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

Appendix 2: Description and calibration methods of the two dynamic models

1 Sanofi Pasteur dynamic transmission model (SPD)

This model was adapted based on a published model of Voirin 2022 (1).

1.1 Demography

Let N_a the population in age group a, μ_a the death rate in age group a, κ_a the aging rate in age group a, and B the birth rate.

We consider 32 age groups. Age group 0 is the first month of life, and age group 31 represents individuals aged 75 years or more.

We assume a steady state population, hence:

$$N_0 = \frac{B}{\kappa_0 + \mu_0}, \quad (1)$$

and for $a > 0$

$$N_a = \frac{\kappa_{a-1} N_{a-1}}{\kappa_a + \mu_a}. \quad (2)$$

We assumed a birth rate B of 100,000 births per year (274 births per day). Death rate values (Table 1) are adapeted from UK life tables. We merged age groups by computing average death rates, and converted to daily death rates by dividing by 365.25. The death rate in age group 31 is based on life expectancy at age 75 years (13.19 years). The population by age group is shown in Table 2.

Table 1: Death rates (day^{-1}) based on UK life tables

Age group a	Description	Death rate μ_a
0–11	[0 mo.–12 mo[	9.7×10^{-6}
12–23	[12 mo.–24 mo[	5.83×10^{-7}
24	[2 yr.–5 yr.[	2.67×10^{-7}
25	[5 yr.–10 yr.[	1.9×10^{-7}
26	[10 yr.–20 yr.[	3.33×10^{-7}
27	[20 yr.–40 yr.[	1.15×10^{-6}
28	[40 yr.–60 yr.[	6.31×10^{-6}
29	[60 yr.–65 yr.[	1.69×10^{-5}
30	[65 yr.–75 yr.[	3.45×10^{-5}
31	[75 yr.– $+\infty$[	2.08×10^{-4}

Table 2: population by age-group

Age	Value
0	8330.87
1	8328.42
2	8325.96
3	8323.5
4	8321.05
5	8318.59
6	8316.14
7	8313.68
8	8311.23
9	8308.78
10	8306.32
11	8303.87
12	8303.73
13	8303.58
14	8303.43
15	8303.28
16	8303.14
17	8302.99
18	8302.84
19	8302.69
20	8302.55
21	8302.4

22	8302.25
23	8302.1
24	298788
25	497808
26	994406
27	1.9723E+06
28	1.88544E+06
29	457237
30	812182
31	1.07127e+06

1.2 No intervention

$$\frac{dM_a}{dt} = \mathbb{1}_{a=0}B - \omega M_a - (\mu_a + \kappa_a) M_a + \mathbb{1}_{a>0}\kappa_{a-1}M_{a-1} \quad (3)$$

$$\frac{dS_{0,a}}{dt} = \omega M_a - \lambda_a S_{0,a} - (\mu_a + \kappa_a) S_{0,a} + \mathbb{1}_{a>0}\kappa_{a-1}S_{0,a-1} \quad (4)$$

$$\frac{dI_{1,a}}{dt} = \lambda_a S_{0,a} - \gamma_1 I_{1,a} - (\mu_a + \kappa_a) I_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1}I_{1,a-1} \quad (5)$$

$$\frac{dP_{1,a}}{dt} = \gamma_1 I_{1,a} - pP_{1,a} - (\mu_a + \kappa_a) P_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1}P_{1,a-1} \quad (6)$$

$$\frac{dS_{1,a}}{dt} = pP_{1,a} - \sigma_1\lambda_a S_{1,a} - (\mu_a + \kappa_a) S_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1}S_{1,a-1} \quad (7)$$

$$\frac{dI_{2,a}}{dt} = \sigma_1\lambda_a S_{1,a} - \gamma_2 I_{2,a} - (\mu_a + \kappa_a) I_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1}I_{2,a-1} \quad (8)$$

$$\frac{dP_{2,a}}{dt} = \gamma_2 I_{2,a} - pP_{2,a} - (\mu_a + \kappa_a) P_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1}P_{2,a-1} \quad (9)$$

$$\frac{dS_{2,a}}{dt} = p\left(P_{2,a} + P_{3,a}\right) - \sigma_2\lambda_a S_{2,a} - (\mu_a + \kappa_a) S_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1}S_{2,a-1} \quad (10)$$

$$\frac{dI_{3,a}}{dt} = \sigma_2\lambda_a S_{2,a} - \gamma_3 I_{3,a} - (\mu_a + \kappa_a) I_{3,a} + \mathbb{1}_{a>0}\kappa_{a-1}I_{3,a-1} \quad (11)$$

$$\frac{dP_{3,a}}{dt} = \gamma_3 I_{3,a} - pP_{3,a} - (\mu_a + \kappa_a) P_{3,a} + \mathbb{1}_{a>0}\kappa_{a-1}P_{3,a-1} \quad (12)$$

where λ_a is the force of infection such that

$$\lambda_a(t) = \beta_0\left(1 + b\cos\left(\frac{2\pi}{T}(t-\varphi)\right)\right)\sum_j \frac{C_{a,j}}{N_j}\left(I_{1,j} + \rho_1 I_{2,j} + \rho_2 I_{3,j}\right). \quad (13)$$

Let $d_{1,a}$ ($d_{2,a}$, $d_{3,a}$) the proportion of individuals infected for the first time (second time, third time and more) in age group a developing a LRTI. The LRTI incidence rate in age group a is

$$\mathcal{I}_a^{\text{LRTI}} = d_{1,a}\lambda_a S_{0,a} + d_{2,a}\sigma_1\lambda_a S_{1,a} + d_{3,a}\sigma_2\lambda_a S_{2,a}. \quad (14)$$

The dynamic transmission model parameters are summarised in Tables 3 and 4.

1.3 Long lasting monoclonal antibodies

Let ξmAbs be the coverage for long lasting monoclonal antibodies and e_{mAbs} their efficacy. Successfully treated children are protected during 5 months without waning.

Table 3: Dynamic transmission model parameters

Notation	Description	Unit	Value	Sources
$1/\omega$	Duration of natural maternal protection	days	60	Input template
$1/p$	Duration of post-infection immunity	days	Fitted	See Table 9
$1/\gamma_1$	Duration of infectious period (1st infection)	days	6.16	Input template
γ_1/γ_2	Reduction of infectious period (2nd infection)		0.87	Input template
γ_2/γ_3	Reduction of infectious period (3rd infection and beyond)		0.79	Input template
ρ_1	Reduction of infectiousness (2nd infection)		0.75	Assumed
ρ_2	Reduction of infectiousness (3rd infection and beyond)		0.51	Assumed
σ_1	Susceptibility reduction after 1st infection		0.89	Input template
σ_2	Susceptibility reduction after 2nd infection and beyond		0.6	Assumed
$d_{1,a}$	Proportion of infected individuals developing a LRTI (1st infection)		See Table 4	Assumed

$d_{2,a}/d_{1,a}$	Reduction of LRTI probability (2nd infection)		0.5	Assumed
$d_{3,a}/d_{1,a}$	Reduction of LRTI probability (3rd infection) and beyond		0.25	Assumed
β_0	Baseline per contact infection prob- ability		Fitted	See Table 9
b	Amplitude of seasonal forcing		Fitted	See Table 9
ϕ	Phase of seasonal forcing	day	Fitted	See Table 9

Table 4: Probability of developing an LRTI in the first RSV infection

Age group a	*Description*	$d_{1,a}$
0–5	[0 m–6 m[	*0.5*
6-11	[6 m–12 m[	*0.4*
12-17	[12 mo.–18 m[	*0.3*
18-23	[18 mo.–24 m[	*0.2*
24-25	[2 y–10 y[	*0.15*
26-28	[10 y–60 y[	*0.1*
29	[60 y–65 y[	*0.15*
30	[65 y–75 y[	*0.25*
31	[75 y– +∞[	*0.4*

$$\mathbb{1}_a^{\text{mAbs}}(t) = \begin{cases} 1 & \text{if individuals in age group } a \text{ are protected at time } t \\ 0 & \text{otherwise.} \end{cases}$$

Protected individuals may get infected with RSV, however they are less infectious by a factor $r^{\text{mAbs}} = 1 - \rho^{\text{mAbs}}$ and they do not develop a LRTI if they are infected. In all simulations $r^{\text{mAbs}} = 0.5$.

Force of infections

$$\lambda_a(t) = \beta_0 \left(1 + b\cos\left(\frac{2\pi}{T}(t-\varphi)\right)\right) \sum_j \frac{C_{a,j}}{N_j} \left(1 - \mathbb{1}_j^{\text{mAbs}}(t)\xi^{\text{mAbs}} e^{\text{mAbs}} r^{\text{mAbs}}\right) (I_{1,j} + \rho_1 I_{2,j} + \rho_2 I_{3,j}) \tag{15}$$

and the LRTI incidence rate

$$\mathcal{I}_a^{\text{LRTI}} = \left(1 - \mathbb{1}_j^{\text{mAbs}} \xi^{\text{mAbs}} e^{\text{mAbs}}\right) (d_{1,a}\lambda_a S_{0,a} + d_{2,a}\sigma_1\lambda_a S_{1,a} + d_{3,a}\sigma_2\lambda_a S_{2,a}) . \tag{16}$$

1.4 Maternal vaccine

Let $\xi_{MV(t)}$ be the maternal immunization coverage and e_{MV} the vaccine efficacy. Successfully treated children are protected during 3 months without waning.

Let $V_{MV(t)}$ the number of individuals in age group a that are protected at time t because of maternal immunization and γ_{MV} the rate of waning of vaccine efficacy.

The spread of RSV is then described by equations (17) to (27). The expression of λ_a and ILRTI are the same as in equations (13) and (14) respectively.

$$\frac{dM_a}{dt} = \mathbb{1}_{a=0}(1 - \xi^{\text{MV}}(t)e^{\text{MV}})B - \omega M_a - (\mu_a + \kappa_a) M_a + \mathbb{1}_{a>0}\kappa_{a-1} M_{a-1} \tag{17}$$

$$\frac{dS_{0,a}}{dt} = \omega M_a - \lambda_a S_{0,a} + \gamma_{\text{MV}} V_a^{\text{MV}} - (\mu_a + \kappa_a) S_{0,a} + \mathbb{1}_{a>0}\kappa_{a-1} S_{0,a-1} \tag{18}$$

$$\frac{dI_{1,a}}{dt} = \lambda_a S_{0,a} - \gamma_1 I_{1,a} - (\mu_a + \kappa_a) I_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1} I_{1,a-1} \tag{19}$$

$$\frac{dP_{1,a}}{dt} = \gamma_1 I_{1,a} - pP_{1,a} - (\mu_a + \kappa_a) P_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1} P_{1,a-1} \tag{20}$$

$$\frac{dS_{1,a}}{dt} = pP_{1,a} - \sigma_1\lambda_a S_{1,a} - (\mu_a + \kappa_a) S_{1,a} + \mathbb{1}_{a>0}\kappa_{a-1} S_{1,a-1} \tag{21}$$

$$\frac{dI_{2,a}}{dt} = \sigma_1\lambda_a S_{1,a} - \gamma_2 I_{2,a} - (\mu_a + \kappa_a) I_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1} I_{2,a-1} \tag{22}$$

$$\frac{dP_{2,a}}{dt} = \gamma_2 I_{2,a} - pP_{2,a} - (\mu_a + \kappa_a) P_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1} P_{2,a-1} \tag{23}$$

$$\frac{dS_{2,a}}{dt} = p\,(P_{2,a} + P_{3,a}) - \sigma_2\lambda_a S_{2,a} - (\mu_a + \kappa_a) S_{2,a} + \mathbb{1}_{a>0}\kappa_{a-1} S_{2,a-1} \tag{24}$$

$$\frac{dI_{3,a}}{dt} = \sigma_2\lambda_a S_{2,a} - \gamma_3 I_{3,a} - (\mu_a + \kappa_a) I_{3,a} + \mathbb{1}_{a>0}\kappa_{a-1} I_{3,a-1} \tag{25}$$

$$\frac{dP_{3,a}}{dt} = \gamma_3 I_{3,a} - pP_{3,a} - (\mu_a + \kappa_a) P_{3,a} + \mathbb{1}_{a>0}\kappa_{a-1} P_{3,a-1} \tag{26}$$

$$\frac{dV_a^{\text{MV}}}{dt} = \mathbb{1}_{a=0}\xi^{\text{MV}}(t)e^{\text{MV}}B - \gamma_{\text{MV}} V_a^{\text{MV}} - (\mu_a + \kappa_a) V_a^{\text{MV}} + \mathbb{1}_{a>0}\kappa_{a-1} V_{a-1}^{\text{MV}} \tag{27}$$

1.5 Disutilities

The disutilities are 3.024×10^{-3} QALY for LRTIs not receiving medical care, and 3.823×10^{-3} QALY for LRTIs receiving medical care.

The disutility of death is the forgone expected discounted lifetime utility. Let us assume that the course of the RSV epidemic has no influence on lifetime utility. Then the expected discounted lifetime utility of an individual in age group a at time t satisfies

$$U_a(t) = u_a dt + (1 - \delta dt)\left[(1 - \kappa_a dt - \mu_a dt)\, U_a(t + dt) + \kappa_a U_{a+1}(t + dt) dt\right] \qquad (28)$$

which can be written as

$$-\frac{dU_a}{dt} = u_a - (\delta + \kappa_a + \mu_a)\, U_a + \kappa_a U_{a+1} \qquad (29)$$

where u_a is the utility per unit time (in our case one day) of being in age group a, and δ is the discount rate.

In our model, we can simply use the steady state of equation (29)

$$\bar{U}_a = \frac{u_a + \kappa_a \bar{U}_{a+1}}{\delta + \kappa_a + \mu_a} \qquad (30)$$

for $a \in \{0 \ldots 30\}$ and

$$\bar{U}_a = \frac{u_a}{\delta + \mu_a} \qquad (31)$$

for $a = 31$.

The values of u_a are adapted from Van den Berg 2012 (2). We assumed u_a to be 1 from birth to age 2 years, and to be constant from age 2 years to age 20 years. When needed, we merged age groups given in (2) by computing average utilities. We assumed life expectancy at age 85 to be 6.6 years (3). The adapted daily utility values are shown in Table 5.

We obtain the values of $\bar{U}_a$ shown in Table 6. For instance, $\bar{U}_0 = 23.92$ QALY and $\bar{U}_{31} = 6.57$ QALY. Compare e.g. with $1/(0.03 + 1/83) = 23.78$ QALY.

Table 5: Expected discounted by utility age group (in QALY)

Age	Value
0	23.9228
1	23.9064
2	23.8899
3	23.8733
4	23.8567
5	23.8401
6	23.8234
7	23.8066
8	23.7898
9	23.773
10	23.7561
11	23.7392
12	23.7222
13	23.6986
14	23.6749
15	23.6512
16	23.6274
17	23.6036
18	23.5797
19	23.5557
20	23.5317
21	23.5076
22	23.4834

23	23.4592
24	23.435
25	23.022
26	22.2683
27	20.5458
28	16.7353
29	11.7325
30	9.97973
31	6.56557

1.6 Outcome probabilities

1.6.1 Primary care

The probability of primary care visit given a LRTI as a function of age is modeled as

$$h(a) = \max\left[h_0 \exp(-h_{\text{dec1}} a), h_{75} \exp(h_{\text{dec2}}(a - 75 \times 12))\right] \quad (32)$$

where a is given in months. Parameters h_0, h_75, h_{dec1}, and h_{dec2} are fitted.

The probability of primary care visit in age group a defined as $[a_0, a_1[$ is $h(a_0)$.

1.6.2 Hospital outpatient care

The input template provides annual secondary care visit rates ra by age group a in the general population. For instance r_0 = 2.3463/1000.

We estimate the probability of secondary care visit given a LRTI in age group a as

$$P_a(\text{secondary care}|\text{LRTI}) = \frac{r_a \times N_a}{\text{LRTIs per year in age group } a} \quad (33)$$

LRTIs per year in age group a

- r_a is the annual secondary care visit rate provided in the template,

- N_a is the steady state population in age group a, and the number of LRTIs per year in age group a is an output of the fitted transmission model.

We obtain the probabilities of secondary care given LRTI shown in Table 6.

1.6.3 Hospitalization

Let $\bar{n}^{\text{hospit}}_{0\text{–}5,m} = \sum_{a=0}^{5} \bar{n}^{\text{hospit}}_{am}$ the *observed* number of hospital visits in age groups 0 to 5 in calendar month m, and $n^{\text{hospit}}_{0\text{–}5,m} = \sum_{a=0}^{5} n^{\text{hospit}}_{am}$ the *output* number of hospital visits in age groups 0 to 5 in calendar month m.

The observed number of primary care visits is such that for $a \in \{0, \dots 5\}$ (see section 3):

$$\bar{n}^{\text{pc}}_{am} = p_a \times 5 \times \sum_{i=0}^{5} \bar{n}^{\text{hospit}}_{im} \tag{34}$$

hence

$$\sum_{a=0}^{5} \frac{\bar{n}^{\text{pc}}_{am}}{p_a} = 6 \times 5 \times \sum_{a=0}^{5} \bar{n}^{\text{hospit}}_{am}. \tag{35}$$

Table 6: Secondary care probability given LRTI by age group. Zeroes: age groups ignored in the present analysis.

Age group	Value
0	0.0757216
1	0.10831
2	0.0976791
3	0.0640325
4	0.0536319
5	0.0610239
6	0.0495876
7	0.0360125
8	0.0357855
9	0.0249307
10	0.0187572

11	0.021518
12	0.00736594
13	0.00768975
14	0.00793333
15	0.00811937
16	0.00827187
17	0.00841137
18	0.012831
19	0.0130669
20	0.0133352
21	0.0136389
22	0.0139745
23	0.014333
24	0.00458097
25	0
26	0
27	0
28	0
29	0
30	0
31	0

The output number of hospitalisation are:

$$\sum_{a=0}^{5} n_{am}^{\text{hospit}} = \frac{1}{6 \times 5} \sum_{a=0}^{5} \frac{\bar{n}_{am}^{\text{pc}}}{p_a}. \tag{36}$$

The total output number of hospital visits in age groups 0 to 5 is distributed according to the observed distribution of hospital visits in age groups 0 to 5. Namely

$$n_{am}^{\text{hospit}} = \frac{\bar{n}_a^{\text{hospit}}}{\sum_{i=0}^{5} \bar{n}_i^{\text{hospit}}} \sum_{i=0}^{5} n_{im}^{\text{hospit}} \tag{37}$$

where $\bar{n}_a^{\text{hospit}} = \sum_{m=0}^{11} \bar{n}_{am}^{\text{hospit}}$.
In older age groups: $n_{am}^{\text{hospit}} = \frac{n_{am}^{\text{pc}}}{12}$.

1.6.4 Intensive care unit (ICU)

ICU admissions are a fraction of hospital admissions.

1.6.5 Death

The input template provides death rates in the general population. We use the same method as for secondary care visits to estimate the probability of death given LRTI in age group a, $P_a(\text{death}|\text{LRTI})$.

1.7 Model fitting

The model is fitted to monthly primary care visit data by age group over one year. We fit the periodic steady state without intervention.

The monthly primary care visit data derives from the hospitalization data as follow.

Below 6 months of age (age groups 0 to 5), for each calendar month m, the number of primary care visits is 5 times the number of hospitalisations: $\bar{n}_{0\text{–}5,m}^{\text{pc}} = 5 \times \bar{n}_{0\text{–}5,m}^{\text{hospit}}$. The number of primary care visits in age group $a \in \{0, \ldots 5\}$ is $\bar{n}_{am}^{\text{pc}} = \bar{n}_{0\text{–}5,m}^{\text{pc}} \times p_a$ where the p_a's are provided in the input template.

In older age groups, the number of primary care visits is 12 times the number of hospitalisations.

We obtain the fitted parameter values using simulated annealing method (Table 7)

Parameter	Description	Unit	Value
p	Rate of loss of short-term immunity	day^{-1}	0.00175402

$1/p$	Mean duration of short- term immunity	day	570.119
β_0	Baseline per contact trans- mission probability		0.237671
b	Seasonality amplitude		0.0790952
ϕ	Seasonality phase	days	93.7254
h_{dec1}	Decrease of h 1		0.0406436
h_0	Healthcare system use at age 0		1
h_{dec2}	Decrease of h 2		0.00504178
h_{75}	Healthcare system use at age 75		0.352061
ω	Rate of loss of maternal protection	day^{-1}	0.0171887
$1/\omega$	Mean duration of maternal protection		58.1778

1.8 Simulations

The transmission model is initialized with the periodic steady state without intervention.

For each scenario, we performed the following simulations:

- simulation over 10 years starting from policy implementation,
- exact (up to some specified precision) steady state under the considered policy.

The figures reported in the Output spreadsheet correspond to steady states.

To get approximated discounted costs and disutilities, divide steady state yearly costs and disutilities by the discount rate.

In a first approach, we plotted the force of infection:

- Although we implement a 50% decrease of infectiousness for individuals treated with mAbs, there is visually no difference in force of infection between (i) no intervention, (ii) seasonal mAbs policy without catchup, and (iii) seasonal mAbs

policy with catchup. This remains true in all considered coverage scenarios.

- Visually, a steady state is reached with maternal immunization after about 3–5 years depending on the considered age group and scenario.

2 London School of Hygiene & Tropical Medicine model (LSHTM)

We used a Bayesian Markov chain Monte Carlo (MCMC) approach to fit the LSHTM dynamics transmission model to the age-specific annual number of hospitalised cases from input template from University of Antwerp. The fitted procedure used a parallel tempering algorithm implemented via the ptmc package (https://github.com/dchodge/ptmc). Further information is contained in a previous study of RSV transmission [Hodgson2020] (3).

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