Protecting infants against RSV disease: an impact and cost-effectiveness comparison of long-acting monoclonal antibodies and maternal vaccination

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The Lancet Regional Health - Europe 2023;■: 100829

Published Online XXX
https://doi.org/10.1016/j.lanepe.2023.100829

Summary

Background Two new products for preventing Respiratory Syncytial Virus (RSV) in young children have been licensed: a single-dose long-acting monoclonal antibody (la-mAB) and a maternal vaccine (MV). To facilitate the selection of new RSV intervention programmes for large-scale implementation, this study provides an assessment to compare the costs of potential programmes with the health benefits accrued.

Methods Using an existing dynamic transmission model, we compared maternal vaccination to la-mAB therapy against RSV in England and Wales by calculating the impact and cost-effectiveness. We calibrated a statistical model to the efficacy trial data to accurately capture their immune waning and estimated the impact of seasonal and year-round programmes for la-mAB and MV programmes. Using these impact estimates, we identified the most cost-effective programme across pricing and delivery cost assumptions.

Findings For infants under six months old in England and Wales, a year-round MV programme with 60% coverage would avert 32% (95% CrI 22–41%) of RSV hospital admissions and a year-round la-mAB programme with 90% coverage would avert 57% (95% CrI 41–69%). The MV programme has additional health benefits for pregnant women, which account for 20% of the population-level health burden averted. A seasonal la-mAB programme could be cost-effective for up to £84 for purchasing and administration (CCPA) and a seasonal MV could be cost-effective for up to £80 CCPA.

Interpretation This modelling and cost-effectiveness analysis has shown that both the long-acting monoclonal antibodies and the maternal vaccine could substantially reduce the burden of RSV disease in the infant population. Our analysis has informed JCVI's recommendations for an RSV immunisation programme to protect newborns and infants.

Funding National Institute for Health Research.

Keywords: RSV; Cost-effectiveness; Mathematical modelling; Vaccination

Introduction

Respiratory syncytial virus (RSV) remains a significant global health problem. Infants less than five years of age are particularly susceptible to severe RSV disease, with an estimated 3.6 million hospitalisations and 101,400 deaths annually occurring in this age group.[1] The majority of severe disease is concentrated in infants <6 months of age, which accounts for 33% of the hospitalisations and 46% of the deaths in children less than five years of age.[2] Until recently, there has been one licensed product to protect against RSV, the monoclonal antibody treatment palivizumab (*Synagis*). However, palivizumab is costly, requiring monthly injections, and thus offered only to infants at the highest risk of complications, which leaves most children vulnerable to infection.[3]

Recently, two effective new products have been developed to protect infants: a maternal vaccine (MV, *Abrysvo*, Pfizer) and a long-acting monoclonal antibody (la-mAB, Nirsevimab, *Sanofi*).[4,5] The maternal vaccine is

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Research in context

Evidence before this study

Recently, the FDA has licensed two products which prevent RSV disease in infants, a maternal vaccine (Abrysvo) and a long-acting monoclonal antibody prophylactic (Nirsevimab). Therefore, as regulatory bodies follow suit, countries must decide which of these products and what programme is suitable to roll out to prevent disease cost-effectively. In many countries, such decisions are informed by impact and cost-effectiveness predictions evaluated from mathematical models. Searching for articles on 8th August 2023 in PubMed for "cost-effectiveness" AND "RSV" AND "vaccines OR prophylactics", we found 57 articles published in the last ten years which evaluate a variety of different intervention programmes. However, as both products have only recently reached licensure, no study has yet considered a head-to-head comparison of these two licensed products, or calculated immunity waning functions using data from clinical trials. Ensuring that herd immunity effects are captured is important, particularly for the maternal vaccine product, which would result in cocooning of neonates, and the head-to-head comparison of programmes into an incremental economic analysis ensures that policymakers are best informed about optimal resource allocation.

Added value of this study

This study uses an existing dynamic transmission model to evaluate the impact and cost-effectiveness of feasible administration programmes which use either a maternal vaccine or a long-acting monoclonal antibody (la-mAB). Using England and Wales as an example, we use published evidence on both products' efficacy and immune waning over time and incorporate it into the mathematical model to evaluate the direct and indirect effects. After considering the population-level impact of both products, we find that both are similar in preventing disease per dose. Further, we determine the conditions under which one of these programmes is optimal to implement, quantifying the influence of coverage and the combined cost of purchasing and administration per dose.

Implications of all the available evidence

This study supplements existing static and dynamic cost-effectiveness models that evaluate upcoming RSV prophylactics' cost-effectiveness. Including herd immunity effects gives more accurate impact estimates for both these products and thus more confidence to policymakers in the UK about optimal resource allocation. Incorporating immune waning from trials allows reliable estimation of how much these products will protect over the RSV season. However, access to and affordability of RSV vaccines is also crucial in LMICs, which carry 95% of RSV-related lower respiratory infection episodes and 97% of RSV-related deaths globally. The framework and results presented here, which include the impact and cost-effectiveness of likely programmes with different delivery mechanisms, can guide country-level policy on effectively introducing RSV vaccines in other geographies, including LMIC, under country-specific administration constraints.

a bivalent prefusion F subunit vaccine which, when given to women 24–36 weeks gestational age, was effective at protecting against medically-attended RSV disease during the first six months of life.[4,6] The la-mAB is an anti-RSV monoclonal antibody with an extended half-life which targets the surface F protein and is 74.5% effective at reducing medically-attended RSV disease up to 150 days post-administration in neonates.[5] Nirsevimab and Abrysvo have been licensed by the FDA and rollout is soon expected.[7,8]

In the UK, decisions regarding immunisation programmes are made based on recommendations and advice from the Joint Committee on Vaccination and Immunisation (JCVI).[9] Alongside clinical and operational considerations, JCVI is required to consider the cost-effective analysis in formulating advice. Where multiple products and programme options exist for a disease, it is insufficient to show that a single product programme is cost-effective by itself; assessment of what is optimal requires analysing all programmes simultaneously.[10] In the case of MV and la-mAB, which have similar efficacy against disease but are administered through different delivery routes (i.e. to newborns at the birth location vs. to mothers during antenatal appointments), this presents a challenging question to public health decision-makers and careful evaluation through mathematical modelling and cost-effectiveness analysis is required.

This study provides a head-to-head cost-effectiveness comparison of maternal vaccine and la-mAB programmes in England and Wales by integrating a transmission model calibrated to data on RSV incidence and clinical trial data into an economic evaluation. We use this evaluation to calculate the optimal programme under a realistic range of purchase and administration costs, the results of which have informed decision-making by the JCVI.[11]

Methods

RSV transmission model structure and data

To evaluate the impact of intervention programmes, we used a previously published model of RSV transmission in England and Wales (described elsewhere[12]), which allows us to capture both direct and indirect (herd protection) effects of preventive interventions. Briefly, our transmission model accounted for 25 age groups: stratified monthly up to 1 year, yearly from 1 to 4 years,

then 5–9, 10–14, 15–24, 35–34, 35–44, 45–54, 55–64, 65–74, 75+ years. Our model considered both symptomatic and asymptomatic infections with asymptomatic individuals less infectious.[13] We accounted for maternal antibody protection of newborns that wanes over time and that immunity develops sequentially after subsequent infections. We assumed that both infection and maternally derived immunity reduce the risk and severity of future infections. Finally, the transmission rate captured empirical data on age-group-specific social mixing rates from England and Wales,[14,15] and seasonal variation in RSV transmission. This model was fitted to the incidence of RSV-positive samples from the Respiratory DataMart System at UKHSA,[16] estimating the seasonal RSV incidence between 2010 and 2017 across all 25 age groups. RSV seasonality was altered after the COVID-19 pandemic in England and Wales, but it now is returning to pre-pandemic seasonality.[17,18] This model assumes that once these interventions are implemented, RSV seasonality will have returned to previous trends.[19] A summary of the underlying model assumptions and the parameterisation of the dynamic transmission model can be found in Section 1.1–1.4 of the SI).

Intervention programmes

Long-acting monoclonal antibodies (la-mABs)

We considered three la-mAB programmes: i) a seasonal programme given at birth between September and February, ii) a seasonal programme given at birth between September and February together with a yearly catch-up of all infants aged 1–6 months during September, iii) a year-round programme given at birth. We assumed a 90% uptake, consistent with Vitamin K supplementation coverage at birth,[20] and that these programmes supplemented the current palivizumab programme (Table 1).

We captured these interventions in our model by assuming that all infants who are immunised (vaccinated and successfully gain efficacious protection) by the la-mABs become temporarily but fully protected from infection before regaining susceptibility to infection (SI Section 1). As la-mAB provides passive protection, we assumed immunisation by la-mAB does not count as an exposure event in the infection-derived immunity process.

Maternal vaccination

We considered two maternal vaccine programmes: i) a seasonal programme available to pregnant women 24–36 weeks gestational age between July and December and ii) a year-round programme available to pregnant women 24–36 weeks gestational age. We assumed 60% uptake, consistent with antenatal pertussis (Tdap) vaccine administration in England between 2019-2022,[21,22] and that these programmes supplemented the existing palivizumab programme (Table 1).

We captured maternal vaccine-derived immunity in infants by assuming that babies born to immunised mothers who successfully gain efficacious protection are all temporarily but fully protected from birth before regaining susceptibility to infection and following the infection-derived immunity model (SI Section 1.3). Similarly, as transplacental antibody transfer provides passive protection, we assumed immunisation by maternal vaccination does not count as an exposure event in the infection-derived immunity process. We also incorporated vaccine protection for the pregnant women themselves.

Efficacy and waning of protection after immunisation

Using a Bayesian framework, we estimated each product's efficacy and waning of protection using data from clinical trials for MV and la-mAB. This framework assumed that the placebo and intervention arms both experience the same time-varying rate of exposure to infection (included as a nonparametric function with Gaussian Process prior) but that a time-varying factor reduces this attack rate in the intervention arm to account for any waning immunity (Fig. 1A, See SI Section 3.1).

We assumed that vaccine-induced immunity against milder health outcomes wanes according to an Erlang-3 distribution (MV (neonates): infection, symptomatic cases, GP consultations; MV (pregnant women): infection, symptomatic cases, GP

Programme	Product	Modelled efficacy	Explanation	Coverage	Annual number of doses
Seasonal	la-mAB	150 days: 77.3 (65.4–86.5)	Given to infants at birth born between September and February	90%	309,066
Seasonal with annual catch-up	la-mAB		Given to infants at birth born between September and February and to infants less than six months of age during September	90%	624,924
Year-round	la-mAB		Given to all infants at birth	90%	619,829
Seasonal	MV	180 days: 49.8 (34.2–62.1)	Given to pregnant women between July and December at 24–36 weeks gestational age	60%	206,571
Year-round	MV		Given to all pregnant women between 24 and 36 weeks gestational age	60%	407,559

Table 1: **The intervention programmes considered in this study.**

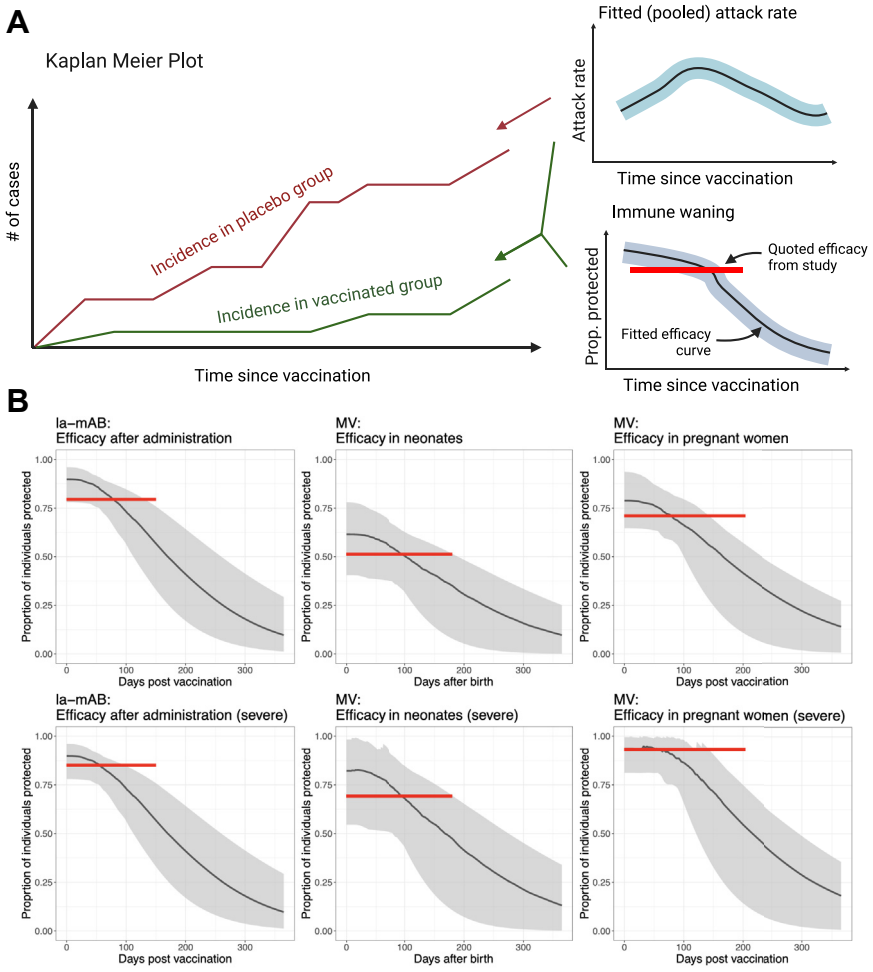

Fig. 1: Estimating waning protection from maternal vaccination and monoclonal antibodies. A) Cartoon of the Bayesian fitting procedure for determining the time-varying protection from infection and disease from Kaplan Meier plots. B) The fitted time-varying probability of protection (mean: black lines, 95% CrI: grey area) with the quoted efficacy from clinical trial studies (red lines).

consultations, A&E; la-mAB: infection, symptomatic cases, GP consultations, A&E and hospitalisation). We assumed a higher efficacy for more severe outcomes using the efficacy against disease for severe lower respiratory tract infection (LRTI) for MV (neonates) and MV (pregnant women), and efficacy against very severe LRTI for la-mAB. Efficacy against more severe outcomes is implemented by linearly approximating the estimated number of infected persons protected from the severe disease at each time point in the model and changing the outcomes proportionally (Fig. 1B, SI Section 3). To characterise waning immunity for the MV in neonates, we used data from the Kaplan Meier plot for RSV-associated LRTI following vaccination (Fig. 2b in Kampmann et al.[4]). In contrast, waning immunity for pregnant women post-vaccination is calculated using the Kaplan Meier plots for RSV-related Acute Respiratory Infection (ARI) (Fig. 2B in Papi et al.[23]). For the la-mAB, waning immunity in neonates after immunisation is calculated using the Kaplan Meier plot for RSV-related LRTI (Fig. 1a in Simões et al.[24]).

Economic model

We used a health service utilisation model to convert the age-stratified RSV incidence projections from the transmission model into six RSV-associated health outcomes: symptomatic infections, GP consultations, accident and emergency (A&E) visits, hospital admissions, intensive care unit (ICU) admissions, and deaths. For this, we first performed a literature review to establish the annual incidence of each outcome per age group and then calculated the risk of health outcome per infection by dividing incidence by the model-projected number of all RSV infections (SI Section 4, Supplementary Fig. S1).

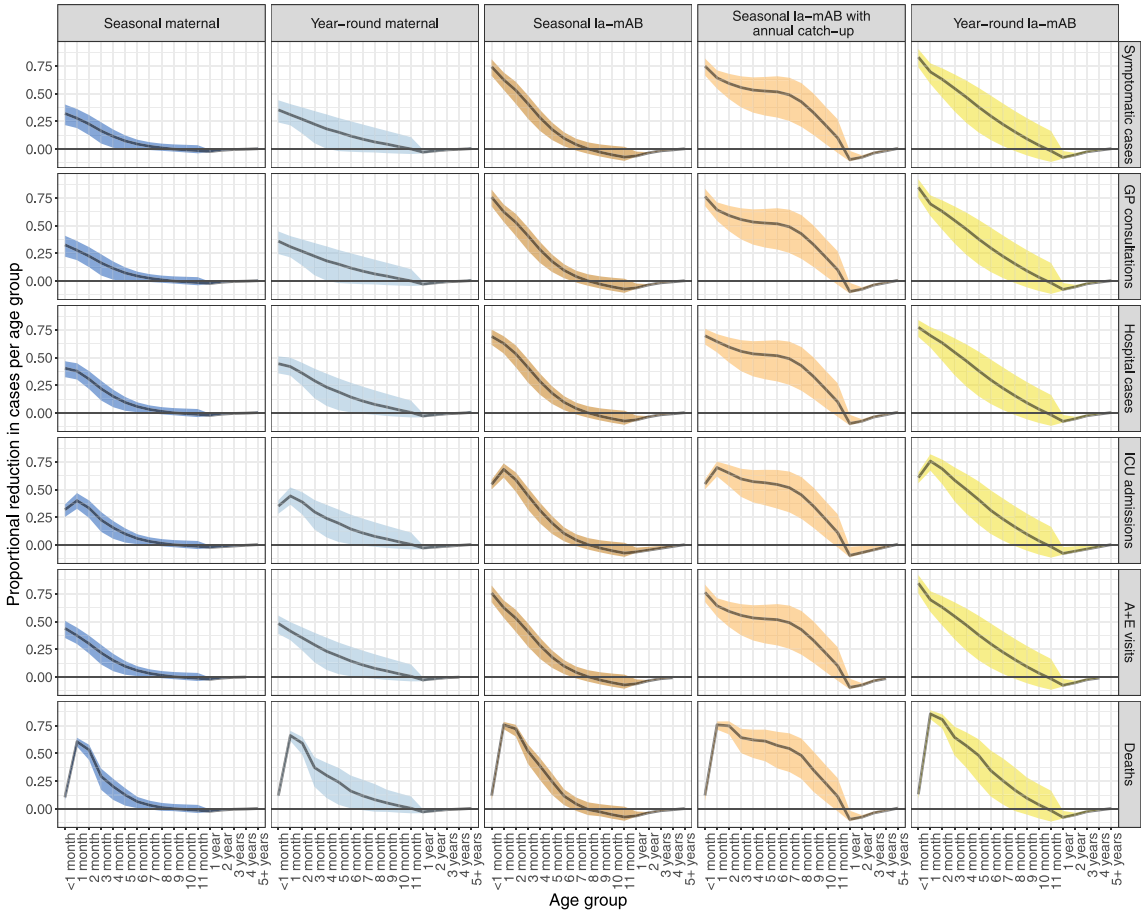

Fig. 2: Impact of the programmes across age groups. Black lines show the median proportional reduction in cases of six health outcomes for the maternal and Ia-mAB programmes. The shaded areas show the 95% CrI of the posterior distribution.

To assess the health benefits, we projected the quality-adjusted life-years (QALYs) loss for the base case scenario (the current palivizumab programme) and each of the five intervention programmes. We used UK-specific estimates for the QALY loss attributed to symptomatic cases, GP-attended cases, hospital admissions, A&E visits, ICU admissions and deaths (Table 2).[27–30] We calculated the cost of each health outcome from the perspective of the National Health Service (NHS) using health and unit costs (GP consultations) and the National Schedule of NHS costs (hospital admissions, A&E visits, ICU admissions).[25,26]

Finally, to calculate the cost of programme delivery, we defined the combined cost of purchasing and administration (CCPA) as the cost of buying and delivering each dose. The programme's total cost was calculated as the CCPA multiplied by the number of doses given (single dose for each product) added to the total cost of the health outcomes.

All costs and effects were calculated over a 10-year time horizon and discounted at a rate of 3.5% per year in line with guidelines set by the National Institute of Clinical Excellence (NICE).[31]

Determining the optimal programme

For each of the five intervention programmes and the status quo scenario, we determined the joint distributions of i) total QALY gain, ii) the total clinical cost saving for each programme. We then selected a total combined cost of purchasing and administration (CCPA) (in £5 intervals from 0–£200) for each product and used the joint distribution for each programme to calculate its Incremental Net Monetary benefit (INMB) distribution. We defined the optimal programme as the one with the highest INMB assuming an ICER threshold of £20,000/QALY.

Finally, we used the distributions of total QALY gain and total cost of each programme to calculate the Expected Value of Perfect Information (EVPI) under a range of CCPAs by calculating the expectation of the INMB for the optimal strategy under each Monte Carlo simulation and subtracting from it the INMB that is

Parameter	Value (95% CI)	Reference
Costs per outcome		
GP consultation	£36.00 (fixed)	[25]
A&E attendance	£185.00 (fixed)	[26]
Hospital admission episode	<15 years: £1100.23 (1029.66–1253.16) ≥15 years: £652.29 (585.37–740.31)	SI Section 4[26]
ICU admission episode	<15 years: £2905.20 (2282.80–3862.67) ≥15 years: £2324.80 (1948.25–2653.25)	SI Section 4[26]
QALY loss per outcome		
Symptomatic infection or GP consultation	<5 years: 2.336×10^{-3} (0.269×10^{-3}–9.255×10^{-3}) ≥5 years: 1.448×10^{-3} (0.135×10^{-3}–5.928×10^{-3})	SI Section 4[27]
Hospital/ICU admission	<5 years: 4.098×10^{-3} (0.624×010^{-3}–13.141×10^{-3}) ≥5 years: 2.990×10^{-3} (0.346×10^{-3}–11.387×10^{-3})	SI Section 4[27]
Death	Depends on life tables	SI Section 4[28–30]

Table 2: **Economic parameters used in this study.**

optimal when averaging across all monte carlo samples.[32] A high EVPI indicates that there is substantial uncertainty in the decision-making process, and acquiring additional information is valuable because it has the potential to greatly improve the decision outcome. A low EVPI suggests that the decision is relatively robust or insensitive to the uncertainty in the input parameters, so acquiring additional information is less valuable because it is unlikely to substantially improve the decision outcome or change the optimal course of action.

Sensitivity analysis

For our univariate sensitivity analysis, we calculated the optimal programme assuming a willingness-to-pay ICER threshold of £30,000/QALY. Further, we considered the impact of changing the coverage of the programmes (70–90% for la-mAB and 50–90% for MV). For our structural uncertainty analysis, we considered how the cost-effectiveness landscape changes if we omit the logistically challenging la-mAB catch-up programme.

Implementation

The waning efficacy models were fitted using Hamiltonian Monte Carlo sampling through Stan (v. 2.2.10)[33] via cmdstanr (v. 0.5.2) R package,[34] the reproducing code can be found at https://github.com/dchodge/effestimator. The intervention programme projections were implemented in rsvie (https://github.com/dchodge/rsvie), which allows custom intervention programmes, varying in implementation, risk of outcomes, costs, and QALYs to be evaluated through the dynamic transmission model.[12] For each of the six programmes, we generated 1000 Monte Carlo simulations, sampling from the posterior RSV incidence, the posteriors of the efficacy waning parameterisation, the confidence intervals for the per-infection risk of each outcome, and the confidence intervals for the costs and QALYs of each intervention programme (SI Section 1.4). To assess impact, we compared each intervention to the base case. Scripts reproducing the results of this study are implemented in R and available at https://github.com/dchodge/rsvmabmat.

Role of the funding source

None.

Results

Waning of protection after immunisation

Our fitted curve modelling the rate of loss immunity due to maternal vaccination and long-acting monoclonal antibodies is consistent with the published efficacy data (Fig. 1B). For MV in neonates, our fitted model efficacy curve (determined through Bayesian inference) has a mean efficacy over the first 180 days after birth of 49.2% (95% Credible Interval (CrI) 30.2–64.5), compared to the quoted efficacy (determined through frequentist methods by the original study) of 51.3% (95% Confidence Interval (CI) 29.4–66.8),[4] while for MV in pregnant women, the mean fitted efficacy over 180 days is 65.9% (95% CrI 51.2–77.2) compared to 71.7% (95% CI 56.2–82.3).[23] For la-mAB, the mean fitted efficacy over 150 days is 78.1 95% CrI (66.1–87.3) compared to 79.5% (95% CI 65.9–87.7).[24] Thus, our results agree with efficacy values reported by the randomised controlled trials when the waning functions are averaged over the timeframe for these studies (SI Section 3). Extrapolating the fitted efficacy curves after the end point of each trial, we find that by one year after immunisation/birth, a higher proportion of infantsare protected with the la-mAB: 15% (95% CrI 1–34) for la-mAB vs. 9% (95CrI 0–23) for MV. Pregnant women were similarly protected, with 14% (95% CrI 0–31) remaining protected one year after receiving the vaccine.

Impact of intervention programmes

The MV programmes are effective at preventing infections in infants aged 0–2 months of age, with the seasonal programme preventing on average between

30% (95% CrI 20–37), 30% (95% CrI 21–38), and 38% (95% CrI 31–45) of annual symptomatic cases, GP consultations and hospital admissions, respectively, and the annual programme preventing 34% (95% CrI 24–41), 33% (95% CrI 24–42), and 42% (95% CrI 35–50) of the same health outcomes. The MV year-round programme is much more effective at preventing disease in the 6–11 month age group compared to the seasonal programme, averting 6.2% (95% CrI −2.9 to 18.0) symptomatic cases, 8.8% (95% CrI −0.1 to 20.8) hospitalisation (compared to 1.4% (95% CrI −1.7 to 5.2) and 2.5% (95% CrI −0.7 to 6.3) for seasonal MV). Both programmes increased health outcomes in those aged 1 year, for example, symptomatic cases increased by 1.9% (95% CrI 0.3–4.6) (seasonal) and 2.5 (0.4–4.4) (year-round) (Fig. 2, Supplementary Figs. S2 and S3).

The la-mAB programmes are effective at preventing disease in infants aged 0–2 months old, with the seasonal programme preventing 68% (95% CrI 60–74), 69% (95% CrI 61–75) and 64% (95% CrI 56–71) of annual symptomatic cases, GP consultations and hospital admissions, respectively, and the annual programme preventing 75% (95% CrI 69–83), 76 (95% CrI 69–84) and 70% (95% CrI 63–76) of the same health outcomes. The seasonal programme with annual catch-up is most effective at preventing outcomes for infants between 6 and 11 months of age, preventing 34% (95% CrI 15–51) of symptomatic cases. Further, the la-mAB seasonal with catch-up programme increases health outcomes in infants aged 1 year more than any other programme (MV or la-mAB), increasing the incidence of symptomatic cases and hospitalisation by 8.3% (95% CrI 1.5–11%) and 8.3 (95% CrI 1.5–11%) respectively (Fig. 2, Supplementary Figs. S2 and S3).

The seasonal programmes are more efficient: for la-mAB, we estimate that one needs to immunise 4 (95% CrI 2–7), 43 (95% CrI 36–55), and 30,578 (95% CrI 25,452–36,873) newborns to prevent one symptomatic case, hospital admission and death respectively, while for MV these numbers are 4 (95% CrI 2–6), 49 (95% CrI 38–63), and 23,213 (95% CrI 19,344–28,000). The least efficient programme is the year-round la-mAB programme where the numbers needed to immunise are 5 (95% CrI 3–11), 66 (95% CrI 49–93), and 50,039 (95% CrI 38,306–68,125) newborns, per symptomatic case, hospital admission and death, respectively (Fig. 3a). The la-mAB programmes see a larger QALY gain compared to the MV programmes, gaining 3819 (vs 3042 for MV) and 5867 (vs 3819 for MV) QALYs for seasonal and year-round programmes, respectively (Fig. 3b). Similarly, the la-mAB programmes see a larger cost saving compared to the MV programmes, saving £118,731,529 (vs £73,650,588 for MV) and £167,160,601 (vs £96,604,729 for MV) QALYs for seasonal and year-round programmes, respectively (Fig. 3c).

Source of infection for each intervention programme

All programmes prevent disease in individuals aged <1 yrs and ≥15 yrs, but increase disease in the 1–14 yrs age group. This effect is greater in the la-mAB programmes than the maternal programme due to the slower waning of immune protection. The MV programmes provide more protection for people 15 years and older (~21% of total QALY gain is ≥ 15 years) in comparison to la-mAB programmes (8–12% of total QALY gain is ≥ 15 years) (Supplementary Fig. S4). This is driven by the direct protection maternal vaccines provide to mothers themselves.

Cost-effectiveness analysis

In our base case using an ICER threshold of £20,000/QALY, we find that if la-mAB is priced above £84, then a seasonal maternal vaccine programme is optimal between £36–80 CCPA, and a year-round programme is optimal up to £35 CCPA (Fig. 4, Supp Figure S11). If the maternal vaccine is priced above £80, then a seasonal la-mAB vaccine programme is optimal up to £55–83 CCPA, and a seasonal Ia-mAB with a catch-up programme is optimal up to £55 CCPA (Fig. 4, Supplementary Fig. S11). We found that the year-round la-mAB programme is dominated by the seasonal Ia-mAB with an annual catch-up programme across all CCPAs.

If both products are priced below £30 then the la-mAB programme is optimal. If both products are priced similarly above £30, then the analysis suggests that both programmes are similarly cost-effective (Fig. 4, Supplementary Fig. S11). In these cases, the EVPI is very high (£20,000,000), suggesting substantial uncertainty in the decision-making process and that acquisition of additional information to decrease uncertainty should be considered.

Sensitivity analysis

Assuming an ICER threshold of £30,000/QALY, the maximum CCPA for the year-round maternal and seasonal maternal vaccine programmes increases to £41 and £100, respectively (Supplementary Fig. S5). For la-mAB, the maximum CCPA at £30,000/QALY is £102 for the seasonal Ia-mAB programme and £62 for the seasonal with the annual Ia-mAB programme with catch-up. If we remove the seasonal Ia-mAB with an annual catch-up programme, the CCPA for the year-round la-mAB programme is £31 (Supplementary Fig. S1).

When we change the coverage rates, this does not affect the maximum CCPA for the programmes considered. However, the gradient which forms the boundary between the two products changes (Supplementary Fig. S6–S10). For illustration, we plot the effect of different coverages assuming the same CCPA for each product in Fig. 5. Under this

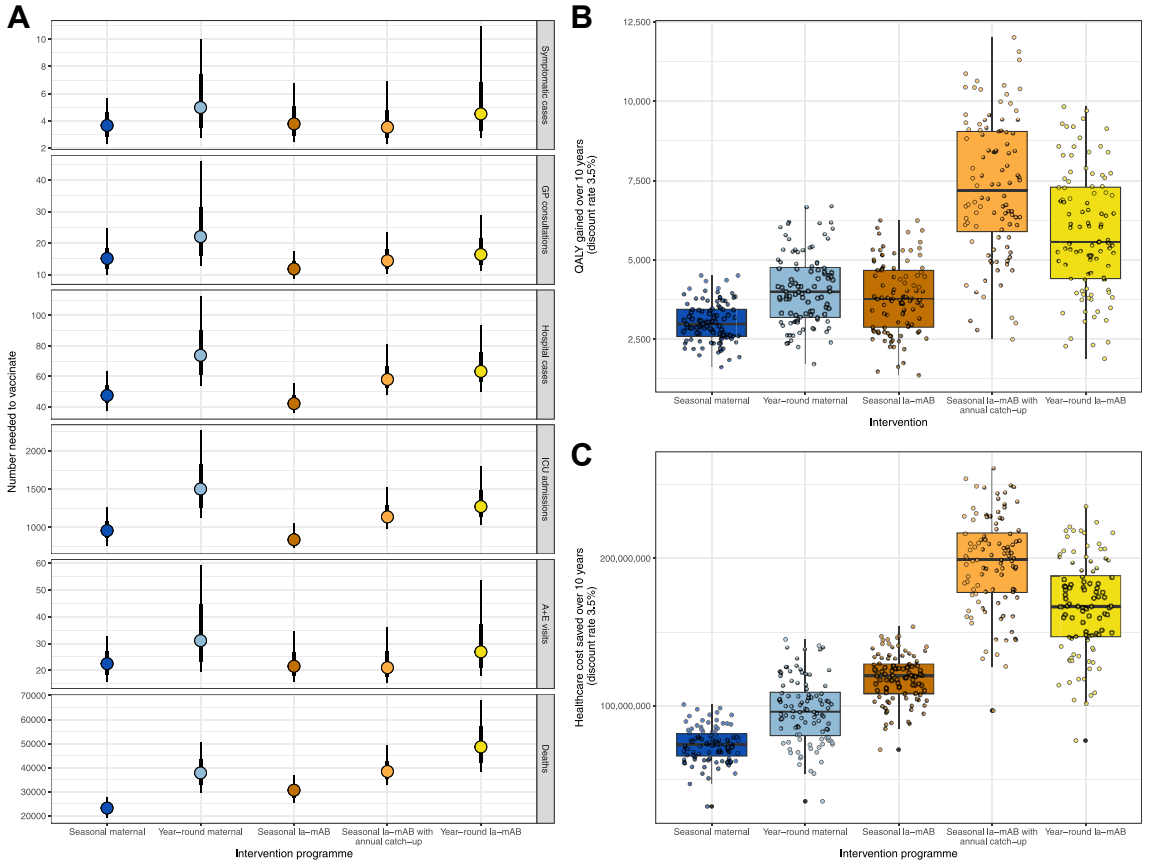

Fig. 3: A) The per dose efficiency for each programme considered. The uncertainty is shown at the 50% CrI (thick black line) and 95% CrI (thin black line) B) The distribution of the discounted QALY gain over ten years for each of the five intervention programmes C) The distribution of the healthcare cost saving over ten years for each of the five intervention programmes (not including the price of implementing the programme).

assumption, the la-mAB programme is optimal except if coverage of maternal vaccine is 90% versus coverage of 70% for la-mAB and the CPPA is below £10 a dose.

Discussion

This study estimates the optimally cost-effective programme for new monoclonal antibodies and maternal vaccines against RSV at various price points in England and Wales. We find that all large-scale programmes are effective at reducing disease burden, and when considering the population-level effects of both products, including their indirect effects, both are similarly effective at preventing RSV disease per dose. However, due to their presumed higher coverage, the la-mAB programmes prevent more disease than the maternal vaccination programmes. Since the prices are unknown, we also provide two-dimensional cost-effectiveness frontiers that show the optimal programme given the combined cost of purchasing and administration per dose of MV and la-mAB. These estimates were used to inform recommendations from the JCVI,[11] but can also be used to help inform other counties with similar resources and RSV epidemiology about the suitability of incorporating these RSV products into their existing national immunisation programme. These products could also cost-effectively benefit LMIC settings, which see the majority of the global disease burden, providing the products are made available at competitive purchasing prices.[35]

When assessing the impact of these programmes, we see a reduction in RSV-related healthcare outcomes in infants but also a small increase in health outcomes in the 1-year age group. This slight increase in incidence arises from an increased age of first infection driven by a higher proportion of susceptibles in the 1-year age group compared to the base case. This shift is a consequence of introducing large-scale short-lived passive immunity into the population, instead of relying on active immunity that builds up an individual's own protection against further infection and disease. This age shift is more pronounced when la-mAB is used, due

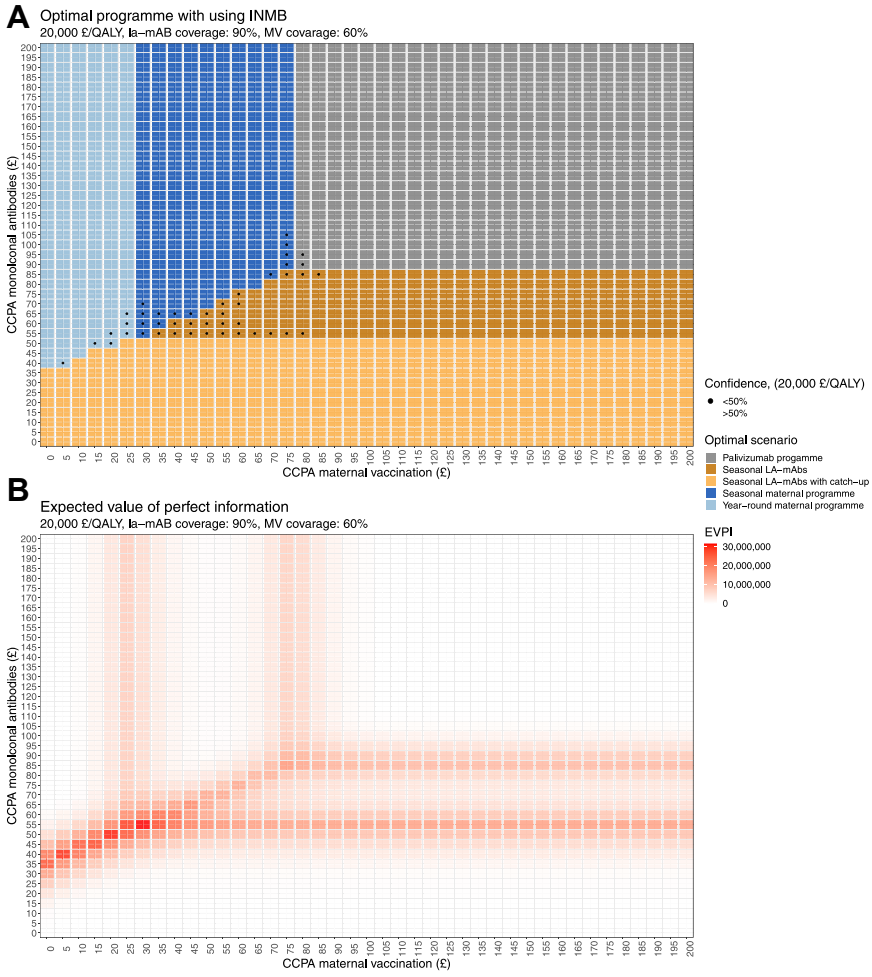

Fig. 4: A) Optimal intervention programmes according to the cost-effectiveness of the programme for a combined cost of purchasing and administration (CCPA) for maternal vaccines (x-axis) and monoclonal antibodies (y-axis) assuming a £20,000/QALY threshold. The optimal programme is the coloured tile corresponding to a CCPA for MV and la-mAB. (B) The EVPI for a given CCPA of maternal vaccines (x-axis) and monoclonal antibodies (y-axis). Note: the year-round seasonal programme is dominated by the seasonal with catch-up programme in the CEA, and therefore not shown in this plot.

to a longer-lasting duration of protection which extends through the first year after administration compared to the maternal vaccine, leaving fewer individuals having acquired active immunity from infection before their first birthday. In CEA analysis, assuming low CCPA for both products, the la-mAB programmes emerge as the optimal choice due to their larger overall impact and favourable cost-effectiveness ratio driven by higher coverage. However, when we assume equal coverage between programmes, other implementation factors must be considered alongside overall health impact, including the feasibility of implementation and the CCPA of the products.

This study makes assumptions about programme implementation due to uncertainty in programme roll-out. For example, we assume uptake of maternal vaccination happens uniformly between 24 and 36 weeks gestational age. However, there is a signal for possible suboptimal response to acellular pertussis when coadministered with Tdap (/dTaP).[36] This interference could be mitigated by separating the administration windows of both vaccines during pregnancy[36] but this could negatively affect uptake of both vaccines. Another assumption this study makes about delivery is that uptake for pregnant women is uniform between 24 and 36 weeks of gestational age. If national campaigns target a different gestational window, e.g. 32–36 weeks as suggested by the CDC,[37] then the timing of a seasonal programme needs to be carefully considered to ensure protection is provided when infants require is most. Further, it is currently unclear how efficacy against RSV in infants relates to gestational age when the vaccine is

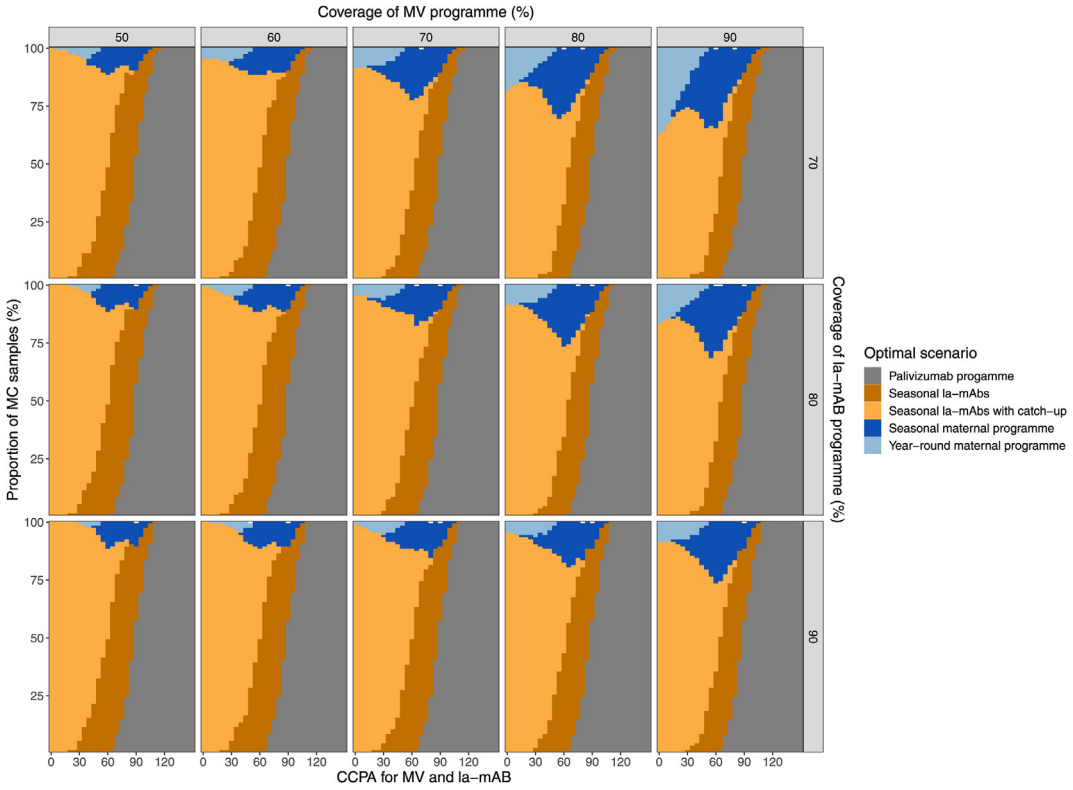

Fig. 5: Stacked bar charts showing the optimal programme from the Monte Carlo samples assuming the same CCPA for MV and la-mAB but different coverages.

received, and there the vaccine effectiveness of gestational-age specific programme will need to be monitored after roll out. Another crucial aspect of implementation which remains unclear is the relative acceptability of the two products and how this will affect coverage. Here we assume that a la-mAB programme would achieve a higher coverage than maternal vaccination (90% vs 60%), however, there remains uncertainty surrounding the achievable coverage for these programmes. Although maternal vaccination programmes have historically achieved higher coverage in England and Wales than assumed here (e.g. Pertussis had nearly 80% coverage at implementation[22]), coverage has fallen in recent years (to as low as 40% for influenza in 2022[38]). It remains unclear as to whether this trend would continue if another maternal vaccine was added to the schedule. On the other hand, a large-scale programme that administers monoclonal antibodies at birth has not been implemented in England and Wales and thus it remains unclear what coverage levels are achievable. Although vitamin K, a product offered at birth to neonates in the UK, typically by intramuscular injection, has seen high levels of uptake (>90%),[20] it remains unclear if the acceptability of the two products is comparable. It is well established that parents trust health professionals and their provision of factual information to support immunisation decisions, therefore ensuring healthcare professionals are supported with appropriate resources and professional support could facilitate high uptake of either the antenatal or infant programme.[39]

There are further implications these vaccines may have on population-level health that this study has not included. First, we assume all vaccines are safe and have no negative contribution to health burden. While the products presented here have been extensively researched and approved as safe by regulatory authorities, rare adverse events or side effects can occur.[40] Though these might not be known until large-scale implementation, should significant adverse events be found in post-licensure surveillance, it would be important to incorporate them into future model iterations. Another potential limitation of this model is that it does not consider risk-group-specific implementations and health outcomes. For the maternal vaccine, identifying any risk conditions that the infant may have is usually difficult, and thus, our model considers the mean effect of vaccination averaged across a variety of risk factors and comorbidities for infant births. However, for the la-mAB, targeted approaches could be

optimal at a very high CCPA if they target those with the highest RSV disease burden. Further analysis and cost-effectiveness studies would be needed to explore the risk-group-specific cost-effectiveness of la-mAB programmes.

Another potential impact of RSV intervention programme implementation, which this model does not consider, is their impact on other seasonal respiratory diseases such as *Streptococcus pneumoniae*. Evidence suggests an RSV co-infection could increase the risk of *S. pneumoniae* disease by enhancing its adherence to respiratory epithelial cells.[41,42] Therefore, infection-blocking RSV immunisation programmes could also reduce pneumococcal disease. If the RSV immunisation programmes considered here effectively prevent respiratory disease from other pathogens, our study would underestimate the CCPA at which the RSV programmes are cost-effective.

To evaluate the immune waning of both products we used publicly available estimates over 150 or 180 days post-vaccination/birth and extrapolated based on estimated waning rate. A faster or slower immune waning rate than assumed would change the maximum purchasing CCPA. In particular, if evidence shows that this immunity persists up to a second season, then the maximum CCPA in this study would be underestimated. Other limitations in accurately evaluating products include the difficulties in comparing endpoints between studies and the challenges in relating medically defined outcomes to clinical outcomes.

This study provides compelling evidence for the substantial impact that population-based interventions using these products could have on preventing RSV disease in infants, as well as the range of acceptable prices England and Wales should be prepared to pay for their implementation. Through the two-dimensional cost-effectiveness frontiers, we allow decision-makers to identify which product and programme is most cost-effective given both the price and administration costs for both products and calculate the certainty around this finding.

Contributors

DH: Conceived and designed the study. Performed the formal analysis and development of the methodology and software. Prepared and created the visualisation and wrote, reviewed and edited the manuscript and supplementary information.

NW and EvL: Performed the formal analysis and development of the methodology and software. Reviewed and edited the manuscript.

CW, JC, SF, and MJ: Conceptualisation and supervision. Reviewed and edited the manuscript.

KA: Conceptualisation and supervision. Wrote, reviewed and edited the manuscript.

Data sharing statement

The data underlying this study are openly available. Researchers can access the data and associated code via https://github.com/dchodge/rsvmabmat or by contacting the corresponding author.

Declaration of interests

All authors declare no conflict of interest.

Acknowledgements

MJ, EvL and DH are funded by the NIHR Health Protection Research Unit in Modelling and Health Economics, a partnership between UKHSA, Imperial College London and LSHTM (grant code NIHR200908). The views expressed are those of the author(s) and not necessarily those of the NIHR, UK Health Security Agency or the Department of Health and Social Care. SF was supported by Germany's Innovation Fund of the Joint Federal Committee (grant number 01VSF18015) and a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant number 208812/Z/17/Z).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100829.

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