Article title: Cost-effectiveness of respiratory syncytial virus preventive interventions: a model comparison study

Appendix 1: Additional methods and results

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1 S. Methods

Five models were included in this model comparison study: three static models developed by University of Antwerp (UA), Novavax (NV), Sanofi Pasteur (SPS: Sanofi Pasteur static model) and two dynamic models developed by Sanofi Pasteur and EPIMOD (SPD: Sanofi Pasteur dynamic model) and London School of Hygiene & Tropical Medicine (LSHTM). The UA, SPS, SPD and LSTHM models were adapted from a previously published cost-effectiveness analyses for respiratory syncytial virus (RSV) preventive strategies in infants (1-4). The NV model is unpublished but is structurally similar to a published model for respiratory RSV vaccination in older adults (5).

1.1 Model structures

The model structures are presented in Figure 1 to Figure 5.

Figure 1: University of Antwerp (UA) static model structure (Li et al. 2022)

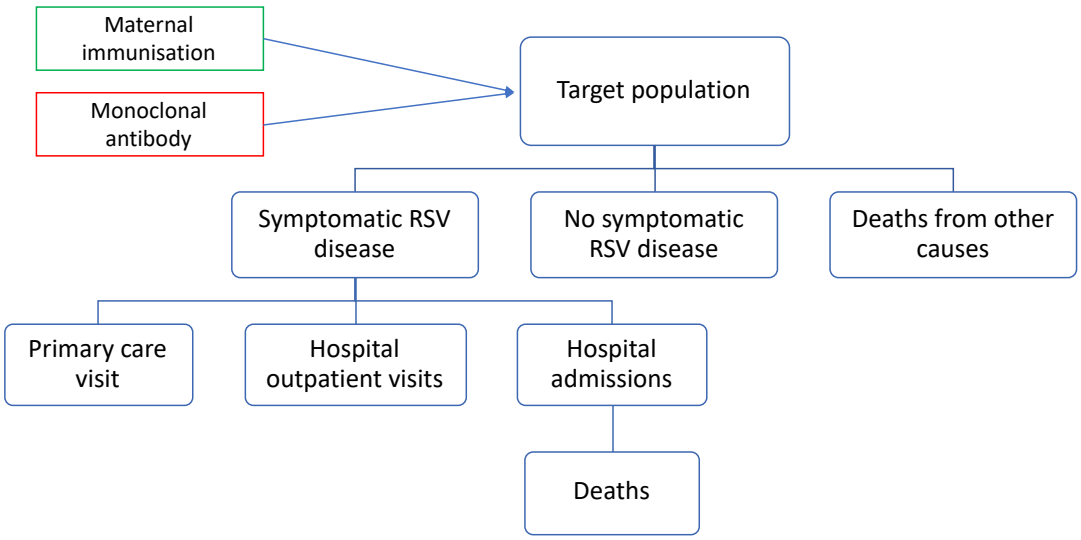
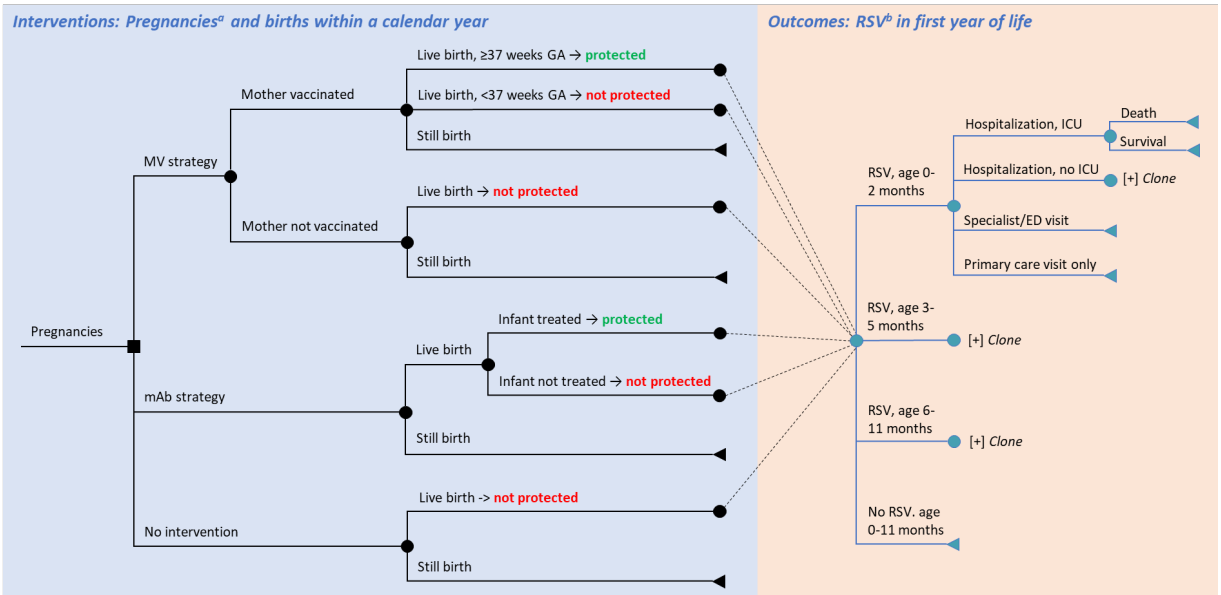
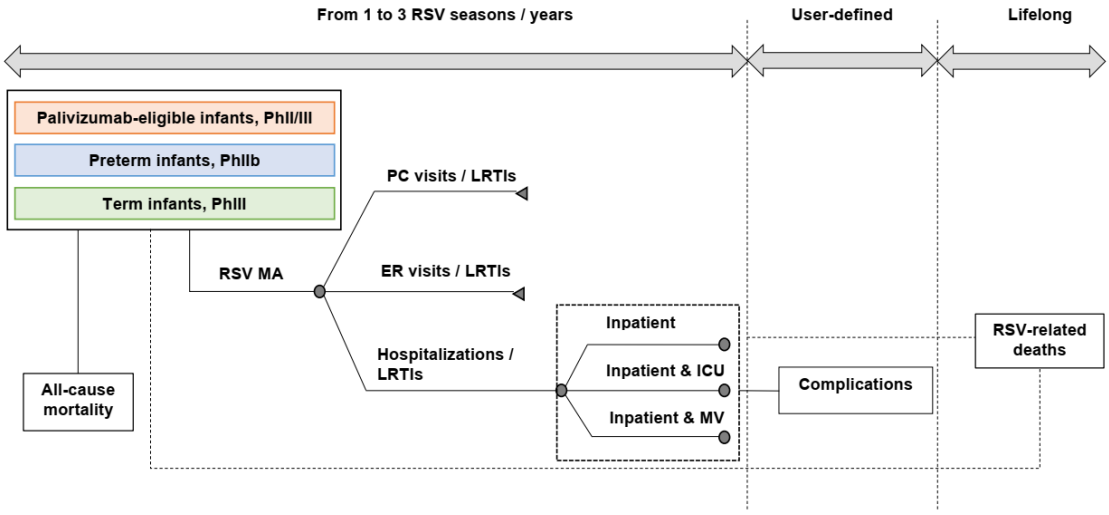


Figure 2: Novavax (NV) static model structure (Herring et al. unpublished)



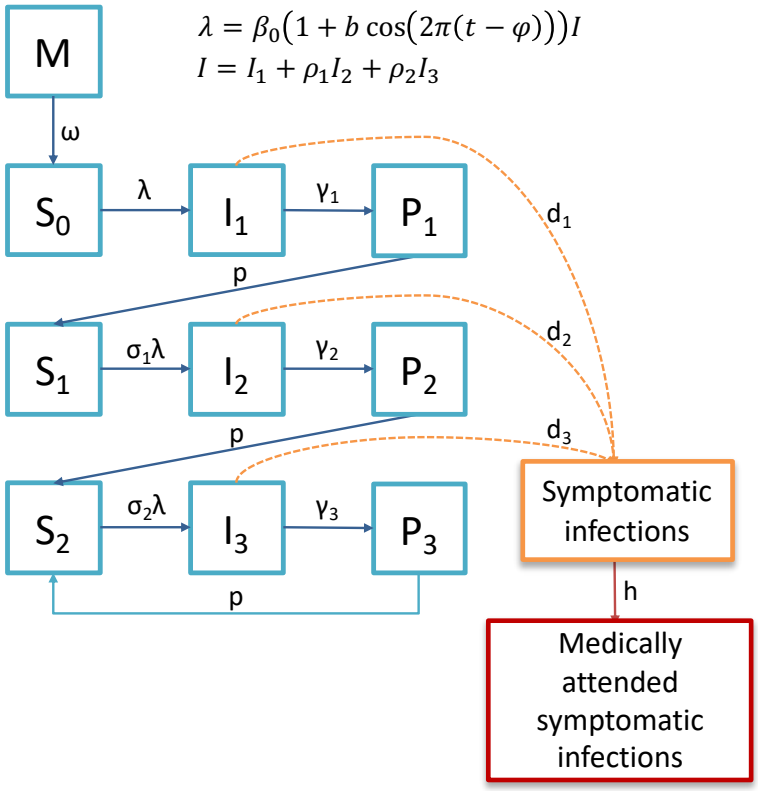
Footnote: ED: emergency department; GA: gestational age; ICU: intensive care unit; mAb: monoclonal antibody; MV: maternal vaccination; RSV: respiratory syncytial virus. [a] The model can be restricted to pregnancies due within the RSV season (October through April). [b] The incidence and severity (i.e., intensity of resource utilisation) of medically-attended RSV varies by age, intervention, and infant protection status.

Figure 3: Sanofi Pasteur static (SPS) model structure (Kieffer et al. 2022)



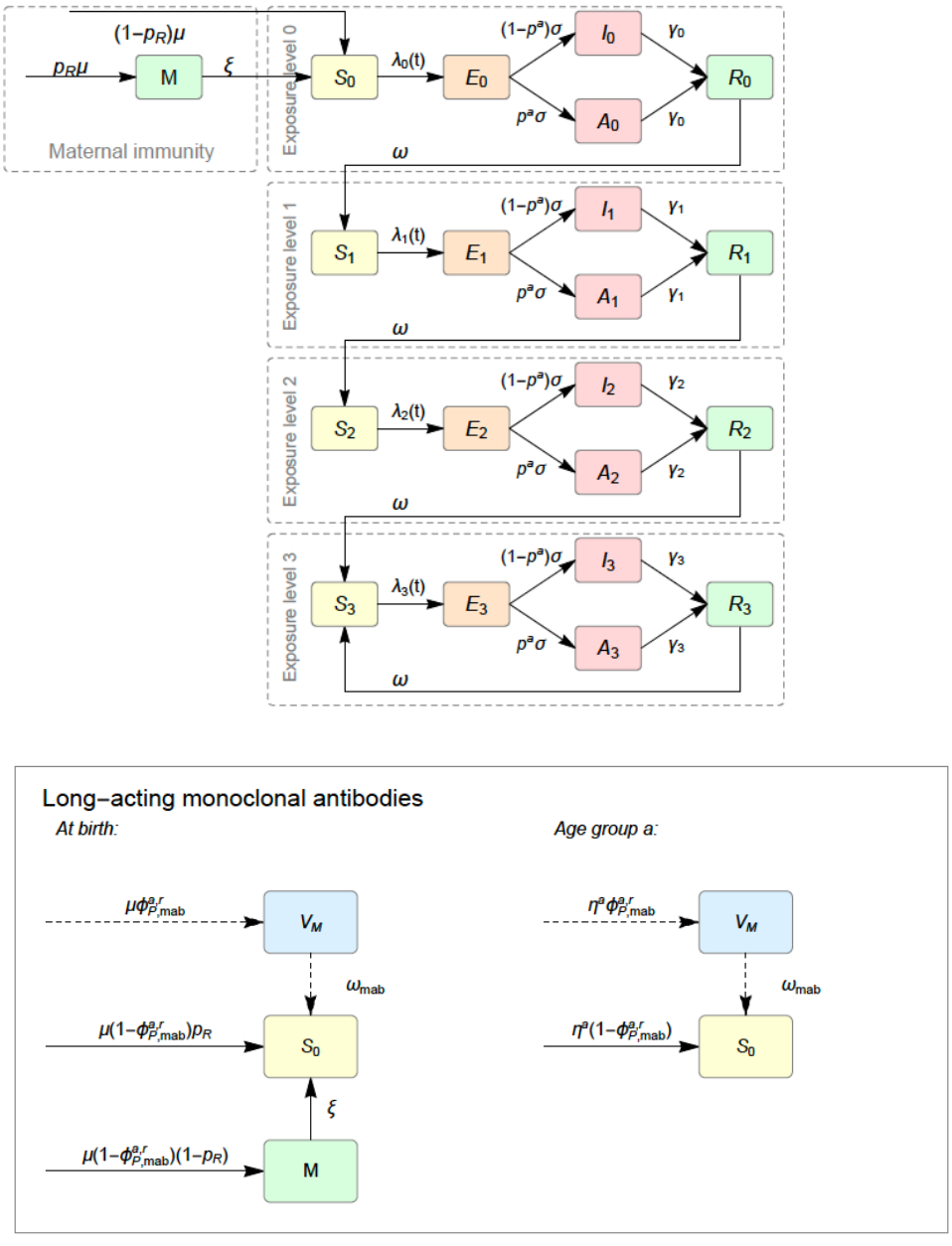
Footnote: RSV = respiratory syncytial virus; ER = Emergency Room; MA = Medically-attended; LRTI = Lower respiratory tract infections; ICU = Intensive care unit; MV = mechanical ventilation

Figure 4: Sanofi Pasteur dynamic (SPD) model structure (Voirin et al. 2022)



Footnote: Newborns benefit from maternal antibody protection (M), after which they become susceptible (S_0) to primary RSV infection. After each infection (I_1, I_2 and I_3), individuals recover and acquire short-term waning immunity (P1, P2, P3), before becoming susceptible again (S_1, S_2).

Figure 5: London School of Hygiene & Tropical Medicine (LSHTM) dynamic model structure (Hodgson et al. 2020)



1.2 Model input table

A standardised hypothetical input data template was reviewed and approved by each modelling group. Uncertainty distributions around input values were defined by each group separately, according to their model features. Table 1 shows the input data, assumptions, and references. The age- and calendar-specific RSV-coded hospitalisation is (detailly) presented in Figure 6.

Table 1: Input parameters used in this study

Parameter	Value	Reference
Demographic data		
Birth cohort	100,000 live births	Hypothetical cohort
Stillbirth rate	7.8 per 100 live births	United Kingdom demographic data and full lifetable were provided (6)
Preterm rate	3.3 per 1,000 live births	
Life expectancy at birth	83 years (both female and males)	
Baseline age-specific mortality rate	0-1 year: 0.000213 1-2 years: 0.000213 2-3 years: 0.000127 3-4 years: 0.000098	
Disease burden	Mean	
RSV-coded hospital admissions rate per 1,000 persons per year	By age (1-month intervals) and by calendar month:(details in Figure 6): 0 month: 34.73 to 59 months: 0.13	Norwegian Patient Registry 2008-2017 (7)

RSV-coded hospital outpatient visits rate per 1,000 persons per year	By age (1-month intervals) and by calendar month 0 month: 2.35 to 11 months: 1.44 24-59 months: 0.13	Data were provided by age (1-month intervals) and by calendar month. In this table, only aggregated annual data are shown.
RSV-coded deaths per 1,000 persons per year	By age (1-month intervals) and by calendar month: Age <6 months 0.0055 Age 6-11 months: 0.0111 Age 1-5 years: 0.0010	Norwegian Cause of Death Registry 2008-2017 (1) Data were provided by age (1-month intervals) and by calendar month. In this table, only aggregated annual data are shown.
Age-specific proportion of RTI primary care visits in 0-5 months of age	0 months: 6.89% 1 month: 12.48% 2 months: 17.63% 3 months: 16.01% 4 months: 19.56% 5 months: 27.43%	Norwegian Patient Registry 2008-2017 (1)
RSV-related primary care visits	Age <6 months: 5 primary care visits for each hospitalisation Age ≥6 months: 12 primary care visits for each hospitalisation	Based on Cromer 2014 (8)

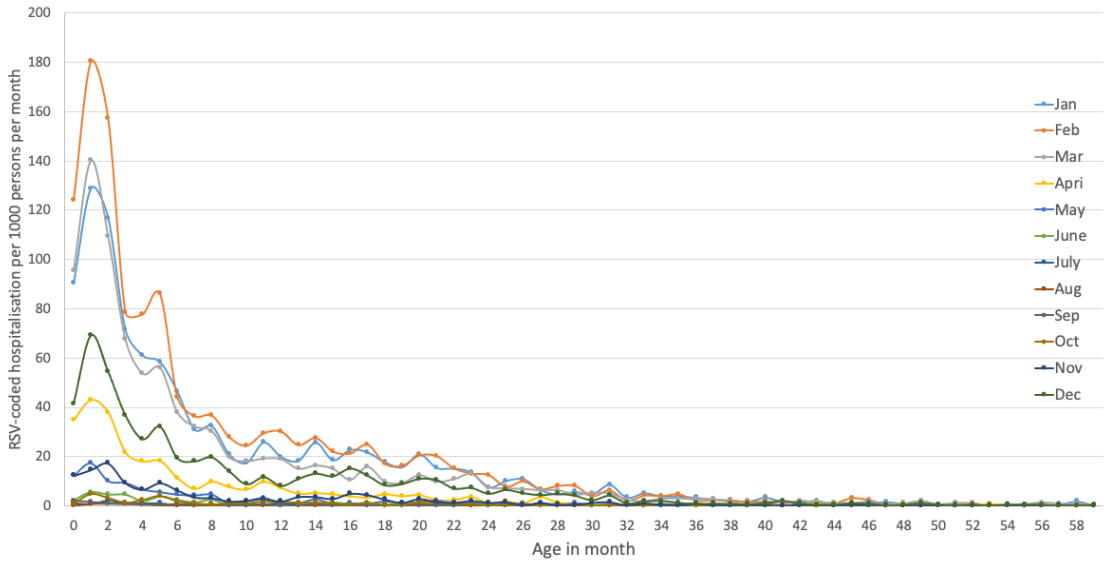
Proportion of Intensive Care Unit (ICU) admission per RSV hospital admission	0 months: 1.85% 1 month: 0.85% 2 months: 0.81% 3 months: 0.76% 4 months: 0.39% 5 months: 0.87% 6 months: 0.27% 7-11 months: 0.20% 1-4 years: 0.77%	Scottish data (7). The ICU proportion was analysed during the study, but they were not published in the article (personal communication from Dr. XXX name hidden per journal requirement)
Utility	Mean [95% Credible Intervals (CrI)]	
QALY loss per medically attended (MA) episode (including hospital)	0.0038 [0.0005-0.0128]	Hodgson 2019 (9)
QALY loss non-medically attended (non-MA) episode	0.0030 [0.0003-0.010]	
Cost (in euros)	Mean	
Cost per hospitalisation	€627 per day	Dutch reference costs (Kostenhandleiding) (10)
Cost per hospital outpatient visit	€104	
Cost per primary care visit	€33	
ICU admission	€2015 per day + €613 ambulance transfer	
Length of stay in hospital or ICU	Hospitalisation: 5.8 days (SD = 4.8) ICU admission: 8.1 days (SD = 8)	Blanken 2018 (11)

Transportation for parents per hospitalisation or ICU admission	€0.19 per kilometre mean 187 kilometres	Blanken 2018 (11)
Cost of productivity loss	Salary loss paid work per day €139	Blanken 2018 (11)
Workdays lost due to RSV-infected child	1 day paid work lost per primary care or hospital outpatient visit Number of days paid work lost equal to length of stay per hospitalisation or ICU admission	Assumptions
Single-dose maternal vaccine (MV)	€37.5 per dose	Assumption based on Meijboom 2012 (12)
Single-dose monoclonal antibody (mAb)	€50 per dose	Assumption
Delivery cost per dose	MV: €5 (year-round) MV: seasonal programmes: €11.36 mAb: €8.32 (delivered at birth)	Assumption based on Meijboom 2012 (12)
Programme implementation costs (one-off)	€200,000 for year-round programme €100,000 for seasonal programme	Assumption
Intervention characteristics	Mean [95% Credible Intervals (CrI)]	
Efficacy against hospital admission or hospital outpatient visit	MV: 44% [20 - 62%] mAb: 78% [52 -90%]	Phase 3 data MV (13) and phase 2b results of mAb (14)
Efficacy against primary care visit	MV: 39% [5-61%] mAb: 70% [52.3-81.2%]	

Duration of protection	MV: 90 days mAb: 150 days	Phase 3 data MV (13) and phase 2b results of mAb (14), varied in scenario analysis
Coverage	Year-round / seasonal program MV: 67% / 44% mAb: 94% / 94%	Based on UK vaccine coverage data (15): MV year-round coverage based on maternal pertussis vaccine coverage, and seasonal MV coverage based on influenza vaccine coverage mAb year-round and seasonal programmes coverage based on rotavirus vaccine coverage (15).

Footnote: CrI: credible intervals; MV: maternal vaccine; mAb: monoclonal antibody.

Figure 6: RSV-coded hospitalisation rate by age (0-59 months) and calendar month per 1,000 persons



1.3 Model description and expected differences in results

Each group presented the model description in the beginning of the model comparison study. A group discussion was organised to predict the expected impact on model outcomes due to model structure before unblinding the test-run results.

Table 2: Key characteristics of the cost-effectiveness models involved in the model comparison

Model	**UA**	**NV**	**SPS**	**SPD**	**LSHTM**	Expected impact of differences on results?
Background						
Representative publication	Li and Bilcke *et al.* (2022) (1)	Herring *et al.* (2019) Presented at project workshop	Kieffer *et al.* (2022) (4)	Voirin *et al.* (2022) (2)	Hodgson *et al.* (2020) (3)	NA
Country of the original model	Norway	United States	United States	United States	England and Wales	NA
Provenance (original or adapted)	Structure adapted from Cromer et al. 2017 (16) and Li et al. 2020 (17)	Original	Original	Adapted from Kinyanjui et al. 2015 (18) and Pan-Ngum et al. 2017 (19)	Original	NA

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Framework						
Target population	Birth cohort followed by month of birth	Birth cohort, option to restrict birth cohort to infants due during RSV season (October – April)	Birth cohort structured per subgroups • palivizumab eligible (not in use in this study) • preterm not eligible to palivizumab • term infants Each subgroup is followed by month of birth	The entire population (32 age groups from 0 months to 75+ years). Elderly population (included, but effects not considered here)	The entire population (25 age groups). Birth cohort including • palivizumab eligible (not in use in this study) • high risk population • all new-borns Elderly population (included, but effects not considered here)	UA, NV and SPD and LSHTM models assumed no impact of MV on RSV in (very) pre-terms. SPS model used adjustment rate on MV antibody transfer. Limited impact on results for MV evaluation given the small number of pre-term infants.
Possible interventions to evaluate	MV, mAb, no intervention	MV, mAb, no intervention	MV, mAb, no intervention	MV, mAb, no intervention	MV, mAb, no intervention (paediatric and older adults' vaccination are possible, but not used in this study)	NA

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Immunisation programmes	Year-round Seasonal (Oct-Apr) Seasonal mAb + catch-up	Year-round Seasonal (Oct-Apr)	Year-round Seasonal (Oct-Apr) Seasonal mAb + catch-up	Year-round Seasonal (Oct-Apr) Seasonal mAb + catch-up	Year-round Seasonal (Oct-Apr) Seasonal mAb + catch-up	No difference between models: year-round MV and year-round mAb infants. However, NV model cannot incorporate the mAb catch-up programme.
Comparators	No RSV intervention	No RSV intervention	No RSV intervention	No RSV intervention	No RSV intervention	All models agreed to compare to no intervention to align the comparison
Time horizon	1 years	Eligible pregnancies during one calendar year; outcomes from RSV occurring in infants during first 12 months of life	1 year	10 years (after steady state)	10 years	The incremental costs and incremental QALY gain, the static models and dynamic models cannot be compared directly due to the time horizon, but ICER can be compared among all models.

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Model structure						
Type of model	Decision tree	Decision tree	Markov, monthly cycle	Transmission model (Compartmental)	Transmission model (Compartmental)	Dynamic models include: • herd immunity, but impact likely limited given short duration of protection of interventions, limited evidence on mAb's impact on transmission, and limited contact with infants • allow for shift in age distribution of RSV infection. This would lead to difference in older age-group (i.e., 6-11month, 1-5 years)
Model structure	Static, tracks infants age in months and time in calendar months	Static cohort model, tracks full-term infants over pre-defined months	Static, tracks infants age in months and time in calendar months	Age-structured (M)SIRS model	Age-structured (M)SEIRS model	Dynamic models model the maternal protection explicitly, but expected limited impact because the static models account implicitly for maternal protection by using age-specific observed disease burden which reflect level of maternal protection

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Input parameters (How each group used/adapted the disease burden data provided via the input data template)						
Hospitalisation	Directly using the age-specific RSV-related hospitalisation by age in month and calendar month for infants 0-59 months of age.	Directly use age-specific RSV hospitalisation by birth month for ages 0-11 months	Calculation of distribution of cases over calendar month (seasonality) and average by age in months for infants 0-11 months	Used age-specific proportion of primary care visits per hospitalised to estimate the hospitalisations	Equated the age-specific RSV hospitalisation to the multiple of the model-predicted incidence and a fitted parameter: the detection rate of hospitalisation.	The disease burden estimation without intervention should be similar among the models, although SPD model was calibrated based on primary care visits, but LSHTM model was fitted on hospitalisations
Hospital outpatient visits	Direct use (same as hospitalisation)	Use age-specific RSV hospital outpatient rates (specialist) by birth month to get overall hospital outpatient visits	same as hospitalisation	Multiply the age-specific hospital outpatient rate by the population size	Equate the age-specific RSV hospital outpatient cases	

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Primary care visits	Age-specific ratio of primary care visits per hospitalised to RSV primary care visits	Age-specific ratio of primary care visits per hospitalised to get overall RSV-LRTI cases, assuming all hospitalisations are accompanied by one primary care visit	Age-specific ratio of primary care visits per hospitalised to RSV primary care visits	Calibrated the age-specific primary care visits to fit with the age structure (32 age groups)	Age-specific proportion of primary care visits per hospitalised to RSV primary care visits	
RSV-related deaths	Multiply the age-specific mortality rate by the population size	Apply age-specific RSV mortality rates by age to estimate the proportion of hospitalised cases • Assumption that death only occurs among those hospitalised • Mortality risk does not vary with vs. without ICU stay	Multiply the age-specific mortality rate by the population size	The burden of deaths was computed as a fraction of MA-LRTIs. RSV related deaths were assumed to have no influence on transmission.	Multiply the age-specific mortality rate by the population size. RSV related deaths were assumed to have no influence on transmission.	No difference between models (for dynamic models: do not impact on transmission)

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Life-years lost due to RSV-related premature death	Life expectancy without quality adjustment	Use a published study on infant mortality (20) to split the non-RSV deaths age <1 year into 0-2, 3-5, and 6-11 months Life expectancy with quality adjustment (21-23)	Life expectancy without quality adjustment	Quality adjusted life expectancy (UK value) (24)	Life expectancy without quality adjustment	SPD and NV models would have lower QALY averted compared to other model, because lifetime QALY lost are lower than the life-year lost.
How was the seasonality modelled?	Seasonality is captured by tracking new-borns with different disease risks from each calendar month of the year	RSV-burden among infants initially specified by month of birth and age in months. Seasonality of immunisation programs based on birth month (October – April)	Seasonality is captured by distributing the cases per calendar month	Seasonal forcing of the force of infection (cosine function), but death seasonality ignored.	Fitting normal distributions with peak during the winter months.	Limited impact, because difference between fitted and observed seasonality should be limited, and only one full seasonal programme is evaluated (October -April).
Disease transmission	Transmission parameters were not used (static model)			Taken into account	Taken into account	See above (dynamic vs static model).

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Contact matrix	Not used			England and Wales (Mossong and van Hoek) (25, 26)	England and Wales (Mossong and van Hoek) (25, 26)	NA
Force of infection	Not used			See Table 3	See Table 3	Similar focus of infection would lead to similar outputs
Efficacy	Efficacy against primary care visit and hospitalisation as provided Did not use the severe hypoxemia efficacy. SPS assumed preterm infants would have 20% of the protection from MV, but UA and NV models assumed preterm infants would have no protection from MV.			Only used efficacy against infection (proxy of efficacy against primary care visit)	Efficacy against infection (proxy of efficacy against primary care visit) and efficacy against hospitalisations	Static models account for higher protection against severe (=hospitalised) RSV cases, potential leading to more favourable (for programmes) results than the dynamic model (SPS) which only assumed efficacy against infections.
Waning	All or nothing approach: full protection, then no protection.	When duration of efficacy stopped mid-age range (i.e., within ages 0-2, 3-5, or 6-11 months), the effect within the age range was scaled proportionally	All or nothing approach: full protection, then no protection.	All or nothing approach: full protection, then no protection.	Prior distribution was used for duration of immunity, the mean of duration of the interventions were adjusted to 3/5 months. Subsequent infections were also included, but less severe.	Potential impact: Models do not use all or nothing approach might have less prevention in age- groups under 6 months while slightly more prevention in age-groups over 6 months as compared to the ones used the approach.

Model	UA	NV	SPS	SPD	LSHTM	Expected impact of differences on results?
Calibration and/or validation method	NA			Simulated annealing	MCMC via a parallel tempering algorithm	Expect limited impact between two dynamic models, if the age-specific force of infections is comparable. More details in Supplementary material 2
Others						
Model running time	Analysis time to run all base cases and scenarios: 2 hours	Instantly available	Instantly available	Calibration process 8 hours Analysis time to run all base cases and scenarios: 10 seconds, including compilation	Calibration process 8 hours Analysis time: 3 hours	

Footnote: LSHTM: London School of Hygiene & tropical medicine. gw: gestational week, MV: maternal vaccine, mAb: monoclonal antibody, LRTI: lower respiratory tract infections, ICU: intensive care unit, MCMC: Markov Chain Monte Carlo, ICER: incremental cost-effectiveness ratio, PSA: probabilistic sensitivity analysis, EVPI: expected value of perfect information, EVPPI: expected value of partially perfect information.

1.4 Comparison of parameters assumed and fitted in the transmission model

Since dynamic models required more input parameters to model the RSV transmission, an in-depth comparison between the parameters used and fitted in the two dynamic models are illustrated in Table 3

Table 3: parameters used and fitted in the two transmission models

LSHTM model (SEIR)		Sanofi Dynamic (SIR)	
Parameters	Value	Parameters	Value
Maternal protection parameters			
Daily number of births: μ	Provided: 100,000/365 = 274 per day	Daily number of births	Provided: 100,000/365 = 274 per day
Rate of loss of maternal-derived immunity: $1/\xi$	60 days (fixed)	Duration of natural maternal protection $1/\omega$	Fitted 58 days
Proportion of infants born with protection at time t: $p_R(t)$	1 (fixed)		
Force of infection (λ) *	Mean (95% confidence interval)		
Probability of RSV transmission per physical contact: q_p	0.090 (0.063– 0.099) (Fitted)		
Reduction in infectiousness of conversation contacts relative to physical contract: q_c	0.008 (0.000–0.033) (Fitted)		
Relative amplitude of transmission during peak: b_1	3.29 (2.68–4.61) (Fitted)		

Seasonal shift in transmission: φ	0.627 (0.593– 0.649) (Fitted)		
Seasonality wavelength constant: ψ	0.22 (0.18–0.26) (Fitted)		
		Baseline per contact infection probability: β_0	Fitted 0.2377
		Seasonality amplitude: b	Fitted: 0.0791
		Seasonality phase: φ	Fitted: 93.73 days
Susceptibility			
Secondary infection (relative to primary infection): δ_1	0.89 (provided and fixed)	Susceptibility reduction after 1st infection: σ_1	0.89 (provided)
Tertiary infection (relative to secondary): δ_2	0.81 (fixed)	Susceptibility reduction after 2nd infection and beyond: σ_1	0.6 (assumed)
Tertiary infection (relative to secondary): δ_3	0.33 (fixed)		
Asymptomatic infection			
Proportion of asymptomatic infections: p^a	By age: $P^{<1}$:0.0916 (fixed) p^{1-4}: 0.163 (fixed) p^{5-14}: 0.516 (fixed) p^{15+y}:0.753 (fixed)		
Infectiousness of asymptomatic infections is reduced by a fact: α	0.94 (0.79– 0.99) (Fitted)		
		Infections	Value
		Reduction in infectiousness (2nd infection): ρ_1	0.75 (assumed)

		Reduction in infectiousness (3^{rd} infection): ρ_2	0.51 (assumed)
Transmission			
Average duration of exposure: $1/\sigma$	4.98 days (fixed)		
Average duration of primary infections (days): $1/\gamma_0$	6.16 (provided and fixed)	Duration of infectious period (1^{st} infection) (days) $1/\gamma_1$	6.16 (provided)
Average duration of secondary infections (days): $1/\gamma_1$	$\gamma_1 \equiv \gamma_0(g_1)^{-1}$		
Decrease in secondary infection duration relative to primary: g_1	0.87 (provided and fixed)	Reduction of infectious period (2^{nd} infection) γ_1/γ_2	0.87 (provided)
Average duration of third infections (days): $1/\gamma_2$	$\gamma_2 \equiv \gamma_0(g_1g_2)^{-1}$		
Decrease in subsequent infection duration relative to primary: g_2	0.79 (fixed)	Reduction of infectious period (3^{rd} infection and beyond) γ_2/γ_3	0.79 (provided)
Average duration of forth infections (days): $1/\gamma_3$	$\gamma_3 \equiv \gamma_0(g_1g_2g_3)^{-1}$ $g_3=1$		
Average duration of post-infection immunity (days): $1/\omega$	358.9 (fixed)	Average duration of post-infection immunity: $1/p$	Fitted: 570 days
Reporting		Proportion of LRTI	
Reporting probability: ε	Age-specific: 0–3 m: 0.0620 (0.0542–0.0722) 4–6 m: 0.0235 (0.0208–0.0269) 7–11 m: 0.0110 (0.0098–0.0125) 1 y: 0.0099 (0.0087–0.0114)	Proportion of infected individuals developing a LRTI (1^{st} infection):	Fitted $d_{1,a}$ 0-5m: 0.5 6-11m:0.4 12-17m: 0.3 17-23m: 0.2

	2–4 y: 0.0029 (0.00250.0035) 5–54 y: 2e-05 (2e-05 – 3e-05) 55-64 y: 0.00018 (0.00014–0.00023) 65–74 y: 0.0010 (0.0008–0.0012) 75 y: 0.0049 (0.0042–0.0059)		2-10y: 0.15 10-60y: 0.1 60-65y: 0.15 65-75y: 0.25 75y+: 0.4
		Reduction of LRTI probability (2nd infection): $d_{2,a}/d_{1,a}$	0.5 (assumed)
		Reduction of LRTI probability (3rd infection): $d_{3,a}/d_{1,a}$	0.25 (assumed)
		Healthcare system use at age 0: h_0	1
		Healthcare system use at age 75: h_{75}	0.3521 (fitted)
		Changes of h parameter number 1	0.0406 (fitted)
		changes of h parameter number 2	0.00504(fitted)
Intervention parameters			
		Protected individuals less infectious by a factor: r^{mAbs}	0.5
Efficacy against symptomatic infections: e^{S}_{mab}	70.1%	Probability of successful treatment: e^{mAbs}	70.1%
Efficacy against hospitalisation infections: e^{H}_{mab}	78.4%		

Average period of protection: ω_{mab}	150 days (median 103 days)	Average period of protection	150 days (no waning)
		mAb coverage: ξ^{mAbs}	94% (provided)
Efficacy against symptomatic infections: e^{S}_{mat}	39% (provided)	Probability of successful treatment: e^{MV}	39% (provided)
Efficacy against hospitalisation infections: e^{H}_{mat}	44% (provided)		
Average period of protection: d^{2}_{mat}	90 days exponential wanning (median 62 days)	Average period of protection γ_{MV}	90 days exponential wanning (gamma distribution, median 62 days)
		Maternal vaccine coverage: ξ^{MV}	67% year-round 44% seasonal

Footnote: Note that the models are using different seasonal forcing assumptions, so the force of infection parameters cannot be compared directly.

1.5 Supplement base case and scenario analyses

As described in the main text, year-round and seasonal programmes compare to no intervention were evaluated using the input values from Table 1. An additional programme: mAb seasonal plus catch-up that infants under six months of age and born outside of the season would be administered mAb in the beginning of the RSV season (October), was also evaluated. Table 4 illustrates the overview of the programmes. Moreover, eight scenario analyses were included using different input values for coverage, intervention efficacy, duration of protection, or hospitalisation rate (Table 5). The upper and lower ranges of one-way sensitivity analysis are presented in Table 6.

Table 4: Overview of the RSV disease prevention programs: Months indicated with a cross refer to the months where the programmes was administered.

Program	Non-RSV season					RSV season						
Month of birth	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Year-round	X	X	X	X	X	X	X	X	X	X	X	X
Seasonal						X	X	X	X	X	X	X
Seasonal							X	X	X	X	X	X
catch-up	Adm	Adm	Adm	Adm	Adm	X						
(mAb only)[a]	Oct	Oct	Oct	Oct	Oct							

Table footnote: [a] Catch-up programmes: if infants were born during the RSV season (October to April), they would receive mAb at birth; if born outside of the season (May to September), they would be called back to receive mAb before the start of the RSV season (October).

Table 5: pre-defined base-case and scenario analyses versus no intervention

Program	Efficacy: MV (13)	Efficacy: mAb (14)	Protection duration: MV (days)	Protection duration: mAb (days)	Programmes	High/Low hospitalisation rate [a]	Coverage: MV	Coverage: mAb
Base case								
Year-round	mean: phase 3 data Against hospitalisation 44% Against primary care visits: 39%	mean: phase 2 data Against hospitalisation 78% Against primary care visits: 70%	phase 3 data: 90	phase 2b data: 150	Year-around	1	67%	94%

Seasonal only [b]	mean: phase 3 data	mean: phase 2 data	90	150	Prevent infections for infants born in October to April	1	44%	94%
Seasonal + catch-up (mAb only)	NA	mean: phase 2 data	NA	150	mAb (only): within season given at birth. Outside season, catch-up in October	1	NA	94%
Scenarios								
Seasonal low coverage	mean: phase 3 data	mean: phase 2 data	90	150	Prevent infections for infants born in Oct to April	1	30%	30%
Seasonal high coverage	mean: phase 3 data	mean: phase 2 data	90	150	Prevent infections for infants born in Oct to April	1	70%	70%
Low efficacy (year-round)	LCI: phase 3 data Against hospitalisation 20%	LCI: phase 2 data Against hospitalisation 52%	90	150	Year-around	1	67%	94%

	Against primary care visits: 5%	Against primary care visits: 52.3%						
High efficacy (year-round)	UCI: phase 3 data Against hospitalisation 62% Against primary care visits: 61%	UCI: phase 2 data Against hospitalisation 90% Against primary care visits: 81.2%	90	150	Year-around	1	67%	94%
Short duration (year-round)	mean: phase 3 data	mean: phase 2 data	60	120	Year-around	1	67%	94%
Long duration (year-round)	mean: phase 3 data	mean: phase 2 data	180	240	Year-around	1	67%	94%
High hospital visits season (year-round)	mean: phase 3 data	mean: phase 2 data	90	150	Year-around	1.5	67%	94%
Low hospital visits season (year-round)	mean: phase 3 data	mean: phase 2 data	90	150	Year-around	0.5	67%	94%

Table footnote: [a] use as multiplicative factor for hospital visits; [b] For maternal vaccine, the seasonal programme only is for baby has delivery date within the RSV season. UCI: upper confidence interval, LCI: lower confidence interval, MV: maternal vaccine, mAb: monoclonal antibody

Table 6: Upper and lower range for one-way sensitivity analysis

Parameters	Base case	Lower range	Upper range	Comments
Hospitalisation rate	1	90%	110%	Use as a multiplicative factor
Secondary outpatient rate	1	80%	120%	Use as a multiplicative factor
RSV-mortality rate	1	90%	110%	Use as a multiplicative factor

Probability of Intensive Care Unit admission	1	90%	110%	Use as a multiplicative factor
Cost per admission day	€ 627	80%	120%	Use as a multiplicative factor
Length-of-stay (days) hospital	5.8	1	11	Assumption
Length-of-stay (days) Intensive Care Unit	8.1	4	16	Assumption
Cost per primary care visit	€ 33	80%	120%	Use as a multiplicative factor
Cost per specialist visit	€ 104	80%	120%	Use as a multiplicative factor
Cost per dose delivery	1	80%	120%	Use as a multiplicative factor
Fixed implementation costs	€ 200,000	0	€ 300,000	Assumption
Paid work per day	€ 139	€ 70	€ 200	Loosely on OECD salary data
Sick leave (days) outpatient	1	0.5	2	Assumption
QALY loss medical (including hospital) care	3.823x10^-3	0.492x10^-3	12.766x10^-3	Based on Hodgson 2020 (9)
mAb cost per dose	€ 50	€ 30	€ 80	Assumption
MV cost per dose	€ 37.5	€ 20	€ 60	Assumption

1.6 Model comparison timeline and steps

An overview of the model comparison timeline is listed below:

- January 2017: An open invitation was sent out via the RESCEU network to express interest in joining a model comparison.
- May 2017: A workshop was organised to establish the framework for analysis and confirm interest. Eight modelling teams joined the initial meeting and expressed their interests to contribute to the model comparison (UA, LSHTM, PATH, National Institute for Public Health and the Environment (also known as RIVM), University of Groningen, Sanofi, Novavax and GlaxoSmithKline).
- May 2017-October 2020: Individual models were developed and refined independently by each group. A common input dataset was compiled by the academic lead partner

(UA). UA also continued to invite potential interesting groups to join the model comparison initiatives.

- November 2020: The formal model comparison was initiated. Prior to the meeting, two modelling groups decided not to participate due to potential conflict of interests and the geographical focus. During the kick-off meeting, each group presented their model structures (five groups with six models). Input template was designed and shared for feedback. A modelling group (University of Groningen), who focused only on an RSV older adults' vaccine, suggested to have a separate model comparison, hence it was not included in this comparison focusing on infants/children.
- January 2021: The input data (in the pre-defined input templates) were shared with all modelling groups for review and comments.
- April 2021: The input data set was discussed and approved by all groups. The output template was shared, including base case and a list of scenario analyses. One group withdrew their participation mainly due to the readiness of the model.
- May-July 2021: Each group performed an initial test-run on the three base cases and two scenarios of high and low coverage. The aim of this test-run was to ensure that the models could run smoothly, were able to use the input parameters, and could produce the predefined outputs under base case and the scenarios. A new group (LSHTM) confirmed their participation in May and performed this test-run. The outcome of this test-run was blinded, and the input and output templates were individually clarified by UA according to the feedback received.
- August 2021: A group meeting was held to examine the potential/expected differences in model outcomes by model structure/concept (the summary is presented in Table 2). Then, the group highlighted the issues, misunderstanding, and difficulties experienced during the test-run, but the test-run outputs were not shared.

- September 2021: UA shared the updated input and output templates. All groups approved the final input dataset and re-ran the test-run with the up-to-date information.
- October 2021: The results of the second test-run were unblinded during a group meeting and all groups were allowed to make changes to adjust misunderstandings about the input data and the translation of assumptions in their specific model applications. Moreover, the group defined the list of scenarios for final run.
- November to December 2021: Each group delivered the final-run outputs.
- January to February 2022: UA performed a consistency check for each model and discussed with the respective modelling groups if needed. Then UA compared the model outputs.
- March 2022: A group discussion was organised to discuss the preliminary model outputs and findings; the model outputs were unblinded during this meeting.
- April 2022: Results and manuscript outline were shared among authors and no numerical change has been made since April.
- May to July 2022: The manuscript was drafted, reviewed by co-authors, then the revised manuscript was further reviewed by three independent reviewers within RESCEU network. An independent reviewer (UA) also reviewed and checked the model comparison results in the main text and supplementary materials.

1.7 Changes made during this comparison

For the input file and output files, the following updates were made:

Input file:

- UA updated the hospitalisation rate and mortality rate among population 5-85 years+ for the dynamic models.

- UA clarified the assumption of pre-term and still birth rates: preterm infants were assumed to be protected by mAb, but not by MV. For still birth, cost of MV shall be included.

Output file:

- UA updated the age-group labelling from 0-3 months, 3-6 months, 7-12 months to 0-2 months, 3-5 months, 6-12 months for clarity.
- The list of scenarios was shortened after the group discussion (Table 5).
- The “asymptomatic infections” and “non-medically attended symptomatic infections” outcomes were added as requested outcomes for the dynamic models.
- The specific costs within each cost category were clarified, for example: non-medical cost (including: productivity losses and transportation), this cost should be included in the societal perspective.

2 S. Results

2.1 Disease burden estimates

This section presents the estimated RSV disease burden without any intervention per year. Table 7 shows the estimated number of primary care visits, hospital outpatient visits, hospitalisations, ICU admissions, non-medically attended (non-MA) symptomatic infections and asymptomatic infections within an RSV season (October to April) and over a calendar year.

Table 7: Estimated RSV-associated disease burden without any intervention per year

	UA		NV		SPS		SPD		LSHTM	
Age	*Within season*	**Year-round**	*Within season birth* [#]	**Year-round**	*Within season*	**Year-round**	*Within season*	Year-round	*Within season*	**Year-round**
Primary care visits										
0-2 months	*2,930*	**3,051**	*2,941*	***3,051***	*2,920*	**3,051**	*2,657*	**2,890**	*2,385*	**2,547**
3-5 months	*4,963*	**5,195**	*3,102*	***5,195***	*4,973*	**5,195**	*3,560*	**3,858**	*4,419*	**4,691**
6-11 months	*5,848*	**6,116**	*2,032*	***6,116***	*5,855*	**6,116**	*4,894*	**5,268**	*5,231*	**5,504**
12-23 months	*7,135*	**7,406**	-	**-**	-	**-**	*6,355*	**6,852**	*6,702*	**7,045**
24-59 months	*3,264*	**3,457**	-	**-**	-	**-**	*2,629*	**2,826**	*3,505*	**3,695**
0-11 month	*13,741*	**14,361**	*8,074*	***14,361***	*13,748*	**14,361**	*11,111*	**12,016**	*12,034*	**12,742**
0-59 month	*24,141*	**25,224**	-	**-**	-	**-**	*20,095*	**21,695**	*22,241*	**23,481**
Hospital outpatient visits										
0-2 months	*113*	**117**	*113*	***117***	*112*	**117**	*108*	**117**	*86*	**91**
3-5 months	*109*	**114**	*69*	***114***	*109*	**114**	*105*	**114**	*91*	**97**
6-11 months	*98*	**104**	*34*	***104***	*100*	**104**	*96*	**104**	*94*	**99**
12-23 months	*89*	**92**	-	**-**	-	**-**	*86*	**92**	*80*	**84**
24-59 months	*36*	**38**	-	**-**	-	**-**	*36*	**38**	*52*	**54**
0-11 months	*320*	**335**	*215*	***335***	*321*	**335**	*309*	**335**	*270*	**287**
0-59 months	*445*	**466**	-	**-**	-	**-**	*430*	**465**	*402*	**426**
Hospitalisations (exclude ICU)										
0-2 months	*1,014*	**1,057**	*1,007*	***1,045***	*1,012*	**1,057**	*865*	**939**	*831*	**887**

3-5 months	*550*	**577**	*342*	***573***	*552*	**577**	*471*	**512**	*493*	**523**
6-11 months	*486*	**509**	*169*	***507***	*487*	**509**	*407*	**438**	*436*	**459**
12-23 months	*588*	**610**	-	**-**	-	**-**	*526*	**567**	*558*	**587**
24-59 months	*269*	**285**	-	**-**	-	**-**	*217*	**234**	*292*	**308**
0-11 months	*2,050*	**2,142**	*1,518*	***2,125***	*2,050*	**2,142**	*1,743*	**1,890**	*1,759*	**1,869**
0-59 months	*2,907*	**3,037**	-	**-**	-	**-**	*2,486*	**2,690**	*2,610*	**2,764**
ICU admissions										
0-2 months	*11*	**12**	*11*	**12**	*11*	**12**	*10*	**10**	*9*	**10**
3-5 months	*4*	**4**	*2*	**4**	*4*	**4**	*3*	**4**	*3*	**4**
6-11 months	*1*	**1**	*0*	**1**	*1*	**1**	*1*	**1**	*1*	**1**
12-23 months	*5*	**5**	-	**-**	-	**-**	*4*	**4**	*4*	**4**
24-59 months	*2*	**2**	-	**-**	-	**-**	*2*	**2**	*2*	**2**
0-11 months	*16*	**17**	*14*	**17**	*16*	**17**	*14*	**15**	*13*	**14**
0-59 months	*23*	**24**	-	**-**	-	**-**	*20*	**21**	*19*	**21**
Deaths										
0-2 months	*0.13*	**0.13**	*0.17*	***0.18***	*0.13*	**0.14**	*0.13*	**0.14**	*0.11*	**0.12**
3-5 months	*0.13*	**0.13**	*0.06*	***0.10***	*0.13*	**0.14**	*0.13*	**0.14**	*0.11*	**0.12**
6-11 months	*0.54*	**0.56**	*0.18*	***0.56***	*0.53*	**0.55**	*0.51*	**0.55**	*0.47*	**0.50**
12-23 months	*0.10*	**0.10**			-	**-**	*0.09*	**0.10**	*0.10*	**0.10**
24-59 months	*0.29*	**0.30**			-	**-**	*0.28*	**0.30**	*0.29*	**0.30**
0-11 months	*0.79*	**0.82**	*0.41*	***0.83***	*0.79*	**0.83**	*0.77*	**0.83**	*0.70*	**0.74**
0-59 months	*1.18*	**1.23**	-	**-**	-	**-**	*1.14*	**1.23**	*1.08*	**1.14**
Non-medically attended symptomatic RSV infections										
0-2 months							*133*	***144***	*6,836*	***7,294***
3-5 months							*631*	***684***	*10,216*	***10,847***
6-11 months							*1,990*	***2,142***	*26,650*	***28,036***
12-23 months							*5,848*	***6,296***	*36,603*	***38,485***
24-59 months							*4,344*	***4,670***	*67,061*	***70,703***
0-11 months							*2,754*	***2,970***	*43,701*	***46,177***
0-59 months							*12,946*	***13,936***	*147,365*	***155,365***
Asymptomatic RSV infections										
0-2 months							*2,801*	***3,048***	*1,021*	***1,090***

3-5 months							*4,236*	***4,596***	*1,534*	***1,629***
6-11 months							*10,694*	***11,532***	*3,267*	***3,437***
12-23 months							*41,486*	***44,747***	*8,557*	***8,997***
24-59 months							*90,540*	***97,532***	*13,816*	***14,566***
0-11 months							*17,731*	***19,175***	*5,822*	***6,156***
0-59 months							*149,758*	***161,453***	*28,195*	***29,718***

Table footnote: UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model.

As shown in Table 7, large differences occurred between the two dynamic models when estimating the non-MA symptomatic and asymptomatic RSV. Among all RSV infections, the percentage of asymptomatic, non-MA symptomatic, and MA symptomatic cases were calculated (Table 8). In the age-group 0-2 months, SPD model estimated approximately half of the cases were asymptomatic infections compared to only 9% assumed by LSHTM model. LSHTM model projected approximately half of the symptomatic cases were MA versus almost all symptomatic cases were MA cases in SPD model in this age-group.

Table 8: percentage of asymptomatic, non-medically-attended symptomatic, and medically-attended symptomatic cases in the two dynamic models

	SPD				LSHTM			
Age	% Asymptomatic infections	% Non-MA symptomatic infections	% MA cases	Sum (all infected cases)	% Asymptomatic infections	% Non-MA symptomatic infections	% MA cases	Sum (all infected cases)
0-2 months	43%	2%	55%	100%	9%	61%	30%	100%
3-5 months	47%	7%	46%	100%	9%	61%	30%	100%
6-11 months	59%	11%	30%	100%	9%	75%	16%	100%
12-23 months	53%	8%	39%	100%	9%	69%	22%	100%
24-59 months	81%	7%	12%	100%	14%	73%	13%	100%
0-11 months	43%	2%	55%	100%	9%	61%	30%	100%
0-59 months	47%	7%	46%	100%	9%	61%	30%	100%

Table footnote: SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model. Non-MA: non-medically-attended, MA: medically-attended.

Table 9 demonstrates the discounted cost and QALYs losses without intervention. The static models used 1-year time horizon, but the dynamic model used 10-year time horizon, we therefore multiplied the static model outputs by 10 and discounted both costs and QALYs annually. Overall, the NV model estimated 20% fewer QALY losses due to RSV compared to the other two static models because QALY losses for hospitalisations were implemented differently in the NV model than in the other two static models. In particular, the NV model did not assign separate QALY losses for the primary care visits assumed to be associated with each hospitalisation (i.e., one QALY loss was assigned per RSV case). The other two static models assigned separate primary care and hospital QALY losses to each primary care visit and each hospitalisation, respectively, including when they might concern the same patient. Moreover, the NV model also used quality-adjusted life expectancy, while the other two static models used life-expectancy without quality adjustment to estimate the discounted QALY losses of RSV-associated deaths (see Table 1 in main text and Table 2).

Table 9 estimated RSV-associated discounted cost and QALY without any interventions over 10 years (3% discounting rate)

	UA			NV			SPS			SPD			LSHTM		
Discounted costs (in € million)															
Age	Direct medical cost	Non-medical cost*	Total cost	Direct medical cost	Non-medical cost*	Total cost	Direct medical cost	Non-medical cost*	Total cost	Direct medical cost	Non-medical cost*	Total cost	Direct medical cost	Non-medical cost*	Total cost
0-2 months	€ 35.23	€ 11.89	€ 47.12	€ 34.76	€ 11.84	€ 48.95	€ 36.51	€ 11.81	€ 48.32	€ 33.27	€ 10.55	€ 43.82	€ 29.93	€ 9.66	€ 39.60
3-5 months	€ 20.10	€ 10.87	€ 30.97	€ 19.63	€ 11.66	€ 32.87	€ 20.62	€ 10.79	€ 31.41	€ 19.53	€ 8.53	€ 28.06	€ 18.34	€ 9.56	€ 27.90
6-11 months	€ 18.66	€ 11.61	€ 30.28	€ 17.40	€ 12.51	€ 29.91	€ 18.28	€ 11.37	€ 29.65	€ 17.85	€ 9.65	€ 27.50	€ 16.16	€ 10.04	€ 26.20
12-23 months	€ 22.43	€ 13.91	€ 36.34				-	-	-	€ 23.55	€ 12.51	€ 36.05	€ 21.08	€ 12.85	€ 33.93
24-59 months	€ 10.53	€ 6.50	€ 17.04				-	-	-	€ 9.71	€ 5.16	€ 14.87	€ 11.17	€ 6.81	€ 17.98
0-11 months	**€ 73.99**	**€ 34.37**	**€ 108.36**	**€ 71.79**	**€ 36.00**	**€ 107.80**	**€ 75.42**	**€ 33.97**	**€ 109.38**	**€ 70.66**	**€ 28.73**	**€ 99.39**	**€ 64.44**	**€ 29.27**	**€ 93.71**
0-59 months	**€ 106.95**	**€ 54.79**	**€ 161.74**				-	-	-	**€ 103.92**	**€ 46.39**	**€ 150.31**	**€ 96.69**	**€ 48.93**	**€ 145.62**

	UA			NV			SPS			SPD			LSHTM		
Discounted QALY Losses															
Age	**episodes**	**deaths**	**Total**	**episodes**	**deaths**	**Total**	**episodes**	**deaths**	**Total**	**episodes**	**deaths**	**Total**	**episodes**	**deaths**	**Total**
0-2 months	141.48	37.03	178.51	102.47	43.71	146.18	142.31	34.95	177.25	99.22	28.56	127.77	305.87	31.45	337.32
3-5 months	196.65	37.01	233.66	174.48	23.61	198.09	197.80	34.95	232.75	145.28	28.47	173.75	457.68	30.53	488.21
6-11 months	224.72	147.94	372.67	205.41	134.27	339.69	226.04	139.78	365.83	229.97	113.38	343.35	930.68	132.41	1,063.09
12-23 months	263.03	26.25	289.28				-	-	-	390.80	20.65	411.45	1,258.01	26.51	1,284.52
24-59 months	117.75	73.79	191.55				-	-	-	215.36	61.51	276.87	1,978.63	78.24	2,056.88
0-11 months	**562.85**	**221.99**	**784.84**	**482.36**	**201.59**	**683.95**	**566.15**	**209.67**	**775.83**	**474.46**	**170.41**	**644.87**	**1,694.23**	**194.38**	**1,888.62**
0-59 months	**943.63**	**322.04**	**1,265.67**				**-**	**-**	**-**	**1,080.62**	**252.56**	**1,333.19**	**4,930.87**	**299.14**	**5,230.01**

Table footnote: UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model, QALY: quality adjusted life-years.

2.2 RSV disease burden averted with intervention

2.2.1 Year-round programmes

The estimated disease burden averted by age-group are presented in Table 10 (per static model) and Table 11 (per dynamic model). When comparing static model (Table 10), the NV model reported slightly more primary care visits averted by mAb because it used a weighted vaccine efficacy duration in the 3-5 months age-group (see: Table 1)

In contrast to the static models, both dynamic models assumed MV protection wanes and therefore estimated a relatively smaller disease burden averted in 0-2 month olds. Transitions out of the protected compartment were governed by an exponential function that assumed a mean duration of stay in the protected compartment of 90 days (implying a median duration of protection of 62 days, and a 37% probability of protection after 90 days). Moreover, The SPD model showed an age-shift increasing primary care visits in children >1 year. By contrast, the LSHTM model's herd effects reduced cases further in children >1 year (Table 11), because it accounted for reduced transmissibility through MV of both infants and mothers. In LSHTM model, 40% RSV infections averted in infants coming from the cessation of the transmission pathway between infants and vaccinated mothers.

Table 10:year-round programme: estimated disease burden averted by three static models

	UA					NV					SPS				
Age	Primary care visit	Hospital outpatient	Hospitalisation	ICU	death	Primary care visit	Hospital outpatient	Hospitalisation	ICU	death	Primary care visit	Hospital outpatient	Hospitalisation	ICU	death
MV															
0-2 months	705	31	280	3	0.04	735	26	287	3	0.05	749	29	293	3	0.04
3-5 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
6-11 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
12-23 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
24-59 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
0-11 months	705	31	280	3	0.04	735	26	287	3	0.05	749	29	293	3	0.04
0-59 months	705	31	280	3	0.04	0	0	0	0	0.00	0	0	0	0	0.00
mAb															
0-2 months	1984	84	759	8	0.10	2010	72	779	9	0.13	2010	77	779	8	0.10
3-5 months	1907	52	278	2	0.07	2282	49	283	2	0.05	1933	48	285	2	0.07
6-11 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
12-23 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
24-59 months	0	0	0	0	0.00	0	0	0	0	0.00	0	0	0	0	0.00
0-11 months	3891	137	1037	10	0.17	4292	122	1062	11	0.18	3943	125	1064	9	0.17
0-59 months	3891	137	1037	10	0.17	0	0	0	0	0.00	0	0	0	0	0.00

Table 11: year-round programme: estimated disease burden averted by two dynamic models

	SPD							LSHTM						
Age	Asymptomatic infection	Non-MA symptomatic infection	Primary care visit	Hospital outpatient	Hospitalisation	ICU	Death	Asymptomatic infection	Non-MA symptomatic infection	Primary care visit	Hospital outpatient	Hospitalisation	ICU	Death
MV														
0-2 months	165	7	157	6	43	0	0.01	84	565	194	7	70	1	0.01
3-5 months	138	20	116	3	24	0	0.00	89	598	251	5	29	0	0.01
6-11 months	106	16	47	1	4	0	0.00	105	850	177	3	15	0	0.02
12-23 months	-108	-36	-37	-1	-3	0	0.00	85	365	67	1	6	0	0.00
24-59 months	-154	-24	-15	0	-1	0	0.00	83	405	21	0	2	0	0.00
0-11 months	408	43	320	11	71	1	0.02	279	2014	622	16	113	1	0.03
0-59 months	147	-18	268	10	66	1	0.01	447	2784	710	17	121	1	0.03
mAb														
0-2 months	-1981	95	1908	77	555	6	0.09	529	3552	1193	43	454	6	0.06
3-5 months	-1935	262	1705	48	302	2	0.06	375	2531	1039	23	122	1	0.03
6-11 months	38	7	17	0	1	0	0.00	244	1938	439	8	37	0	0.04
12-23 months	308	38	44	1	4	0	0.00	430	1840	337	4	28	0	0.00
24-59 months	60	-15	-9	0	-1	0	0.00	228	1108	57	1	5	0	0.00
0-11 months	-3879	363	3630	126	858	8	0.15	1147	8021	2670	73	612	7	0.13
0-59 months	-3511	386	3665	126	861	8	0.15	1805	10970	3064	78	645	7	0.14

The base case incremental cost-effectiveness ratios (ICERs) are presented in Table 2 in the main text. From a societal perspective, the UA and the SPS models estimated ICERs of €11,658 and €1,635 per QALY gained, respectively, whereas the NV model reported mAb to be dominant. The higher ICER for the UA model is likely caused by an artefact of the probabilistic implementation, which used the log-normal distribution to sample hospital length-of-stay (LoS) and the interventions' efficacy (sample size = 1,000, random seed number in R: 20190118). The resulting sampled means were slightly lower than the provided mean (which was directly used in the other two static models). Changes in sample size or random seed in the UA model would therefore lead to changes in its output, although sensitivity analysis demonstrated no effect on the qualitative results and ranking of the strategies.

In addition to the base case, Table 12 illustrates the ICERs from both dynamic models when excluding the QALY gain from non-MA symptomatic cases. The within-dynamic model differences are still large, but it supported the main reasons explained in the main text: for MV, the SPD model estimated 40-50% less MA cases averted compared to the LSHTM model and more than 50% less QALY gained due to the age-shift of infections and not considering indirect protection from the vaccinated mothers (Table 11). For mAb, the SPD model assumed all-or-nothing protection over 5 months, resulting in more disease burden averted compared to the LSHTM model, hence more direct medical cost averted, QALY gained and lower ICERs from both perspectives.

Table 12: year-round programs exclude the QALY gain from the non-MA symptomatic infections: Expected incremental cost-effectiveness ratios (discount rate 3%, cumulative value over 10 years)

	QALY gain from MA cases #	Direct medical cost	Intervention costs [a]	Direct costs	ICER per QALY gained (payer)	Non-medical cost	Total costs	ICER per QALY gained (societal)
MV (67% coverage)								
SPD	12	-€2,383,575	€24,800,671	€22,417,095	**€1,896,565**	€2,530,847	-€823,597	**€ 1,826,886**
LSHTM	28	-€4,158,218	€23,677,256	€19,519,038	**€699,094**	€699,094	-€1,757,456	**€ 636,149**
mAb (94% coverage)								
SPD	153	-€31,071,021	€47,561,842	€16,490,821	**€107,969**	€136,235	-€10,901,641	**€ 36,593**
LSHTM	125	-€22,150,079	€46,382,850	€24,232,770	**€194,189**	€194,189	-€8,513,684	**€ 125,965**

Table footnote: # exclude the QALY gain from the non-MA symptomatic infections. [a] intervention costs includes cost of intervention, delivery costs, and implementation costs. SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model. MV: maternal vaccine, mAb: monoclonal antibody

2.2.2 Seasonal programmes

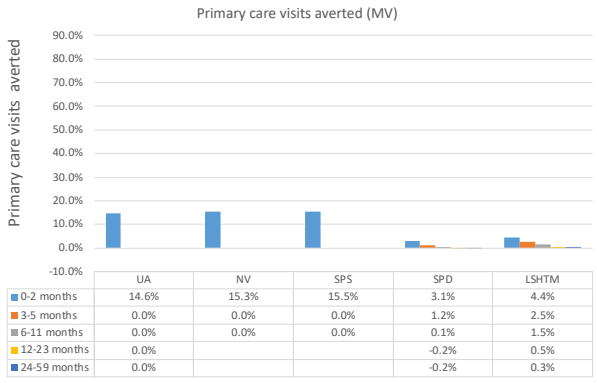
For the MV and mAb seasonal programmes, the percentage reductions in primary care visits and non-ICU hospitalisations are reported in Figure 7, where a similar trend as the year-round programme is observed. The expected ICERs per intervention are presented in Table 13.

Both MV and mAb seasonal programmes prevented less RSV disease burden compared to year-round programmes. Three static models estimated MV seasonal programme would avert approximately 17% of non-ICU hospitalisations, whereas mAb would avert 70% of non-ICU hospitalisations. Both dynamic models also estimated lower percentages of primary care visits and non-ICU hospitalisations averted for both MV and mAb seasonal programmes compared to their estimates of year-round programmes.

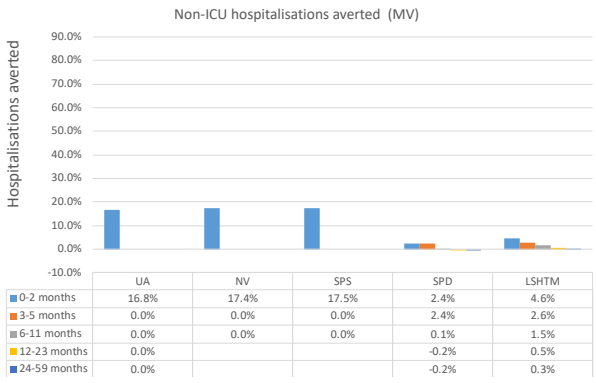
In terms of cost-effectiveness, all five models calculated lower ICERs for both MV and mAb seasonal programmes compared to the year-round programs from payer's and societal perspectives. For mAb, four models assuming all-or-nothing waning concluded that mAb was

dominant versus no prevention from a societal perspective. However, LSHTM model which assumed exponential waning, showed an ICER below €16,000 from a societal perspective over a 10-year horizon (Table 13).

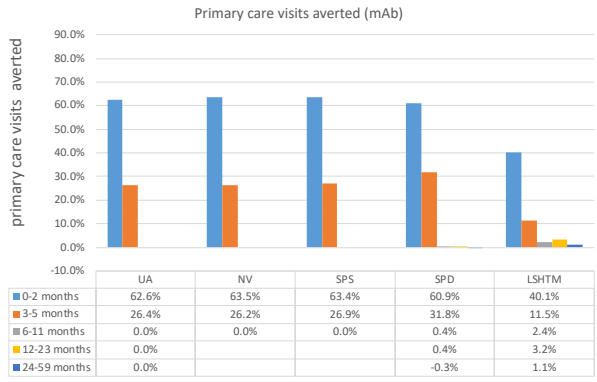
Figure 7: seasonal programmes: model-based primary care visits (left column) and non-ICU hospitalisations averted by maternal vaccine (MV: top row) and monoclonal antibody (mAb: bottom row) compared to the disease burden estimates without any intervention.



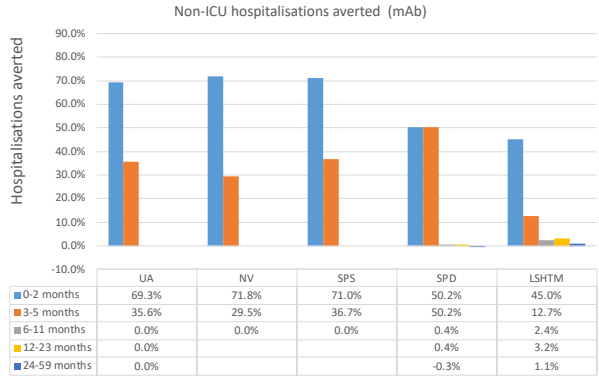
	UA	NV	SPS	SPD	LSHTM
0-2 months	14.6%	15.3%	15.5%	3.1%	4.4%
3-5 months	0.0%	0.0%	0.0%	1.2%	2.5%
6-11 months	0.0%	0.0%	0.0%	0.1%	1.5%
12-23 months	0.0%			-0.2%	0.5%
24-59 months	0.0%			-0.2%	0.3%



	UA	NV	SPS	SPD	LSHTM
0-2 months	16.8%	17.4%	17.5%	2.4%	4.6%
3-5 months	0.0%	0.0%	0.0%	2.4%	2.6%
6-11 months	0.0%	0.0%	0.0%	0.1%	1.5%
12-23 months	0.0%			-0.2%	0.5%
24-59 months	0.0%			-0.2%	0.3%



	UA	NV	SPS	SPD	LSHTM
0-2 months	62.6%	63.5%	63.4%	60.9%	40.1%
3-5 months	26.4%	26.2%	26.9%	31.8%	11.5%
6-11 months	0.0%	0.0%	0.0%	0.4%	2.4%
12-23 months	0.0%			0.4%	3.2%
24-59 months	0.0%			-0.3%	1.1%



	UA	NV	SPS	SPD	LSHTM
0-2 months	69.3%	71.8%	71.0%	50.2%	45.0%
3-5 months	35.6%	29.5%	36.7%	50.2%	12.7%
6-11 months	0.0%	0.0%	0.0%	0.4%	2.4%
12-23 months	0.0%			0.4%	3.2%
24-59 months	0.0%			-0.3%	1.1%

Table 13: seasonal programs: QALYs gained, incremental costs and incremental cost-effectiveness ratios of either MV or mAB versus current practice, from the health care payer's and societal perspectives (discount rate 3% per year MV: €37.5 per dose and €8.32 delivery cost, mAb: €50 per dose and €5 delivery cost)

	QALY gains	Direct medical cost	Intervention costs [a]	Direct costs	**ICER per QALY gained (payer)**	Non-medical cost averted	Total costs	**ICER per QALY gained (societal)**
MV								
UA^	3	-€ 670,933	€ 1,194,433	€ 523,500	**€ 198,717**	-€ 217,867	€ 305,633	**€ 129,280**
NV ^	3	-€ 712,700	€ 1,194,433	€ 481,733	**€ 182,852**	-€ 232,559	€ 249,175	**€ 94,579**
SPS ^	3	-€ 722,222	€ 1,190,833	€ 468,611	**€ 142,378**	-€ 226,475	€ 242,136	**€ 73,568**
SPD*	5	-€ 1,205,960	€ 9,624,137	€ 8,418,178	**€ 1,733,256**	-€ 399,284	€ 8,018,894	**€ 1,651,046**
LSHTM*	57	€ 2,245,670	€ 9,703,034	€ 7,457,363	**€ 131,423**	€ 921,321	€ 6,536,043	**€ 115,186**
mAb								
UA^	21	-€ 3,560,217	€ 3,397,880	-€ 162,337	**Dominant**	-€ 1,280,944	-€ 1,443,281	**Dominant**
NV^	17	-€ 3,625,946	€ 3,297,880	-€ 328,066	**Dominant**	-€ 1,343,334	-€ 1,671,400	**Dominant**
SPS^	21	-€ 3,768,411	€ 3,297,880	-€ 470,531	**Dominant**	-€ 1,298,979	-€ 1,769,510	**Dominant**
SPD*	135	-€ 26,363,196	€ 27,827,741	€ 1,464,545	**€ 10,867**	-€ 9,169,981	-€ 7,705,436	**Dominant**
LSHTM*	289	-€ 17,025,670	€ 27,530,639	€ 10,504,969	**€ 36,376**	€ 6,074,306	€ 4,430,663	**€ 15,342**

Table footnote: * Cumulative value over 10 years. ^ ICERs are calculated for children under age 1 year. [a] intervention costs includes cost of intervention, delivery costs, and implementation costs UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model.

2.2.3 The mAb seasonal plus a catch-up programme

The estimates of disease burden averted by age-group are presented in Table 14 (per static model) and Table 15 (per dynamic model). NV model was initially developed for MV and cannot perform this scenario. The expected ICERs from healthcare payer's and societal perspectives are reported in Table 16. Compared to the year-round and seasonal mAb programmes without catch-up, the mAb seasonal programme with catch-up had similar MA

cases averted among children in the 0-2 months age-group, but the catch-up component further reduced MA cases in the 3-5 months and 6-11 months age-groups in all four models.

Table 14:mAb seasonal plus a catch-up programme: estimated disease burden averted by two static models

	UA					SPS				
Age	Primary care visit	Hospital outpatient	Hospital isation	ICU	death	Primary care visit	Hospital outpatient	Hospitalis ation	ICU	death
mAb										
0-2 months	1951	83	744	8	0	1976	76	763	8	0
3-5 months	3370	82	413	3	0	2917	66	377	2	0
6-11 months	1619	33	149	0	0	1653	30	154	0	0
12-23 months	0	0	0	0	0	0	0	0	0	0
24-59 months	0	0	0	0	0	6546	171	1294	10	0
0-11 months	6940	197	1306	11	0	0	0	0	0	0
0-59 months	6940	197	1306	11	0	0	0	0	0	0

Table 15: mAb seasonal plus a catch-up programme: estimated disease burden averted by two dynamic models

	SPD							LSHTM						
Age	Asymptomatic infection	Non-MA symptomatic infection	Primary care visit	Hospital outpatient	Hospital isation	ICU	death	Asymptomatic infection	Non-MA symptomatic infection	Primary care visit	Hospital outpatient	Hospital isation	ICU	death
0-2 months	-1878	91	1808	74	576	6	0.09	514	3455	1165	42	439	5	0.06
3-5 months	-2616	389	2261	66	314	2	0.08	517	3448	1485	31	166	1	0.04
6-11 months	-1786	478	1399	32	116	0	0.14	565	4499	1000	19	83	0	0.08
12-23 months	460	59	67	1	6	0	0.00	653	2792	511	6	43	0	0.01
24-59 months	49	-24	-15	0	-1	0	0.00	335	1631	84	1	7	0	0.01
0-11 months	-6280	958	5467	171	1006	9	0.30	1597	11403	3650	91	689	7	0.18
0-59 months	-5772	993	5520	172	1010	9	0.30	2585	15826	4245	99	738	7	0.20

UA: University of Antwerp model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model, MV: maternal vaccine, mAb: monoclonal antibody

Table 16: mAb seasonal plus catch-up programs: QALYs gained, incremental costs and incremental cost-effectiveness ratios of either MV or mAB versus current practice, from the health care payer's and societal perspectives (discount rate 3% per year, MV: €37.5 per dose and €8.32 delivery cost, mAb: €50 per dose and €5 delivery cost)

	QALY gains	Direct medical cost	Intervention costs [a]	Incremental direct costs	ICER per QALY gained (payer)	Non-medical cost	Incremental total costs	ICER per QALY gained (societal)
mAb (94% coverage)								
UA^	42	-€ 5,063,767	€ 5,682,080	€ 618,313	€ 14,640	-€ 2,127,102	-€ 1,508,789	Dominant
SPS^	40	-€ 5,109,345	€ 5,682,080	€ 572,735	€ 14,240	-€ 2,034,840	-€ 1,462,105	Dominant
SPD*	271	-€ 37,228,886	€ 47,561,842	€ 10,332,955	€ 38,168	-€ 14,271,701	-€ 3,938,746	Dominant
LSHTM*	632	-€ 25,491,150	€ 46,683,568	€ 21,192,418	€ 33,548	-€ 10,639,867	€ 10,552,552	€ 16,705

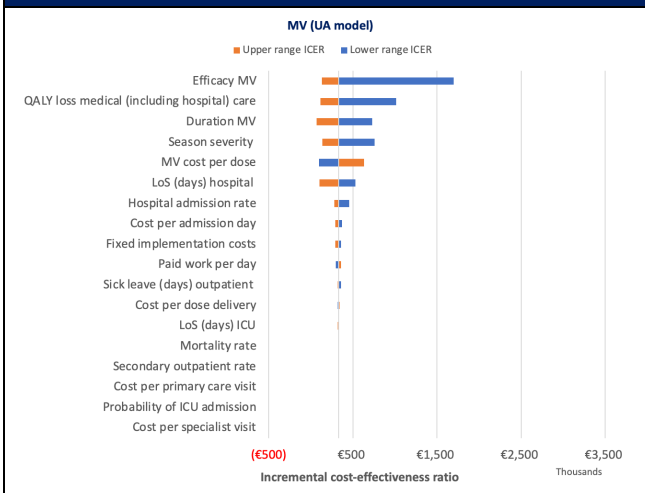
Table footnote: [#] excluding the QALY gain from the non-MA symptomatic infections averted. [a] intervention costs includes cost of intervention, delivery costs, and implementation costs UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model. MV: maternal vaccine, mAb: monoclonal antibody

2.3 One-way sensitivity analysis

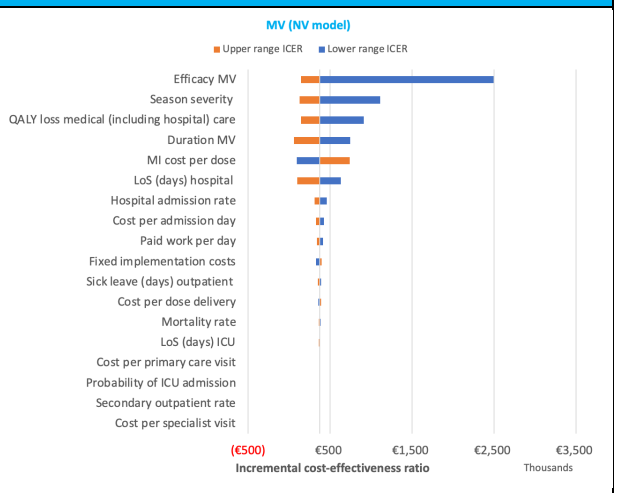
The impact of each of the individual parameters on the ICER from a societal perspective per intervention per model are presented in tornado diagrams. As illustrated in Figure 8 and Figure 9, the top five key drivers are similar, but they rank differently for MV and mAb across models.

Figure 8: Tornado diagrams for maternal vaccines year-round programs: impact on ICER from a societal perspective.

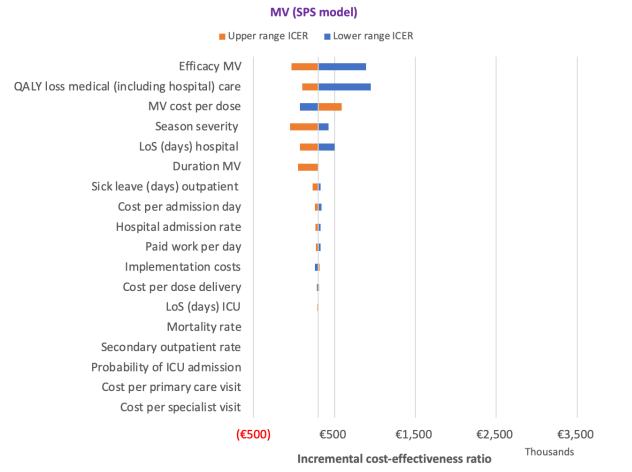
University of Antwerp (UA)



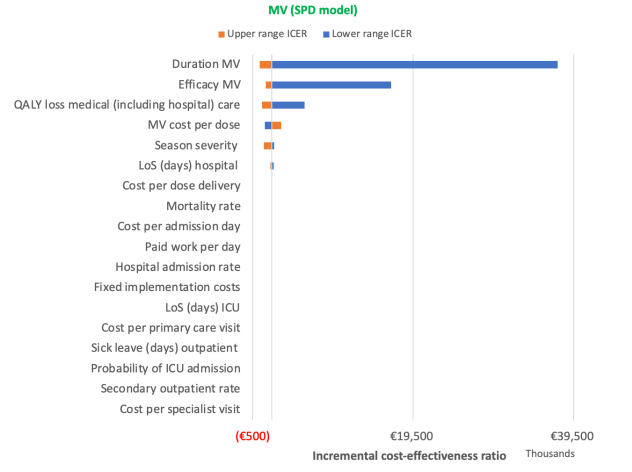
Novavax (NV)



Sanofi Pasteur static (SPS)



Sanofi Pasteur dynamic (SPD)



London School of Hygiene & Tropical Medicine (LSHTM)

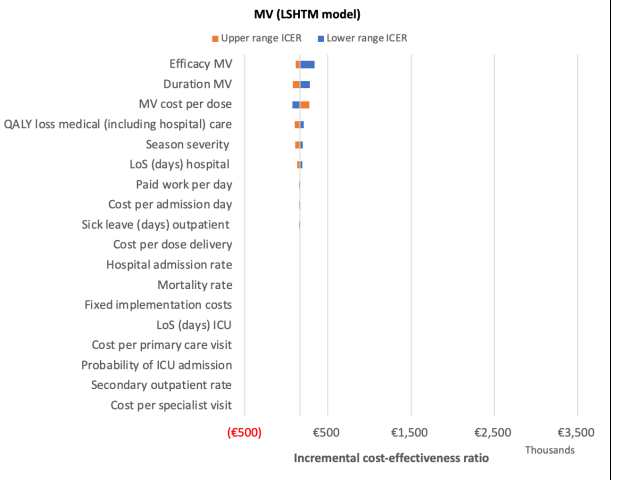
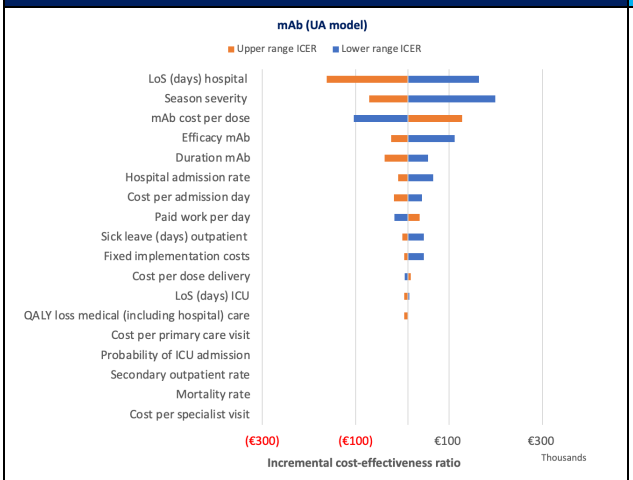
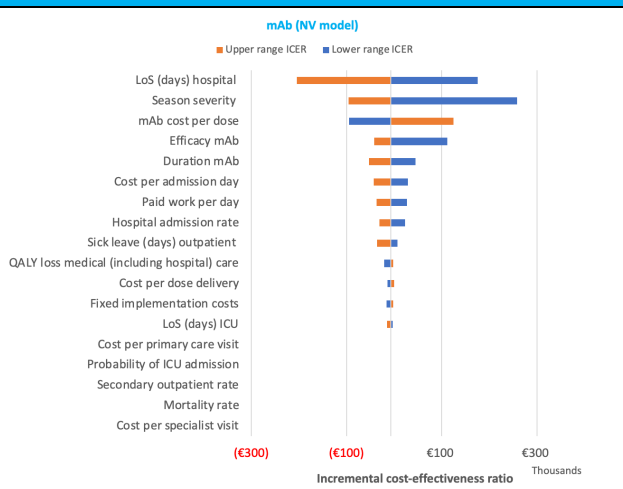


Figure 9: Tornado diagrams for monoclonal antibody year-round programs: impact on ICER from a societal perspective.

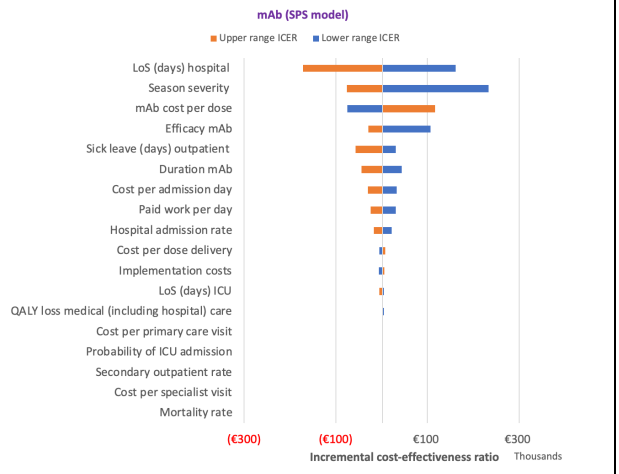
University of Antwerp (UA)



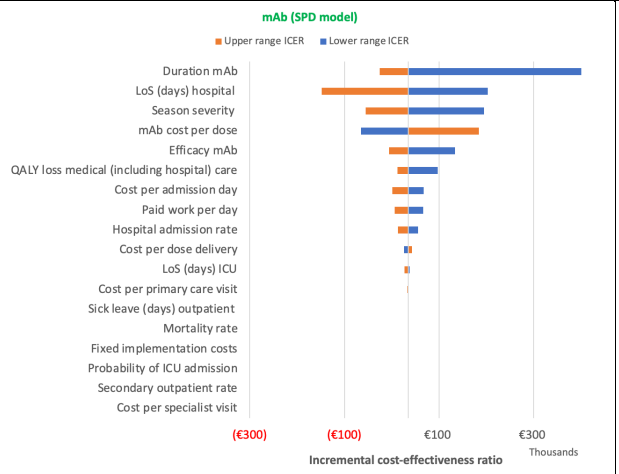
Novavax (NV)



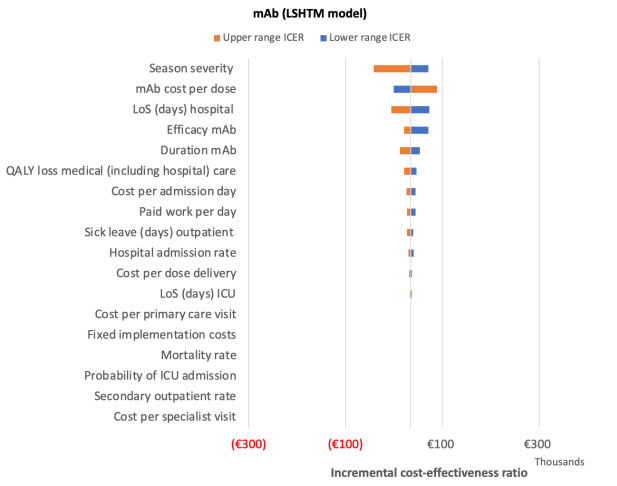
Sanofi Pasteur static (SPS)



Sanofi Pasteur dynamic (SPD)



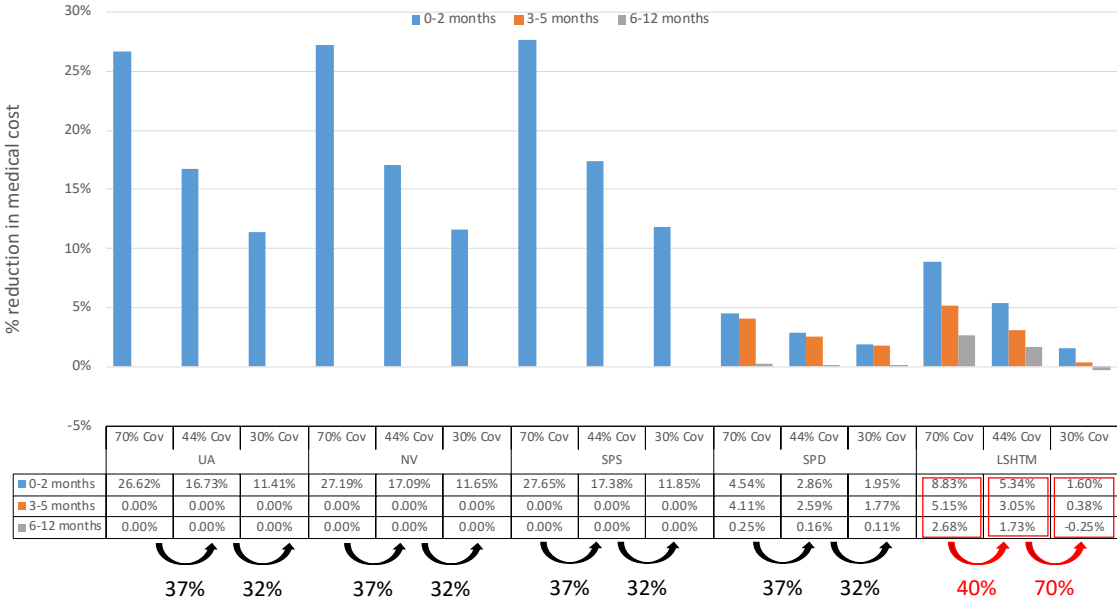
London School of Hygiene & Tropical Medicine (LSHTM)



2.4 Sensitivity analysis: impact of seasonal programmes and intervention coverage

We further investigated the impact of interventions' coverage under two scenarios of 70% and 30% coverage for both MV and mAb seasonal programmes compared to the base case seasonal programmes (Coverage: MV 44% and mAb 94%). The reductions of RSV-associated medical costs (without intervention costs) for three coverages are demonstrated per model and intervention in Figure 10 and Figure 11. By default, static models found medical costs averted to scale linearly with coverage (i.e., 37% decrease in MV coverage from 70% to 44% led to 37% reduction in medical costs averted). Between the two dynamic models, SPD model showed close to linear changes across all age-groups for both MV and mAb, but the LSHTM model showed a non-linear reduction for both MV and mAb due to herd immunity.

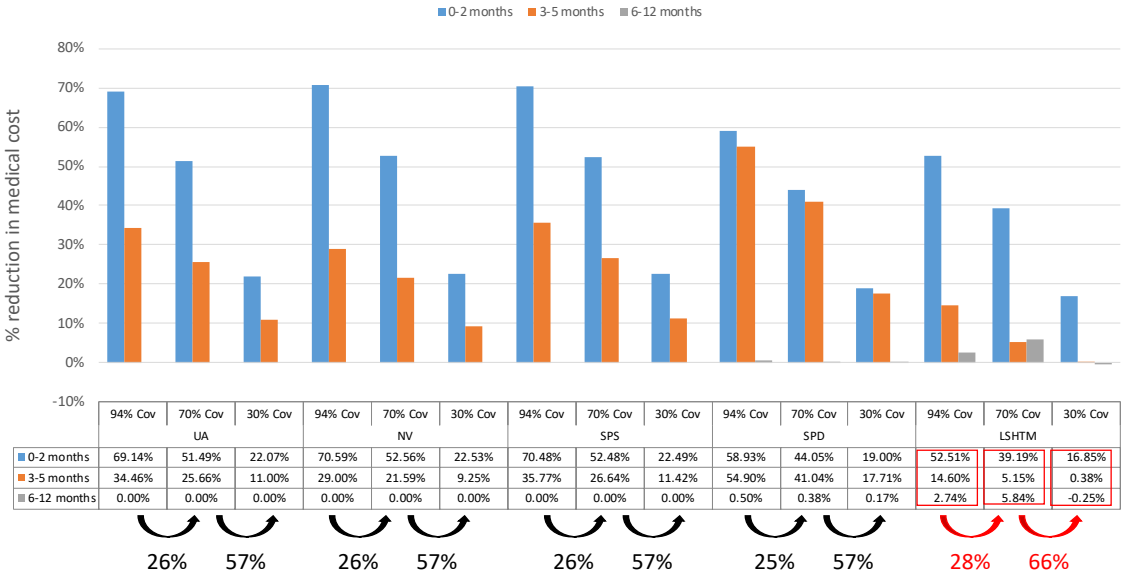
Figure 10: maternal vaccine (MV) seasonal programmes: % reduction of medical cost averted with 70%, 44% and 30% coverage. The arrows show the relative decreases in costs from 70% coverage to 44% and 44% to 30% (black arrows: linear reduction, red arrows: non-linear reduction)



	70% Cov	44% Cov	30% Cov	70% Cov	44% Cov	30% Cov	70% Cov	44% Cov	30% Cov	70% Cov	44% Cov	30% Cov	70% Cov	44% Cov	30% Cov
	UA			NV			SPS			SPD			LSHTM		
0-2 months	26.62%	16.73%	11.41%	27.19%	17.09%	11.65%	27.65%	17.38%	11.85%	4.54%	2.86%	1.95%	8.83%	5.34%	1.60%
3-5 months	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	4.11%	2.59%	1.77%	5.15%	3.05%	0.38%
6-12 months	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.25%	0.16%	0.11%	2.68%	1.73%	-0.25%

37% 32% 37% 32% 37% 32% 37% 32% 40% 70%

Figure 11: monoclonal antibody (mAb) seasonal programmes: reduction of medical cost with 94%, 70% and 30% coverage. The arrows show the relative decreases in costs from 94% coverage to 70% and 70% to 30% (black arrows: linear reduction, red arrows: non-linear reduction).



	94% Cov	70% Cov	30% Cov	94% Cov	70% Cov	30% Cov	94% Cov	70% Cov	30% Cov	94% Cov	70% Cov	30% Cov	94% Cov	70% Cov	30% Cov
	UA			NV			SPS			SPD			LSHTM		
0-2 months	69.14%	51.49%	22.07%	70.59%	52.56%	22.53%	70.48%	52.48%	22.49%	58.93%	44.05%	19.00%	52.51%	39.19%	16.85%
3-5 months	34.46%	25.66%	11.00%	29.00%	21.59%	9.25%	35.77%	26.64%	11.42%	54.90%	41.04%	17.71%	14.60%	5.15%	0.38%
6-12 months	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.50%	0.38%	0.17%	2.74%	5.84%	-0.25%

26% 57% 26% 57% 26% 57% 25% 57% 28% 66%

Reference

1. Li X, Bilcke J, Vazquez Fernandez L, et al. Cost-effectiveness of Respiratory Syncytial Virus Disease Prevention Strategies: Maternal Vaccine Versus Seasonal or Year-Round Monoclonal Antibody Program in Norwegian Children. J Infect Dis. 2022.

2. Voirin N, Virlogeux V, Demont C, et al. Potential Impact of Nirsevimab on RSV Transmission and Medically Attended Lower Respiratory Tract Illness Caused by RSV: A Disease Transmission Model. Infect Dis Ther. 2022; 11: 277-92.

3. Hodgson D, Pebody R, Panovska-Griffiths J, et al. Evaluating the next generation of RSV intervention strategies: a mathematical modelling study and cost-effectiveness analysis. BMC Med. 2020; 18: 348.

4. Kieffer A, Beuvelet M, Sardesai A, et al. Expected Impact of Universal Immunization With Nirsevimab Against RSV-Related Outcomes and Costs Among All US Infants in Their First RSV Season: A Static Model. J Infect Dis. 2022; 226: S282-S92.

5. Herring WL, Zhang Y, Shinde V, et al. Clinical and economic outcomes associated with respiratory syncytial virus vaccination in older adults in the United States. Vaccine. 2022; 40: 483-93.

6. Office for National Statistics. Population estimates: Summary for the UK, mid-2020. Office for National Statistics, 2021.

7. Reeves RM, van Wijhe M, Tong S, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. J Infect Dis. 2020; 222: S599-S605.

8. Cromer D, van Hoek AJ, Jit M, et al. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect. 2014; 68: 363-71.

9. Hodgson D, Atkins KE, Baguelin M, et al. Estimates for quality of life loss due to Respiratory Syncytial Virus. Influenza Other Respir Viruses. 2020; 14: 19-27.

10. Institute for Medical Technology Assessment Erasmus Universiteit Rotterdam. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Kostenhandleiding: - Zorginstituut Nederland, 2016.

11. Blanken MO, Frederix GW, Nibbelke EE, et al. Cost-effectiveness of rule-based immunoprophylaxis against respiratory syncytial virus infections in preterm infants. Eur J Pediatr. 2018; 177: 133-44.

12. Meijboom MJ, Rozenbaum MH, Benedictus A, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. Vaccine. 2012; 30: 4691-700.

13. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. N Engl J Med. 2020; 383: 415-25.

14. Madhi SA, Polack FP, Piedra PA, et al. Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants. N Engl J Med. 2020; 383: 426-39.

15. GOV.UK. Vaccine uptake guidance and the latest coverage data. 2021.

16. Cromer D, van Hoek AJ, Newall AT, et al. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. Lancet Public Health. 2017; 2: e367-e74.

17. Li X, Willem L, Antillon M, et al. Health and economic burden of respiratory syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries. BMC Med. 2020; 18: 82.

18. Kinyanjui TM, House TA, Kiti MC, et al. Vaccine Induced Herd Immunity for Control of Respiratory Syncytial Virus Disease in a Low-Income Country Setting. PLoS One. 2015; 10: e0138018.

19. Pan-Ngum W, Kinyanjui T, Kiti M, et al. Predicting the relative impacts of maternal and neonatal respiratory syncytial virus (RSV) vaccine target product profiles: A consensus modelling approach. Vaccine. 2017; 35: 403-09.

20. Ely DM, Driscoll AK, Matthews TJ. Infant Mortality by Age at Death in the United States, 2016. NCHS Data Brief. 2018: 1-8.

21. In: Szende A, Janssen B, Cabases J, eds., Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht (NL), 2014.

22. Briggs AH, Goldstein DA, Kirwin E, et al. Estimating (quality-adjusted) life-year losses associated with deaths: With application to COVID-19. Health Econ. 2021; 30: 699-707.

23. Janssen B, Szende A. Population Norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, eds., Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht (NL), 2014.

24. van den Berg B. Sf-6d population norms. Health Econ. 2012; 21: 1508-12.

25. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008; 5: e74.

26. van Hoek AJ, Andrews N, Campbell H, et al. The social life of infants in the context of infectious disease transmission; social contacts and mixing patterns of the very young. PLoS One. 2013; 8: e76180.