possible impact of RSV vaccines in the low income country setting of Kenya [8,15]. Poletti

260 and colleagues used a stochastic individual-based modelling approach to simulate vaccine

261 implementation for several key population groups, including pregnant women [15]. Their

262 study, based on the social structure of rural Kenya, found that maternal vaccination could

263 reduce RSV infection in infants by 31.5%, assuming a four month duration of natural

264 maternally-derived immunity and an additional four months of vaccine-derived protection, and

265 that for this vaccine strategy, the reduction in RSV infections was not greatly affected by sub-

266 optimal coverage. While in our study we found that vaccine coverage is important, our model

267 was for a different setting and assumed a different duration of protection.

268 Maternal vaccination is a realistic public health strategy and has been successfully

269 implemented for other diseases such as influenza and pertussis. Mathematical models are

270 instrumental in assessing the health and economic benefits of such an intervention, and are

271 needed to aid decision-making about the cost-effectiveness of immunisation policies for

272 different jurisdictions. A key strength of this study is that the model was validated using

273 population-level linked data from WA, allowing a more accurate assessment of the vaccine

274 impact. However, our model structure is also flexible enough that it can be adapted to account

275 for the demography, hospitalisation data and contact patterns in other regions, to allow

276 assessment of the likely vaccine impact elsewhere. This model can also be readily updated to

277 incorporate information about vaccine characteristics as clinical trials progress.

278   While the importance of transplacental transfer of protective antibodies from a pregnant

279   woman to her unborn child is known, there is a gap in understanding how maternal antibodies

280   interact with the infant immune system, and the factors that influence the transfer and decay of

281   these antibodies [44]. Our parameters for maternally-derived immunity were based on a single

282   seropositivity study [30], however, our parameter choices are broadly aligned with the current

283   understanding about the duration and protectiveness of RSV-specific antibodies in neonates. A

284   recent study of children in Kenya found that RSV-specific antibody seroprevalence was high

285   in the first three months of life, with 100% of children in the study seropositive in the 0–<1

286   month age group, and 75% seropositive in the 2–<3 month age group [33]. We found that our

287   model was sensitive to assumptions about maternal antibody protection, so we tested two

288   reduced maternal protection scenarios (Tables 3 and S5). Reducing the level of natural

289   maternally-derived protection increased the vaccine impact in 0–2 month old children, but did

290   not greatly change the impact in the older age groups.

291   We incorporated scaling parameters to fit the modelled incidence to the number of RSV-related

292   hospitalisations in our dataset. However, the paucity of data on the proportion of RSV

293   infections that are hospitalised by age made it difficult to validate these scaling parameters. A

294   further challenge was that in many settings, the highest numbers of RSV hospitalisations are

295   observed in 0–2 month old children compared to any other age group, yet this is the age group

296   in which RSV-specific antibody seroprevalence is typically highest. In the sensitivity analysis,

297   we found that the hospitalisation scaling factor for children 0–2 months of age decreased

298   considerably when we removed maternally-derived protection from the model, meaning a

299   smaller percentage of the modelled 0–2 month old infections resulted in a hospitalisation.

300   Examination of respiratory viral testing trends in the WA population birth cohort showed a

301   significant variation across ages in that children younger than one month are twice as likely to

302   undergo viral testing compared to those aged 1–5 months, and are five times more likely than

303 children aged 6–23 months [19]. As the hospitalisation scaling parameter takes into account

304 the probability of RSV testing, it is plausible that infants in the 0–2 month age group who do

305 become infected are much more likely to be hospitalised, providing support for our parameter

306 values. However, understanding the interactions between age, immunity, and hospitalisation

307 risk, and modelling these interactions, is an area for ongoing research.

308 Our model was fitted to data for children under two years of age, therefore we needed to use

309 other data to accurately parameterise the force of infection for older children and adults. We

310 scaled the infectiousness for older individuals such that the age of the infector was consistent

311 with observations from this birth cohort [40]. As the herd immunity effect due to a maternal

312 vaccine is small in our model, we observed little impact of the contact structure in young

313 children on our findings. This suggests that simple cohort models may be reliable alternatives

314 to dynamic models for assessing the impact of a maternal vaccine. By fitting the model to RSV

315 data in children younger than two years, we ensured that the force of infection acting on infants

316 reflects the available data, and we do not expect this force of infection to change noticeably

317 following the implementation of a vaccine.

318 It is understood that an individual's susceptibility to RSV is dependent on both age and the

319 history of infection. In our model we focussed on age as the main determinant of susceptibility,

320 and introduced a parameter to scale susceptibility to infection in older age groups, although

321 others have incorporated additional disease states in the modelling framework to account for

322 initial and subsequent infections [8,13]. There is evidence that increasing age is more important

323 than previous exposure to infection in influencing reduced susceptibility to disease in older

324 infants and children [46]. Further, our focus was on infant RSV infections. We fitted to linked

325 data on early-life infections with RSV and demonstrated that the model effectively captures

326 hospitalisation risk in children under two years of age.

327   Our modelling framework incorporated only a single type of RSV vaccine intervention, based

328   on the current information about RSV vaccine development progress. However, with a

329   maternal RSV vaccine unlikely to offer protection to infants older than six months, it may be

330   infeasible for this type of vaccine to exist as a standalone preventative strategy for RSV [44].

331   With vaccine candidates for infants, older children, and the elderly also in various stages of the

332   clinical trials pipeline, there is scope for further development of mathematical models to

333   estimate the reduction in disease burden in other target population groups, and to assess the

334   likely public health impact of combined vaccine interventions.

345   *Conflict of interest statement:* ABH, PTC, CCB, FJL, SD, PF and HCM have no interests to
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Figure captions

Figure 1. Schematic diagram for the maternal vaccination model, with vaccine-induced immunity assumed to last no longer than six months. The compartments S_i, E_i, I_i, R_i, and V_i represent, respectively, the susceptible, exposed, infectious, recovered, and vaccinated populations, for each age cohort i. The parameters λ_i, δ_i, γ, and ν represent, respectively, the transmission, latent, recovery and immunity rates. Reduced susceptibility due to natural maternally-derived immunity is represented by σ_i. The parameter ρ_i represents vaccine effectiveness and κ represents coverage. Dashed lines represent cohort ageing processes.

Figure 2. Comparison of the modelled number of RSV infections (panels (a) and (b)) and hospitalisations (panels (c) and (d)) per month in the age groups 0–2 months and 3–5 months, per 1000 children in that age group, over a time period of 24 months. The blue line represents the base model, and the red shaded area represents the range of outputs of the vaccination model for vaccine effectiveness levels between 60% and 90%.

Tables

504 Table 1. Model parameters for the default scenario where the reduced infectiousness parameter

505 ω = 0.6. Fitted parameter sets for other values of ω are in Table S1.

Parameter	Definition	Fixed/Fitted	Value	Reference
$1/\delta$	Latent period (days)	Fixed	4	[26,27]
$1/\gamma$	Infectious period (days)	Fixed	9	[9,27,28]
$1/\nu$	Immunity period (days)	Fixed	230	[21]
σ_1	Reduced susceptibility in first age cohort due to naturally-derived maternal immunity (0 months of age)	Fixed	0.08	[30]
σ_2, σ_3	Reduced susceptibility in age cohorts 2 and 3 due to naturally-derived maternal immunity (1 and 2 months of age)	Fixed	0.45	[30]
N	Total population of Greater Perth for ages 0-79 years	Fixed	1,861,923	[20]
ω	Reduced infectiousness in children 10 years and older	Fixed	0.6	
κ	Vaccine coverage	Fixed	0.5	[41]
$1 - \rho_i$	Reduced susceptibility due to vaccine, relative to naïve individual, in month i	Fixed	$0.2, i \leq p_{vacc}$ $1, i > p_{vacc}$	[41]
p_vacc	Maximum duration of vaccine-induced protection in months	Fixed	6	[8,15]
b_0	Transmission coefficient	Fitted	0.015	
b_1	Amplitude of seasonal forcing	Fitted	0.397	
ϕ	Phase of seasonal forcing function	Fitted	0.985	
h_{0-2}	Proportion of modelled infections leading to hospitalisation in the 0–2 month age group		0·424	
h_{3-5}	Proportion of modelled infections leading to hospitalisation in the 3–5 month age group		0·088	
h_{6-11}	Proportion of modelled infections leading to hospitalisation in the 6–11 month age group		0·047	
h_{12-23}	Proportion of modelled infections leading to hospitalisation in the 12–23 month age group		0·020	

506

507   Table 2. Avoided hospitalisations over a 24 month period for a range of scenarios,

508   represented as the number of avoided hospitalisations per 1000 children in that age group (the

509   risk difference), and as a percentage risk reduction (1 – RR, where RR is the relative risk).

510   The default parameter set has vaccine coverage of 50%, vaccine effectiveness of 80%, and

511   maximum duration of vaccine-induced immunity of six months. Note that the measure of

512   vaccine effectiveness described here is relative to a completely naïve individual, without

513   natural maternal antibody protection. All other parameter values are reported in Table S1.

Scenario	0–2 month age group per 1000 (percentage reduction)	3–5 month age group per 1000 (percentage reduction)
Default		
50% coverage, 80% effectiveness, 6 months duration	13 (26%)	12 (40%)
Coverage		
30% coverage	8 (16%)	7 (24%)
70% coverage	18 (37%)	17 (56%)
Effectiveness		
60% effectiveness	3 (6%)	9 (30%)
70% effectiveness	8 (16%)	10 (35%)
90% effectiveness	18 (37%)	14 (46%)
Waning effectiveness	6 (13%)	5 (18%)
Duration		
3 months vaccine-induced immunity	12 (25%)	0 (0%)
4 months vaccine-induced immunity	13 (26%)	4 (13%)
Higher effectiveness and coverage		
90% effectiveness, 70% coverage	25 (51%)	19 (63%)
Lower effectiveness and coverage		
70% effectiveness, 30% coverage	5 (10%)	6 (21%)

514

515

516 Table 3. Sensitivity analysis for natural maternally-derived immunity parameters. This table

517 shows the avoided hospitalisations over a 24 month period for the scenario with lower natural

518 maternally-derived immunity, compared to the default scenario, represented as the number of

519 avoided hospitalisations per 1,000 children in that age group, and as a percentage reduction.

520

Scenario	0–2 month age group per 1000 (percentage reduction)	3–5 month age group per 1000 (percentage reduction)
Default $\sigma_1 = 0.08, \sigma_2 = \sigma_3 = 0.45$	13 per 1000 (26%)	12 per 1000 (40%)
Reduced natural maternal immunity $\sigma_1 = 0.25, \sigma_2 = \sigma_3 = 0.65$	16 per 1000 (33%)	12 per 1000 (40%)
No natural maternal immunity $\sigma_1 = \sigma_2 = \sigma_3 = 1$	20 per 1000 (41%)	12 per 1000 (41%)

521