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Evaluating the next generation of RSV intervention strategies: a mathematical modelling study and cost-effectiveness analysis

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Abstract

Background: With a suite of promising new RSV prophylactics on the horizon, including long-acting monoclonal antibodies and new vaccines, it is likely that one or more of these will replace the current monoclonal Palivizumab programme. However, choosing the optimal intervention programme will require balancing the costs of the programmes with the health benefits accrued.

Methods: To compare the next generation of RSV prophylactics, we integrated a novel transmission model with an economic analysis. We estimated key epidemiological parameters by calibrating the model to 7 years of historical epidemiological data using a Bayesian approach. We determined the cost-effective and affordable maximum purchase price for a comprehensive suite of intervention programmes.

Findings: Our transmission model suggests that maternal protection of infants is seasonal, with 38–62% of infants born with protection against RSV. Our economic analysis found that to cost-effectively and affordably replace the current monoclonal antibody Palivizumab programme with long-acting monoclonal antibodies, the purchase price per dose would have to be less than around £4350 but dropping to £200 for vaccinated heightened risk infants or £90 for all infants. A seasonal maternal vaccine would have to be priced less than £85 to be cost-effective and affordable. While vaccinating pre-school and school-age children is likely not cost-effective relative to elderly vaccination programmes, vaccinating the elderly is not likely to be affordable. Conversely, vaccinating infants at 2 months seasonally would be cost-effective and affordable if priced less than £80.

Conclusions: In a setting with seasonal RSV epidemiology, maternal protection conferred to newborns is also seasonal, an assumption not previously incorporated in transmission models of RSV. For a country with seasonal RSV dynamics like England, seasonal programmes rather than year-round intervention programmes are always optimal.

Keywords: Respiratory syncytial virus, Transmission model, Maternal vaccination, Monoclonal antibodies

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Background

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection in children under 5 years of age globally, causing 48,000–74,500 deaths annually [1]. The sole pharmaceutical prevention strategy, a monoclonal antibody (Palivizumab), is costly and only available to infants in high-income countries and only to those at most risk of RSV-related complications [2]. This gap in prevention strategies leaves the majority of infants vulnerable to infection.

There are currently over 40 RSV prophylactic candidates in pre-clinical or clinical trials [3]; those furthest along in development include long-acting monoclonal antibodies (e.g. MEDI8897 by *MedImmune*) [4], and maternal, childhood, and elderly vaccines (e.g. RSV F-nanoparticle vaccine by *Novavax*, ChAd155-RSV by *GlaxoSmithKline*, and Ad26.RSV.preF by *Jensen*, respectively) [5, 6]. Although missing its primary endpoint, a recent stage III trial of the *Novavax* RSV F-nanoparticle vaccine showed promising results, preventing RSV-related lower respiratory tract infections and hospitalisations in babies born to vaccinated mothers in the South Africa site [5], while stage II trial results suggest that the *MedImmune* MEDI8897 long-acting monoclonal antibodies are effective at preventing RSV disease in neonates for at least 150 days post-administration—five times longer than a single dose of Palivizumab [4]. Stage II trial results for the adenovirus vectored vaccines *GlaxoSmithKline* ChAd155-RSV and *Jensen* Ad26.RSV.preF suggest that they are well tolerated and safe in their respective target groups of infants and the elderly, respectively, though we currently lack efficacy results [6].

Deciding which, if any, of this suite of pharmaceutical prophylactics to adopt requires an integrated approach in which all the health benefits accrued by targeted specific subpopulations (intervention strategies)—both by direct and indirect protection and across all ages—can be accurately compared. Moreover, with multiple new prophylactics likely to arrive to license at a similar time, understanding the relative efficiency of potential intervention strategies at controlling RSV burden, and therefore what we should be willing to pay for them, will dominate decision-making on future RSV intervention strategies.

In this study, we developed such an integrated approach by combining a novel age-stratified epidemiological transmission model for RSV into a cost-effectiveness framework. The model was calibrated using a Bayesian inference framework to 7 years of RSV incidence data from England. The cost-effectiveness analysis was undertaken according to the National Institute of Clinical Excellence (NICE) reference case [7]. Using this approach, we were able to determine the maximum purchasing prices for the next generation of RSV intervention strategies to be cost-effective and affordable.

Methods

RSV model structure

We modelled the number of individuals in six different epidemiological states (M , S , E , I , A , and R). When a susceptible individual (S) acquires infection, they move to an exposed but not infectious state (E) for an average of $1/\sigma$ days, after which they become infectious with either symptomatic (I) or asymptomatic (A) infection. After an infectious period of $1/\gamma$ days, individuals move to a protected state (R) for a period of $1/\omega$ days, after which they become susceptible to reinfection (S). We assume that only babies born to mothers who have recently been infected with RSV and who therefore have high levels of antibody (and thus, in state R) are maternally protected (M) for a period of $1/\xi$ after birth, with the remaining babies born susceptible to infection (S) (Additional file 1: Section 1) [8–11]. We tested this assumption to the alternative where all babies are born with temporary maternal immunity, similar to previous models (e.g. Kinyanjui et al. [12]) using the deviance information criterion (DIC) (Additional file 1: Section 1) [8–11]. We stratified individuals into 25 age groups (monthly up to 11 months of age, and then 1, 2, 3, 4, 5–9, 10–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75+ years) and also tracked the number of individuals who had experienced zero, one, and two or more previous infections (denoted by the subscripts 0, 1, 2, 3). Consistent with empirical data, we assume that the proportion of individuals who experienced asymptomatic infection is dependent on age [13] and the duration of infection and susceptibility to infection are dependent on the number of previous RSV infections [14, 15]. We assume that the contact rate between two age groups is proportional to the mean number of daily physical and conversational contacts made between those age groups—parameterised using empirical data from England and Wales (Additional file 1: Section 1) [8–11]. We captured the strongly seasonal dynamics of RSV in temperate climates by multiplying the per-contact transmission rate with a seasonal forcing term (Additional file 1: Section 1) [8–11].

To capture the current impact of administering Palivizumab, we tracked infants who are eligible in England: those born at less than 34 weeks gestational age are less than 9 months of age at the start of the RSV season (October) and suffer from either bronchopulmonary dysplasia or congenital heart disease [2]. We refer to these infants as very-high-risk (VHR). For VHR infants, we assumed that 90% receive Palivizumab with 33.8% acquiring immediate protection which lasts for an average of $1/\omega_{\text{pai}} = 150$ days, after which they return to the primary susceptible compartment (S_0) [16].

Model parameterisation and calibration

We used a Bayesian Markov chain Monte Carlo (MCMC) approach [17] to fit the model to the confirmed number of positive weekly RSV samples in England collected via the Respiratory DataMart System (RDMS) between July 2010 and June 2017 [18]. We constructed the prior distributions for all epidemiological parameters after a comprehensive synthesis of the literature (Table 1) (Additional file 1: Section 2) [8, 13–15, 19–28]. We used a binomial likelihood function that assumes an age-specific reporting rate of RSV-positive samples. To estimate how the reporting rates of RSV infection varied across ages, we tested five different assumptions about the age stratification (number and age grouping) using the deviance information criterion (DIC) (Additional file 1: Section 3) [17, 18, 25, 29, 30]. The output of the calibration is a joint posterior distribution for all the fitted parameters of the transmission model. To compare our model to the weekly number of RSV-positive samples, we multiplied the model-predicted

weekly incidence of symptomatic cases with the fitted age-specific reporting rates.

Intervention model structure

Status quo

We assume that Palivizumab is currently administered to 90% of VHR infants at birth between October to February inclusive (PAL-VHR-S, Additional file 1: Section 4) [28, 31–36]. We compare this status quo to the following three alternative intervention strategies.

Long-acting monoclonal antibodies

We tracked the number of infants protected by long-acting monoclonal antibodies, V_M , who remain protected after birth for an average of $1/\omega_{\text{mab}} = 250$ days after which they return to S_0 (Additional file 1: Section 4) [28, 31–36]. However, we relaxed this assumption in an uncertainty analysis. We evaluated three seasonal programmes that administer a single dose of long-acting

Table 1 Posterior distributions of the model parameters used in the transmission model of RSV. *Cri* credible interval

Parameter		Mean value (95% Cri of posterior where applicable)	Reference for fixed value or prior distribution
μ	Daily number of live births	1863 (fixed)	[8]
$1/\xi$	Average duration of maternally derived immunity (days)	133.5 (119.6–146.1)	[19–21]
$1/\omega$	Average duration of post-infection immunity (days)	358.9 (350.7–364.7)	[22, 23]
$1/\sigma$	Average duration of exposure (days)	4.98 (4.54–5.37)	[24]
$1/\gamma_0$	Average duration of primary infection (days)	6.16 (5.68–6.63)	[15]
g_1	Decrease in secondary infection duration relative to primary	0.87 (0.83–0.91)	[15]
g_2	Decrease in subsequent infection duration relative to secondary	0.79 (0.73–0.86)	[15, 24]
$p^{<1}$	Proportion asymptomatic (< 1 years)	0.0916 (0.031–0.158)	[13]
p^{1-4}	Proportion asymptomatic (1–4 years)	0.163 (0.092–0.223)	[13]
p^{5-14}	Proportion asymptomatic (5–14 years)	0.516 (0.460–0.572)	[13]
p^{15+}	Proportion asymptomatic (15+ years)	0.753 (0.656–0.829)	[13]
α	Relative reduction in infectiousness for asymptomatic infections	0.634 (0.541–0.724)	Fitted
q_p	Probability of RSV transmission per physical contact	0.0972 (0.093–0.099)	Fitted
q_c	Relative reduction in probability of RSV transmission per conversational contact compared to physical contact	0.998 (0.996–1.000)	Fitted
b_1	Relative amplitude of transmission during peak	1.998 (1.992–2.000)	Fitted
φ	Seasonal shift in transmission	0.614 (0.607–0.624)	Fitted
ψ	Seasonality wavelength constant	0.236 (0.220–0.252)	Fitted
<i>Susceptibility</i>			
δ_1	Secondary infection (relative to primary)	0.89 (0.85–0.93)	[14]
δ_2	Tertiary infection (relative to secondary)	0.81 (0.74–0.85)	[14]
δ_3	Subsequent infections (relative to tertiary)	0.33 (0.31–0.37)	[14]
<i>Probability that an RSV infection is reported</i>			
ϵ^j	0–4 years	$\exp(-4.602-0.233j)$	[14, 25]
ϵ^{17}	5–54 years	0.0000305 (0.0000290–0.0000320)	[22]
ϵ^{18}	55+ years	0.000147 (0.000134–0.000160)	[22]

monoclonal antibodies at birth (i) to those who are currently eligible for Palivizumab (MAB-VHR-S), (ii) to both VHR infants and infants who are at heightened risk (HR) of developing complications due to respiratory disease (MAB-HR-S), and (iii) to all infants regardless of risk (MAB-ALL-S). We evaluated two additional seasonal programmes that extend administration (iv) to all VHR and high-risk (HR) infants under 6 months (MAB-HR-S+) and (v) to all infants under 6 months (MAB-ALL-S+) throughout October only [6]. We assume that these programmes would replace the existing Palivizumab programme, that they all achieve the same coverage as Palivizumab, and that the efficacy per course is 70.1% (95% confidence Interval (CI) 52.3–81.0%) [4, 37].

Childhood/elderly vaccination

We assumed that a single dose of a vaccine conferred the same protection as that of a natural infection, such that 83.0% (95% CI 75.0–88.0%) of vaccinated individuals in the i th previous infection group who are susceptible (S_i) are moved to the respective recovered group (R_i) after a delay reflects the build-up of antibody immunity (Additional file 1: Section 4) [28, 31–36, 38]. We considered two vaccination programmes aimed at infants aged 2 months old: one administered seasonally (VAC-INF-S) and one year-round (VAC-INF-A), both achieving a coverage of 90%, consistent with the DTaP/IPV/Hib/HepB/PCV/Rota primary series vaccination coverage in England. We also considered two seasonal vaccination programmes aimed at elderly persons: one for those aged 75 years and older (VAC-75-S) and one for those aged 65 years and older (VAC-65-S), both achieving a coverage of 70%, consistent with vaccination coverage for the elderly influenza vaccine programme [39, 40]. Finally, we considered three seasonal programmes aimed at pre-school children (aged 2–4 years, VAC-2-4-S) and school-age children (aged 5–9 years, VAC-5-9-S, and aged 5–14 years, VAC-5-14-S) that achieve a coverage of 45% and 60%, respectively, consistent with the live attenuated influenza vaccination programme in England [39]. We assumed that the speed at which this coverage is achieved is age-dependent and consistent with that achieved for influenza vaccination. For all the childhood/elderly vaccination programmes considered, we assumed that they would be administered in addition to the existing Palivizumab programme in the UK.

Maternal vaccination

To evaluate the direct effect on infants of vaccinating pregnant women, we used the results of Novavax's maternal vaccine stage III trial that found 41.4% (95% CI 4.1–64.2) of infants born to these mothers are protected against infection for the first 3 months of life (Table 2) [5].

Consistent with the trial, we assume pregnant women are vaccinated at any point between 28 and 32 weeks gestation (Additional file 1: Section 4) [28, 31–36].

To evaluate the indirect effects of maternal vaccination while maintaining computational tractability and epidemiological realism, we used a previously published method for evaluating the impact of parental vaccination [36]. In brief, this method tracks the number of mothers of infants less than 1 year of age, and the number of these women who are participating in a maternal vaccination programme. The contact rate between mothers and their children is explicitly modelled using the number of household and non-household contacts, as reported by the Great Britain arm of the POLYMOD study [10, 11]. Accordingly, the force of infection between mothers and their infants is updated to reflect the vaccination status of the mother. We assume that the vaccinated mothers are themselves temporarily protected from infection consistent with the protection afforded by the childhood/elderly vaccination assumptions above (Additional file 1: Section 4) [28, 31–36]. We considered two maternal vaccination programmes, which are given in combination with the existing Palivizumab programme: a seasonal programme (MAT-S) and one administered year-round (MAT-A), with a coverage of 60% as observed for prepartum Tdap vaccination in England [5, 39].

Optimising seasonal administration

To allow an unbiased comparison of the seasonal programmes, our framework assumes the programmes are given continuously for 5 months. For programmes that administer Palivizumab and long-acting monoclonal antibodies, we assume administration occurs during the Palivizumab-recommended time period of October to February. To determine the period of administration for the remaining intervention programmes, we chose the 5-month period that resulted in the largest QALY gain relative to status quo.

Economic model

Clinical outcomes

For each intervention strategy, the economic model estimated the number of cases averted for five different RSV-associated clinical outcomes: symptomatic infection, GP consultations, hospital admissions, hospital bed days, and deaths. The number of symptomatic cases averted is estimated directly from the transmission model. To estimate the number of cases averted for the remaining four outcomes, we first calculated the per-infection probability that an individual experiences each clinical outcome by dividing the reported annual incidence rates for each outcome taken from previous burden studies in England (Additional file 1: Section 5) [41–51] by the transmission model-estimated annual

Table 2 Intervention model parameters. *CrI* credible interval

Parameter	Mean value (95% CI where applicable)	Reference
<i>Palivizumab</i>		
Delay between administration and protection (days)	Immediate (fixed)	[16]
ω_{pal} Average period of protection (days)	150 (fixed)	[16]
e_{pal} Efficacy on VHR infants (%)	33.8 (0.0–66.6) ¹	[16]
<i>Long-acting monoclonal antibodies</i>		
Delay between administration and protection (days)	Immediate (fixed)	[4]
ω_{mab} Average period of protection (days)	275 (fixed)	[4]
$e_{\text{mab}}^{\text{S}}$ Efficacy against symptomatic infection (%)	70.1 (52.3–81.0) ²	[37]
$e_{\text{mab}}^{\text{H}}$ Efficacy against hospitalisation (%)	78.4 (51.9–90.3) ³	[37]
<i>Childhood/elderly vaccine</i>		
d_{vac} Delay between administration and protection (days)	11.4 (2.8–22.1) ⁴	[38]
ω Average period of protection (days)	Same as post-infection immunity (1/ ω)	[38]
e_{vac} Efficacy against all infections (%)	83.0 (75.0–88.0) ⁵	[38]
<i>Novavax vaccine</i>		
$d_{\text{mat}}^{\text{D}}$ Average period of protection (days)	133.5 (119.6–146.1)	Same as maternally derived immunity
$e_{\text{mat}}^{\text{S}}$ Efficacy against symptomatic infection (%)	41.4 (4.1–64.2) ⁶	[5]
$e_{\text{mat}}^{\text{H}}$ Efficacy against hospitalisations (%)	53.5 (23.0–71.9) ⁷	[5]

Fitted distributions¹Gamma (3.7623, 0.0898)²W(11.898, 0.732)³W(11.611, 0.819)⁴W(2.42, 12.87)⁵W(31.464, 0.845)⁶W(3.327, 0.461)⁷W(5.354, 0.580)

incidence for RSV under the status quo. Then, to calculate the number of cases averted for each outcome under each intervention strategy, we multiplied the estimated number of RSV cases averted from the intervention model by the per-infection probability of each outcome.

Quality of life loss

In line with our previously estimated quality-adjusted life year (QALY) loss estimates per RSV episode for England, we assume that each GP consultation or hospitalisation resulted in a QALY loss of 4.098×10^{-3} (0.624×10^{-3} – 13.141×10^{-3}) and 2.990×10^{-3} (0.346×10^{-3} – 11.387×10^{-3}) for under fives and over fives, respectively, while other symptomatic non-healthcare seeking infections resulted in a QALY loss of 2.336×10^{-3} (95% CI 0.269×10^{-3} – 9.255×10^{-3}) and 1.448×10^{-3} (95% CI 0.135×10^{-3} – 5.928×10^{-3}) [52]. QALY loss due to death was commensurate with the remaining number of expected healthy years of life remaining in the individual (Additional file 1: Section 5) [41–51].

Costs

Costs were calculated in 2018 GBP, from the perspective of the NHS. The cost per GP consultation was calculated by assuming an average GP consultation time of 9 min

at a cost of £4.00 a minute (£36.00) [53, 54]. The cost per hospital bed day for children less than 5 years of age was calculated using the non-elective costs for paediatric bronchitis (Health Resource group (HRG) PD15A–D)—the main cause of RSV-associated hospitalisations [55, 56]. The cost per hospital bed day for children 5 years and older was determined using the non-elective costs for unspecified acute lower respiratory infection (HRG DZ22K–Q) [56]. We assumed maternal, infant, and elderly vaccines take 15 min to administer in a GP clinic at a cost of £9 per course (assuming one dose per course) [54]. Similarly, we assumed long-acting monoclonal antibodies and Palivizumab take 15 min to administer in hospital by a nurse at a cost of £11.50 per course for long-acting monoclonal antibodies and £57.50 per course (5 doses) for Palivizumab [54]. A course of Palivizumab costs £4035 (5 doses at £807 each) (see Table 3) [56].

Cost-effectiveness analysis

We conducted three separate cost-effectiveness analyses. First, we calculated the incremental cost-effectiveness ratio (ICER) of replacing the Palivizumab with any of the long-acting monoclonal programmes (MAB-VHR-S, MAB-HR-S, MAB-HR-S+, MAB-ALL-S, and MAB-ALL-S+). Second, we calculated the ICERs of supplementing

Table 3 Health and economic parameters used in the cost-effectiveness analysis

	Parameter	Mean value (95% CI where applicable)	Reference
T	Time horizon	10 years	–
r	Discount rate	3.5%	[7]
Probability of clinical outcomes			
r_G^a	Per-infection probability of GP consultation	0–4 years: 0.006–0.065	[41]
		5–14 years: 0.017–0.018	[44]
		15+ years: 0.014–0.132	[42]
r_D^a	Per-infection probability of death	0–4 years: 8.197×10^{-6} – 3.698×10^{-5}	[41]
		5–14 years: 6.731×10^{-6} – 6.896×10^{-6}	[44]
		15+ years: 4.663×10^{-6} –0.002	[42]
$r_H^{a,f}$	Per-infection probability of hospital admissions	VHR, 0–8 months: 0.133–0.391	[57]
		HR, 0–11 months: 0.013–0.130	[46]
		NR, 0–11 months: 0.010–0.097	[46]
		NR, 1–4 years: 0.004–0.008	[29]
		NR, 5–64 years: 4.688×10^{-5} – 8.004×10^{-5}	[44]
		NR, 65+ years: 6.197×10^{-5} –0.019	[42]
$r_B^{a,f}$	Number of hospital bed days per hospitalisation	VHR, 0–8 months: 8–25	[57]
		HR, 0–11 months: 5–7	[46]
		NR, 0–11 months: 1–5	[46]
		NR, 1–64 years: 2	[47]
		NR, 65+ years: 3	[48]
Costs			
<i>Per GP visit</i>			
Θ_{GP}	All ages	£36.00 (fixed)	[53, 54]
<i>Per hospital bed day</i>			
Θ_H^a	Paediatric (< 5 years of age)	£725.29 (718.13–733.99) ¹	[56]
Θ_H^a	Adult (≥ 5 years of age)	£425.24 (415.16–435.70) ²	[56]
<i>Administration of prophylactics (per course)</i>			
Δ_{pal}	Palivizumab	£57.50 (fixed)	[54]
Δ_{mab}	La-mABs	£11.00 (fixed)	[54]
Δ_{mat}	Maternal vaccine	£9.00 (fixed)	[54]
Δ_{vac}	Vaccine	£9.00 (fixed)	[54]

Table 3 Health and economic parameters used in the cost-effectiveness analysis (Continued)

	Parameter	Mean value (95% CI where applicable)	Reference
<i>Purchasing prices (per course)</i>			
ρ_{pal}	Palivizumab	£4035.50 (fixed)	[56]
ρ_x	La-mABs, Maternal vaccine and vaccine	Not known	
QALY loss			
<i>Symptomatic infection</i>			
Q_S^a	Paediatric (< 5 years of age)	2.336×10^{-3} (0.269×10^{-3} – 9.255×10^{-3}) ³	[52]
Q_S^a	Adult (≥ 5 years of age)	1.448×10^{-3} (0.135×10^{-3} – 5.928×10^{-3}) ⁴	[52]
<i>Hospital admissions</i>			
Q_H^a	Paediatric (< 5 years of age)	4.098×10^{-3} (0.624×10^{-3} – 13.141×10^{-3}) ⁵	[52]
Q_H^a	Adult (≥ 5 years of age)	2.990×10^{-3} (0.346×10^{-3} – 11.387×10^{-3}) ⁶	[52]
<i>Deaths</i>			
	Life expectancy	81.0 years	[51]
Q_S^a	Age-specific QALY loss	See Additional file 1: Section 5.2.	

Fitted distributions
¹ $N(725.293, 4.1264)$
² $N(425.242, 5.2781)$
³ $\text{Gamma}(1.57764, 0.0014807)$
⁴ $\text{Gamma}(1.41075, 0.0010264)$
⁵ $\text{Gamma}(2.0017, 0.00204726)$
⁶ $\text{Gamma}(1.60289, 0.00186539)$

the Palivizumab programme with the childhood or elderly vaccine programmes (VAC-INF-S, VAC-INF-A, VAC-2-4-S, VAC-5-9-S, VAC-5-14-S, VAC-75-S, VAC-65-S). Third, we calculated the ICER of supplementing the Palivizumab programme with the maternal vaccine programmes (MAT-S, MAT-A). For each of these three cost-effective analyses, using the non-dominated programmes only, we calculated the maximum price per course that would make each strategy cost-effective, assuming a cost-effectiveness threshold of £20,000/QALY (Additional file 1: Section 5) [41–51]. All costs and effects were discounted at a rate of 3.5% over a 10-year time horizon [7]. For each intervention strategy, we calculated the credibility intervals using 1000 Monte Carlo samples. For each Monte Carlo sample, we first estimated the number of RSV cases averted over the time horizon per outcome for an intervention strategy by sampling from the joint posterior distribution and running the intervention model for 10 years. Then, by sampling from the per-infection probability of each outcome occurring, we converted the number of RSV cases averted to the number of outcomes averted. Finally, we combined sampled values from the cost distributions with the number of each clinical outcome averted to

calculate the distribution of the maximum price per prophylactic course.

Affordability

Consistent with NICE guidelines, an intervention strategy is considered affordable in England if it costs less than £20 million annually during the first 3 years of implementation [58]. Using this definition, we calculated the affordable purchasing price per course for each non-dominated programme, by subtracting the total, undiscounted cost of administering the intervention strategy for the first 3 years from £60 million (3 years at £20 million each) and dividing by the total number of courses given during this period [58].

Calculations and code

The model was programmed in C++ with the code available at https://github.com/dchodge/rsv_trans_model. The figures were generated in Mathematica version 11.0.0 [59].

Role of the funding source

The funding source had no role in this study.

Results

RSV epidemiology

Our model comparison analyses suggested that maternal immunity was conferred seasonality according to the prevalence of recently infected pregnant mothers (Additional file 2: Fig. 1). Furthermore, we found that there is a likely exponential decrease in the reporting rates between the ages of 0–4 years, and fixed reporting rates for 5–54 years and 55 years and over (Additional file 2: Fig. 2).

The model reproduces the age distribution of RSV incidence (Fig. 1a–c, Additional file 2: Fig. 3–4). Using the calibration method, we are able to estimate parameters that have been difficult to evaluate directly from epidemiological studies (Additional file 2: Fig. 5). First, our model predicts that between 68 and 81% of infants experience an RSV infection in their first year of life, with subsequent infection risk generally decreasing with age (Fig. 1d). Deviations away from this decreasing trend occur in age groups which have the highest number of daily contacts (Fig. 1d). Second, we estimated the average duration of maternal immunity and post-infection immunity as 134 days (95% CrI 120–146) and 359 days (95% CrI 351–365), respectively. While our estimate for the duration of maternal immunity agrees with previous observations [60], our estimate for the post-infection immunity is slightly longer than previous studies [23, 60]. This difference may be due to study type or setting. For instance, an experimental challenge study found reinfection was likely after 2–6 months [23], and a birth cohort study in Kenya found most reinfections occur 6–12

months after primary infection [60]. Third, the model estimated that asymptomatic infections are 63% (95% CrI 54–72%) as infectious as symptomatic infections (Table 1). This value is commensurate with the relative decrease in the viral load in asymptomatic infections when compared to symptomatic [13]. Finally, we found that 62% of babies are born with protection to RSV during March, compared with 38% prior to the RSV season in September and October (Additional file 2: Fig. 2).

Probability of clinical outcomes

The average probability of consulting a GP due to RSV infection is highest in children less than 5 years of age (0.006–0.065) and adults 65 years and older (0.103–0.132). The average probability of death per-infection is highest in adults over 75 years (0.002) and rare in children and other adults in the remaining age groups (less than 3 in every 100,000 infections). The average probability of hospitalisation is highest in infants below 1 year of age (0.010–0.097), with peak risk occurring at 1 month of age, and lowest risk in persons aged 5–45 years of age (less than one in every 10,000 infections). HR and VHR infants have an increased risk of hospitalisation of 0.0138–0.129 and 0.14–0.37, respectively, compared with other infants (0.010–0.097). Similarly, the average number of bed days experienced per hospitalisation is greatest in infants less than 1 year of age (1–5) with the longest stays occurring at 1 month of age, and HR and VHR infants seeing an increase in the number of bed days of 5–7 and 8–25, respectively (Additional file 2: Fig. 6).

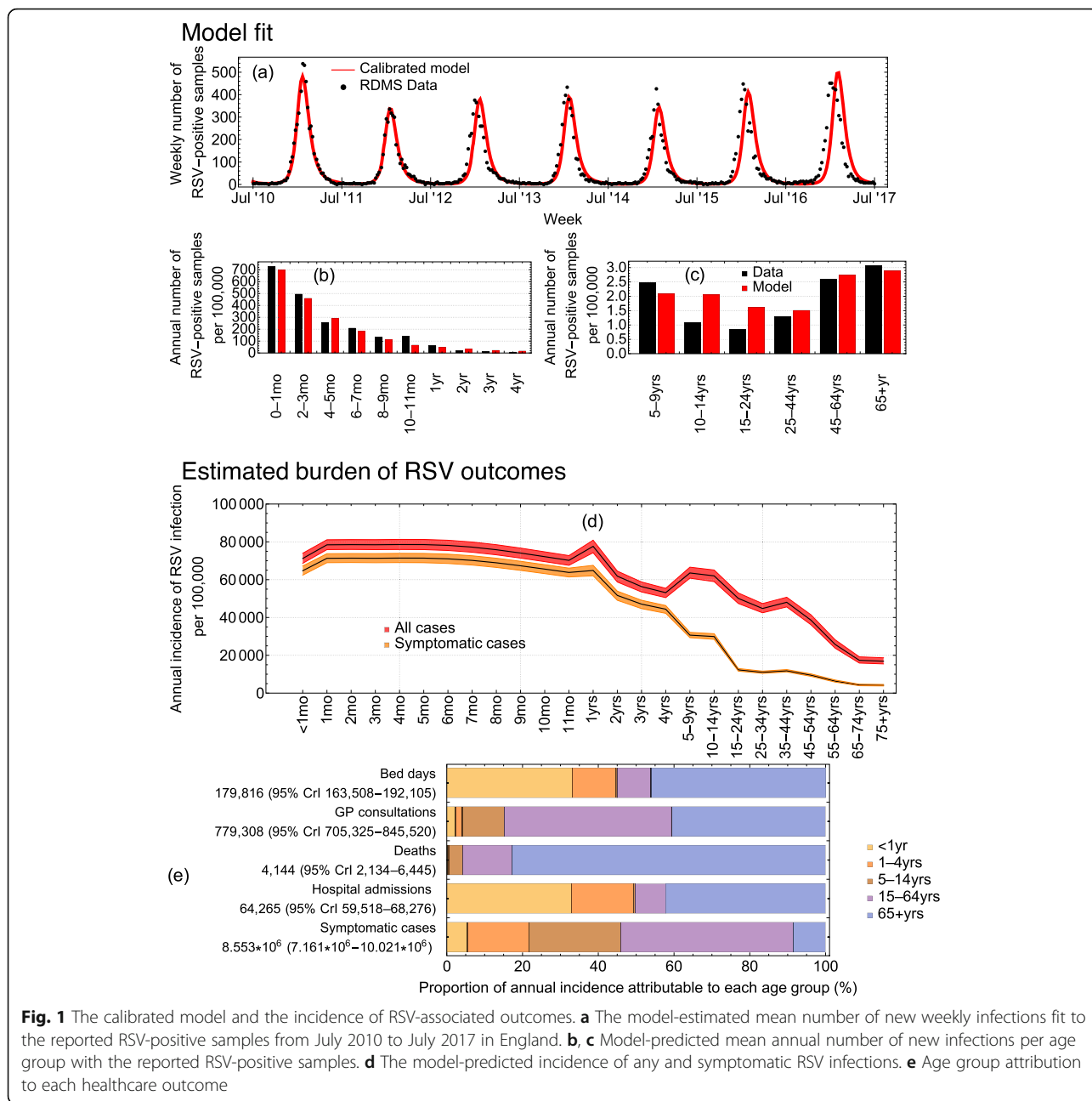
Impact of intervention strategies

Long-acting monoclonal antibodies

The seasonal programmes aimed at VHR infants or VHR and HR infants (MAB-VHR-S and MAB-HR-S, respectively) are the most efficient at preventing RSV hospitalisations, preventing 51 (95% CI 43–55) and 36 (95% CI 30–39) hospital cases per 1000 administered courses (Fig. 2a). These intervention programmes are not effective in raising the median age of primary infection (Fig. 2b).

Childhood/elderly vaccination

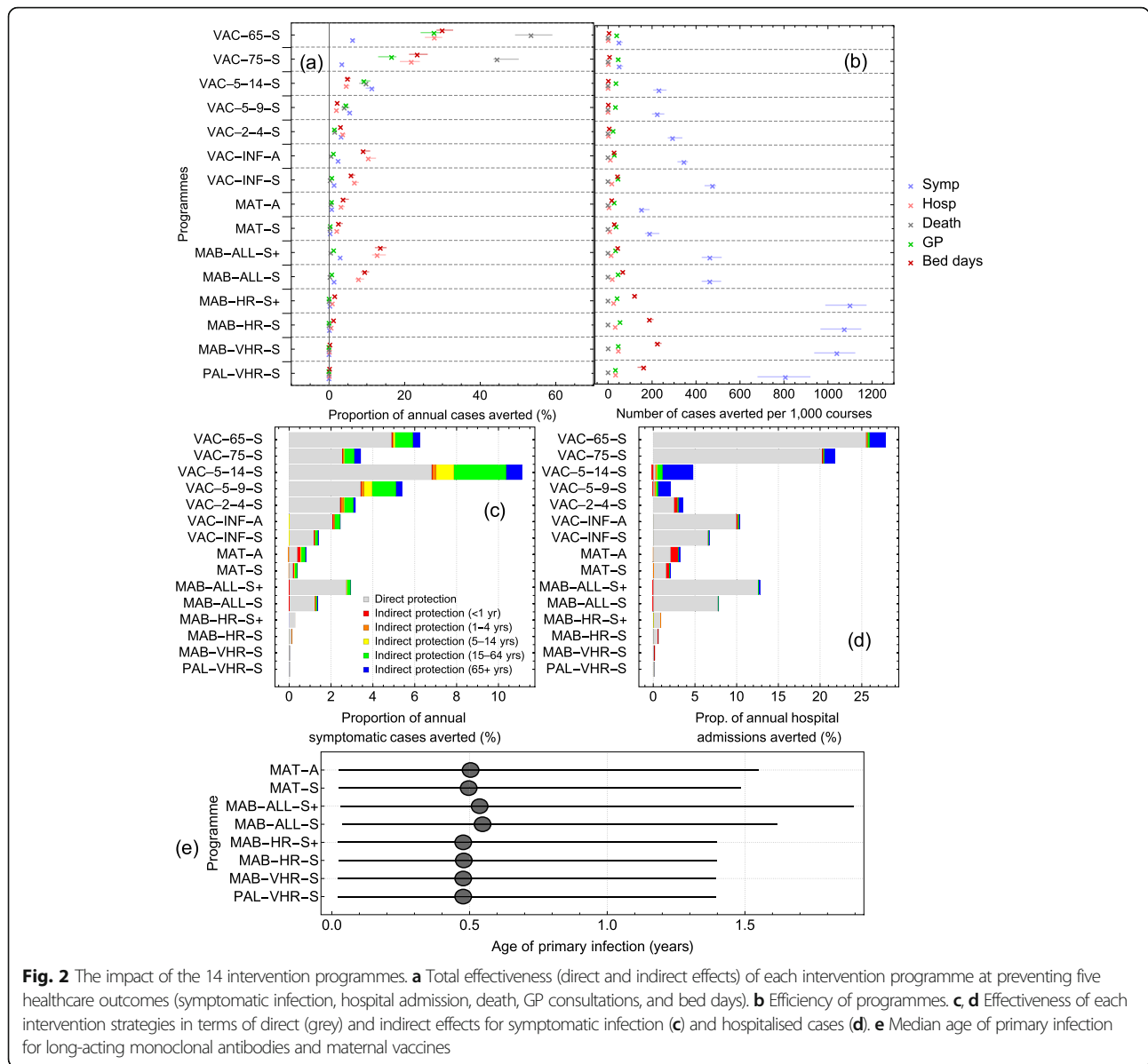
We found that to maximise the health benefit of the seasonal vaccination programmes, the optimal period of administration is between November and March for elderly programmes, October to February for the VAC-2-4-S and VAC-5-9-S programmes, and August to December for the VAC-5-14-S programme (Additional file 2: Fig. 7). Vaccinating individuals 65 years and over is the most effective programme at preventing the total number of GP consultations, hospitals, bed days, and deaths (23%, 25%, 26%, and 49% reductions, respectively)



(Fig. 2a). However, the large size of the target group means this programme is inefficient, preventing 19.03, 1.63, 4.34, and 0.25 cases of GP consultations, hospitals, bed days, and deaths respectively per 1000 vaccine courses. The most effective school-age programme is the 5–14-year-old programme, preventing 4.5% (95% CrI 3.9–5.4) of hospitalised cases. School-age programmes confer considerable herd protection, with 91.5% of the 5–9-year-old programme and 94.9% of 5–14-year-old programme of averted hospitalised cases due to indirect protection (Fig. 2c, Additional file 2: Fig. 8).

Maternal vaccination

Our results suggest that, to maximise the health benefit for a seasonal third trimester maternal programme, the optimal period of administration is from August until December (Additional file 2: Fig. 7). Such a programme prevents 8.5 (95% CrI 7.4–10.3) hospitalised cases per 1000 vaccine courses administered, with 22–30% of the hospitalised cases prevented in infants less than 1 year of age attributable to indirect protection from vaccinated mothers (Fig. 2d). Though the seasonal maternal programme is more efficient than its year-round



counterpart, it is less efficient at preventing hospitalised cases than any of the long-acting monoclonal antibody programmes.

Maximum purchasing price

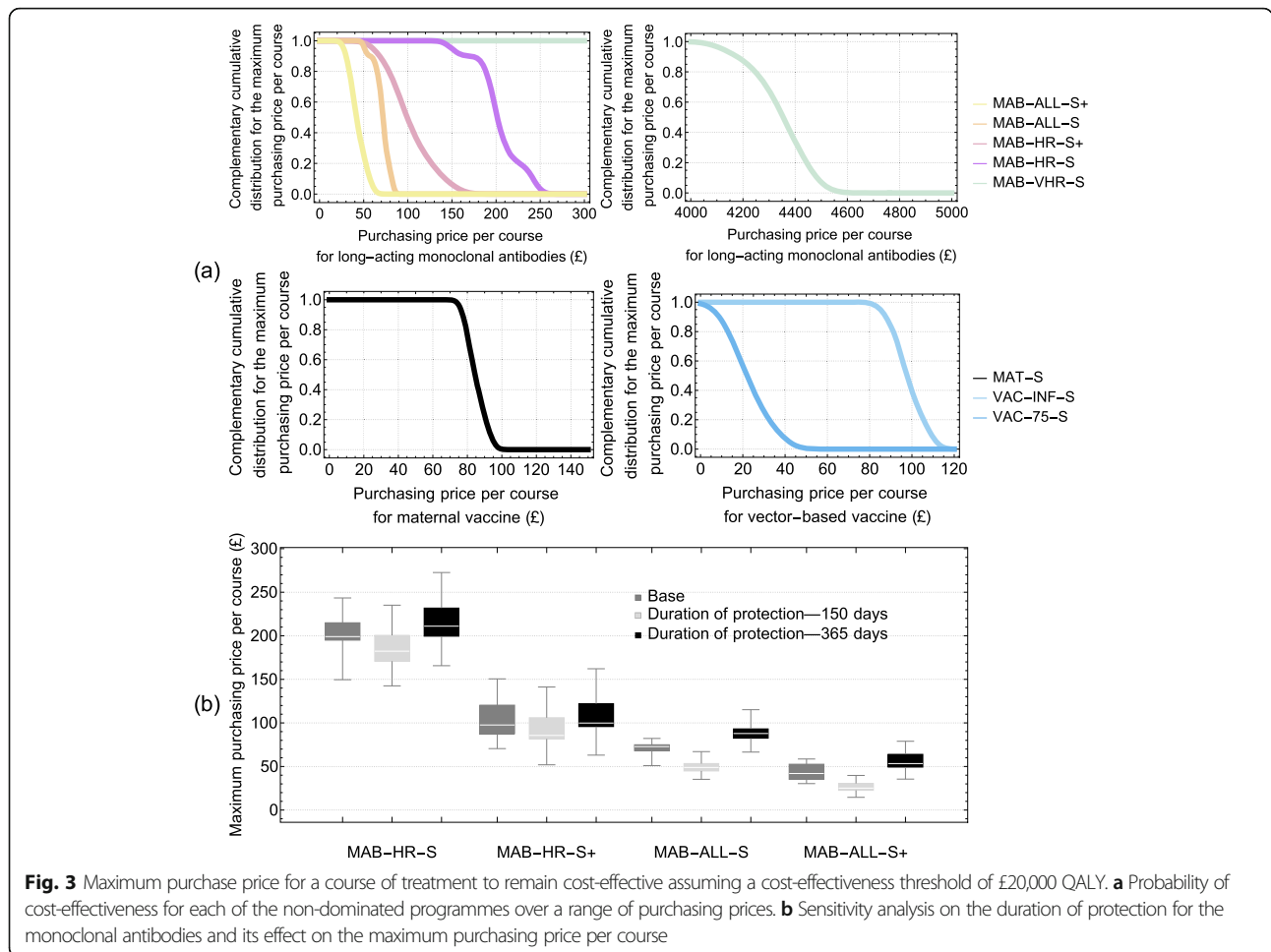
Long-acting monoclonal antibodies

The maximum purchasing price per course for the long-acting monoclonal antibody programme to be cost-effective when administered seasonally to only the VHR infants is £4342.97 (95% CrI £4126.31–4462.25) (Fig. 3a). For this seasonal programme to remain cost-effective after extending to HR neonates (MAB-HR-S), and then to all HR infants less than 6 months at the start of season (MAB-HR-S+), requires substantially lower

maximum purchasing prices per course of £201.15 (95% CrI £149.61–243.42) and £87.03 (95% CrI £64.80–116.99), respectively (Fig. 3a). If the duration of protection varies between 150 and 365 days, the maximum purchasing price for the MAT-HR-S programme would also vary between £185.79 and 215.02, respectively (Fig. 3b).

Maternal vaccination

The year-round maternal vaccination programme (MAT-A) was dominated by the seasonal strategy (MAT-S). The maximum purchasing price per course for the seasonal maternal vaccination (MAT-S) to be cost-effective is £85.27 (95% CrI £77.79–93.80) (Fig. 3a).



Childhood/elderly vaccination

The year-round vaccine programme aimed at infants 2 months of age (VAC-INF-A) is dominated by its seasonal counterpart (VAC-INF-S), while the 65 years and over programme (VAC-65-S) is dominated by the 75 years and older programme (VAC-75-S). Further, the pre-school (VAC-2-4-S) and school-age programmes (VAC-5-9-S, VAC-5-14-S) are subject to extended dominance by the 75 years and older programme (VAC-75-S). For the seasonal vaccine programme aimed at infants aged 2 months of age (VAC-INF-S), the maximum purchasing price per course to remain cost-effective is £94.76 (95% CrI 89.09-99.24). Targeting those aged 75 years (VAC-75-S) and older requires a lower purchasing price per course of £20.71 (95% CrI 10.32-34.64) (Fig. 3a).

Affordability

The long-acting monoclonal antibody programmes MAB-VHR-S, MAB-HR-S, and MAB-HR-S+ and the seasonal maternal programme (MAT-S) are affordable if implemented for a cost-effective purchasing price per

course (affordable thresholds are £9395.75, £1712.46, £873.08, and £121.02, respectively). The seasonal infant programme aimed at 2-month-olds (VAC-INF-S) and the 75 years and older programme (VAC-75-S) are affordable if implemented for £79.62 and £3.63, respectively—81% and 16% of the estimated mean maximum purchasing price per course (Table 2).

Discussion

This study used a mathematical modelling approach calibrated to 7 years of RSV incidence data to evaluate RSV epidemiology and surveillance in a developed country. Integrating this model into a cost-effectiveness framework, we evaluated the likely maximum dose prices of the new generation of RSV preventive pharmaceuticals to make them cost-effective and affordable in England. Our epidemiologic analysis found that maternal protection for infants is likely seasonal, with more babies born with protection against RSV towards the end of the RSV season in March. Our economic analysis found that replacing the existing seasonally administered Palivizumab programme with long-acting monoclonal antibodies

(MAB-VHR-S) would be cost-effective and affordable at a maximum course price of £4403 (95% CrI 4338–4511). Extending the programme to heightened risk (MAB-HR-S) or all infants (MAB-ALL-S) would remain cost-effective and affordable at approximately £200 and £90, respectively. A seasonal maternal vaccination programme (MAT-S) would be cost-effective and affordable with a maximum purchasing price per course of £85 (95% CrI 79–91).

This is the first study to use a dynamic transmission model to evaluate how Palivizumab, monoclonal antibodies, and maternal vaccines impact the incidence of RSV-related healthcare outcomes within a single framework. Consequently, this model gives a comprehensive overview of the impact of all currently proposed RSV programmes. This study is also the first to directly link the impact of potential programmes from a dynamic transmission model to a cost-effectiveness analysis (CEA) according to the NICE reference case—the gold standard approach for CEA in England and Wales, and the first to use EQ-5D-based QALY estimates for RSV. The CEA accounts for both the direct and indirect effects of intervention strategies. This approach is of particular importance when comparing the health benefits of vaccinating school-age children through which all reductions in hospitalisations are through indirect protection of other high-risk groups, with those of providing direct protection to newborns where all averted cases are in the newborns themselves.

Our model is the first to test the hypothesis that maternal protection to newborns is seasonal, contrary to the routine assumption in models in which all babies are born with protection to RSV. We found evidence for our alternative hypothesis. This seasonal change in the number of protected newborns could provide an explanation for previous findings that hospitalisation rates increase for babies born at the start of the RSV season, when our model predicts the lowest fraction of maternally protected infants, and infants born at the end of the RSV season when the maternal protection is highest experience the lowest risk of RSV-related hospitalisation [61]. Epidemiological evidence for seasonal changes in maternal protection has also been provided in studies looking at seasonal changes in RSV-specific antibody level from cord titres at birth [26]. As cord titre influences the rate of severe infections in the first year of life [21], seasonal changes could indicate temporal vulnerability in the infant population.

The maternal vaccine in this model is based on Novavax's RSV F-nanoparticle formulation. Recent stage III trial results for this product failed to meet its primary endpoint of 40% efficacy against RSV lower respiratory tract infections (LRTI) during the first 3 months of life across all trial sites. However, variations in efficacy were observed depending on region and gestation age at

administration. Regional variation in efficacy saw South Africa with promising efficacy estimates of 57% (95% CI 33–73%) against RSV LRTI, whereas the US site saw no evidence of efficacy [5]. Although in this analysis, we assume the efficacy of the maternal vaccine is as estimated across all sites, we acknowledge that care should be taken when these results are projected onto the UK, which experiences seasonal RSV similar to the US trial site. Efficacy was also found to vary with gestational age at administration, with vaccination at the start of the third trimester (28–32 weeks) experiencing an efficacy of 54% (95% CI 23–72%) against RSV-associated hospitalisation and showing superior antibody transfer when compared to administration later in the third trimester (efficacy of 26% (95% CI –23–56)). In our study, we have chosen the efficacy given at 28–32 weeks gestation as the healthcare delivery system in England is such that specific uptake periods are feasible in GP clinics if individuals are notified at the relevant time. However, uptake during this specific window may be less feasible in countries with differing healthcare policy, and thus, lower coverage rates may be observed than used in this study.

There are two potential intervention programmes against RSV which we did not evaluate in this study but may be suitable for further consideration. First, we did not examine targeted vaccination of high-risk elderly due to lack of data on clinical risk-specific hospitalisation and mortality rate within this age group. Second, we did not consider combined approaches, primarily because it is not possible to determine unique maximum purchasing prices per dose for multiple prophylactics simultaneously. However, for some approaches that combine strategies which prevent disease in different age groups (e.g. elderly and infant vaccination), the maximum purchase price for the combined approach will be approximately the sum of that for both strategies. Determining the cost-effectiveness of combination approaches which prevent disease in similar age groups (e.g. maternal and long-acting monoclonal antibody programmes) will be possible when the purchasing price for at least one of the strategies has become available.

Though the results of this analysis suggest that the long-acting monoclonal antibodies and maternal programmes are cost-effective, implementation of these programmes will present clinical and logistical challenges that this analysis has not considered. For example, we assume the same administration price per dose for all the monoclonal antibody programmes. However, administration of monoclonal antibodies to the under 6 months, rather than just newborns, will likely be more expensive and achieve lower rates of uptakes, all else equal, as they will need to make a separate appointment at a GP or hospital setting for dose administration.

Consequently, our results may overestimate the impact and cost-effectiveness of these programmes. Further, in estimating the per-infection risk for RSV-related outcomes, there were no clinical-risk-specific estimates for death and for GP consultations available in the literature, meaning the probability of these outcomes occurring may be underestimated in VHR or HR infants, implying costs and QALY burden of some of the intervention strategies may be conservative. Further studies which help estimate the burden of specific outcomes in England would help reduce uncertainty and increase the accuracy of the model predictions.

Conclusions

In this study, we have used a Bayesian approach to synthesise existing epidemiological and clinical information to estimate the uncertainty in the model parameters and to incorporate uncertainty arising from these parameter estimates to help inform decision-makers about the implementation of new RSV intervention strategies. Our analysis finds that, regardless of the intervention strategy, seasonal administration of a programme is always optimal. Moreover, we found little evidence that strategies aimed at children 2 years and older and those targeted at the elderly would be cost-effective or affordable, respectively. In contrast, long-acting monoclonal antibodies and maternal vaccines may be a cost-effective replacement or addition to the existing Palivizumab programme, respectively. The scope of the intervention programme however will depend on the purchasing price at when these pharmaceuticals are made available.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12916-020-01802-8>.

Additional file 1. Supplementary methods text.

Additional file 2: Figure S1. DIC for the ten model choices. **Figure S2.** Top. The proportion of infants born with protection over an epidemic season **Figure S2.** Bottom. A comparison of the posterior distributions for the detection model. **Figure S3.** A comparison between the model-predicted number of detected samples and the annual number of positive samples from RDMS. **Figure S4.** Top. The source of the infection for each demographic group in the analysis. **Figure S4.** Bottom. The magnitude of the force of infection relative to age group 1. **Figure S5.** Smooth histogram plots comparing the prior and posterior distributions. **Figure S6.** Estimated per-infection probability of GP consultations (top left), deaths (top right), hospital admission (bottom left) and number of bed days (bottom right). **Figure S7.** The total discount QALY loss over ten years. **Figure S8.** Impact of intervention programmes at preventing total proportion of RSV-related deaths.

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Authors' contributions

DH, KEA, MB, JPG, and RP conceived and designed the study. DH performed the mathematical modelling and cost-effectiveness analysis with

interpretations from KEA, MB, JPG, and RP. DH and KA drafted the manuscript with critical revisions from JPG, MB, and RP. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed in this current study are available in the corresponding author's repository (https://github.com/dchodgve/rsv_trans_model). Some of the data used in this analysis are not publicly available due to patient identification issues.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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