Technical Appendix for "Modeling the transmission of measles and rubella to support global management policy analyses and eradication investment cases"

Executive Summary

This document provides the technical details about the measles and rubella transmission model. Due to the differential use of rubella immunization by sex in some populations and the role of maternal immunity in transmission, Figure 1 shows a schematic of the immunity states used to track pregnancies through three time periods (0-<20 weeks since the maternal last menstrual period, 20-<39 weeks, and the last week of pregnancy from which we allow a fraction of fetal infections to the birth of an infected and infectious newborn). Figure 2 shows a schematic of the immunity states used to track all individuals for each area modeled into 35 age groups: 0-<6, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16-<18, 18-<21, 21-<24 months, and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and 50+ years and separately by sex.

The following sections describe the abbreviations and notation used, the computed quantities and equations for flows at each time step, the equations we used for updating immunity state values for each age group at each time step using the flow equations, the thresholds used to characterize die out, importations, and outbreak response dynamics, the expressions for characterizing the force of infection and population immunity considering age and subpopulation heterogeneity in mixing (for those populations that include an under-vaccinated subpopulation), and the algorithm we developed to support fitting of national inputs to incidence trends.

Abbreviations, notation, and symbols

We use the following notation, symbols, and abbreviations to describe the model equations. The equations are the same for both sexes, so we generally ignore indexing by sex, but the model tracks females and males separately and uses the indexing for pregnancy-related equations as needed.

Immunity states (ISs) in the model for each virus v (where v = M for measles or R for rubella), shown here with no subscripts (i.e., virus-specific, age-specific, and sex-specific states implied, see Figure 2 for model schematic) [people]

MIR	maternally immune infants with antibodies derived from mothers with infection-induced immunity
MIV	maternally immune infants with antibodies derived from mothers with vaccine-induced immunity
MIR1	maternally immune infants with antibodies derived from mothers with infection-induced immunity who received a dose of vaccine
MIV1	maternally immune infants with antibodies derived from mothers with vaccine-induced immunity who received a dose of vaccine
S	fully susceptible individuals who received no prior vaccine doses

S1 fully susceptible individuals who received a dose of vaccine but did not "take" (i.e., no seroconversion)
E_j exposed individuals incubating an infection according to a two-stage process, *j*=1,2
I_j infected/infectious individuals according to a two-stage process, *j*=1,2
R individuals who recovered from an infection
VRI1 individuals incubating successfully immunized by a first routine immunization dose
VRI2 individuals incubating successfully immunized by a second routine immunization dose
VSIA individuals incubating successfully immunized by a preventive SIA (pSIA) dose
VORI individuals incubating successfully immunized by an outbreak response SIA (oSIA) dose

Total population [people] and examples of notation with subscripts for age group a, mixing age group a_m, virus v, and/or female sex f

N total population (= sum of all individuals in all ISs and all age groups)
N_a total population size in age group *a*
NM_{a_m} total population size in mixing age group a_m
$S_{a,v}$ fully susceptible individuals in age group *a* for virus *v*
$S_{f,a}$ fully susceptible females in age group *a*
$S_{f,a,v}$ fully susceptible females in age group *a* for virus *v*

Thus, for *A* indicating the number of age groups with age group 0 indicating the youngest age group and *A-1* indicating the oldest age group:

$$N(t) = \sum_{a=0}^{A-1} N_a(t)$$

$$NM_{a_m}(t) = \sum_{b=c(a_m)}^{c(a_m+1)} N_b(t)$$

Pregnancy immunity states (*PISs*) in the model for each virus v (no subscripts shown, see Figure 1 for schematic), [pregnancies]

PS pregnancies of fully susceptible women
PI_{0to20} pregnancies of women infected by virus *v* at the time of becoming pregnant (0 weeks) or 0 to <20 weeks since her last menstrual period (LMP)
PI_{20plus} pregnancies of women infected by virus *v* 20 or more weeks since LMP
PR pregnancies of women already recovered from an infection with virus *v* prior to becoming pregnant
PV pregnancies of women vaccinated against virus *v* prior to becoming pregnant

Fetal immunity states (*FISs*) and total fetuses in the last week of pregnancy

FI population of fetuses about to be born to women infected at the time of pregnancy or 0-<20 weeks since LMP and still infectious (i.e., CRS plus CRI for rubella) or infected later in pregnancy and still infectious (i.e., CRI but not CRS for rubella, CMI for measles)
FS population of fetuses about to be born to fully susceptible women
FR population of fetuses infected and recovered during pregnancy and about to be born (rubella only, includes CRS cases for infections that occurred early in pregnancy, but no CRI)

FMIR population of fetuses about to be born to women infected and recovered prior to their pregnancy or infected during pregnancy for which the fetus only received maternal antibodies

FMIV population of fetuses about to be born to women vaccinated prior to their pregnancy (ignores very small number of vaccinations that occur during pregnancy)

N_{fet} total number of fetuses by sex (=FI + FS + FR + FMIR + FMIV)

Co-flow immunity states tracked to give only one dose to any individual during and SIA round

$PS1_{SIAa}$ number of individuals who received a pSIA dose in the current pSIA but did not "take"

$OS1_{SIAa}$ number of individuals who received an ORI dose in the current oSIA but did not "take"

Symbols

t time [day], model uses time step of 1 day

μ_a mortality rate, varies by age group *a* and sex [1/day]

α population growth rate by sex [percent/day]

ν birth rate = number of surviving infants by sex [people/day]

δ_v transition rate of incubation for virus v = 1/(one half the duration of the exposed (latent) period) [1/day]

γ_v transition rate of infectiousness for virus v = 1/(one half the duration of infectiousness) [1/day]

R_{0v}^{ave} average basic reproduction number for virus v

s_v seasonal amplitude of R_0 for virus v (i.e., difference between the average R_0 at a peak or trough)

s_C number of annual seasonality cycles (= 1 for non-temperate climates, 2 for temperate climates)

t_{peak} day(s) of seasonal peak

r_a aging rate for age group *a* [1/day] (=0.5/365 for infants 0 to 6 months, (1/(12*365) for 7, 8, 9, 10, 11, 12, 13, 14, and 15 months, 0.25/365 for 16-18, 19-21, and 22-24 months, 1/365 for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 years, and 5/365 for 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 years, and 0 for ≥50 years (no aging out of the last age group)

$k_{ISa,v}$ exponential decay rate for waning of maternal immunity for immunity state (i.e., IS = MIR or MIV) for age group *a* and virus v

$\kappa(a_m)$ proportion of potentially infectious contacts of individuals in mixing age group a_m reserved for individuals within the same mixing age group (also noted just as κ, since model assumes the same κ for all a_m)

ζ_j transition rate of fetal development stage j = 1/x [1/day] where x = 140 for j=1 (i.e., 0 to <20 weeks since LMP), 133 for j=2 (i.e., 20-39 weeks since LMP), and 7 for j=3 (i.e., week 39, the last week of pregnancy)

Computed quantities and equations for flows at each time step

We use the following intermediate equations to simplify the notation for the overall differential equation models.

$R_{0v}(t)$ basic reproduction number as a function of time reflecting variability due to seasonality computed using a sine function (= $R_{0v}^{ave}\{1+s_v \sin(2\pi\, s_C\, (t-t_{peak})/365 + \pi/2))\}$

$\beta_v(t)$ rate of sufficiently close contacts for transmission (= $(R_{0v}\,(\delta_v+\mu)^2(\gamma_v+\mu)^2)/(\delta_v^2(2\gamma_v+\mu))$)

$\lambda_v(t)$ force of infection (= $\beta_v\,(I_1+I_2)/N$) (see below for adjustment for mixing)

Equation for aging (*Ag*) out of immunity state IS for age group *a* by sex per time step, which equals aging in to the next immunity state (i.e., $Ag_{\mathrm{IS}_{a+1}}$) for the time step

$$Ag_{IS_a} = r_a \mathrm{IS}_a dt$$

Equation for deaths (*D*) out of IS_a for age group *a* with individuals >1 year old (i.e., excludes infants)

$$D_{IS_a} = \mu_a \mathrm{IS}_a dt$$

Equation for births (*B*) by sex into IS_0 for IS=MIR, MIV, S, I, and R only for rubella and MIR, MIV, S, and I only for measles, with age group *1* representing the age group of 0 to 6 months of age (i.e., the youngest age group in the model) and considering the fraction of fetuses in the corresponding fetal immunity state (FIS) (i.e., MIR corresponds to FMIR). If the model includes both a general population and an under-vaccinated subpopulation, then births are attributed proportional to the relative fractions of the two populations as part of the total population (not shown).

$$B_{IS_1} = \frac{\nu \mathrm{FIS}}{N_{fet}} dt$$

Equations for waning of maternal immunity (*W*) for infants out of MIR_a, $MIR1_a$, MIV_a or $MIV1_a$ for age group *a* (waning rate independent of receipt of a vaccine dose while still maternally immune)

$$W_{MIR_a} = k_{MIR_a} \mathrm{MIR}_a dt$$
$$W_{MIR1_a} = k_{MIR_a} \mathrm{MIR1}_a dt$$
$$W_{MIV_a} = k_{MIV_a} \mathrm{MIV}_a dt$$
$$W_{MIV1_a} = k_{MIV_a} \mathrm{MIV1}_a dt$$

Equations for flow (*f*) of fully susceptible individuals in S and S1 for age group *a* into E_{1_a} due to infection and transitions then into the exposed (latent), infected/infectious, and recovered immunity state

$f_{E_{1_a}} = \lambda_{a_m}(\mathrm{S}_a + \mathrm{S1}_a)dt$, with $f_{SE_{1_a}} = \lambda_{a_m}\mathrm{S}_a dt$ and $f_{S1E_{1_a}} = \lambda_{a_m}\mathrm{S1}_a dt$ for the components

$$f_{E_{2_a}} = \delta \mathrm{E}_{1_a} dt$$
$$f_{I_{1_a}} = \delta \mathrm{E}_{2_a} dt$$
$$f_{I_{2_a}} = \gamma \mathrm{I}_{1_a} dt$$
$$f_{R_a} = \gamma \mathrm{I}_{2_a} dt$$

Equations for flow (*f*) of fully susceptible individuals in S and S1 and maternally immune infants in MIR and MIV for age group *a* according to receipt of a vaccine dose (i.e., numbers of individuals by sex who receive RI1, RI2, pSIA, or ORI doses). Since RI doses occur as individuals age from into the target age group, the model uses the appropriate flows for aging

(i.e., Ag_{IS_a} for age group *a*). The model subsequently uses these flows combined with vaccine take rates to then determine flows of individuals into the appropriate vaccine immunity states (VRI1, VRI2, VPSIA, VOR) or into S1 (for those that do not "take") and also the flows of maternally immune individuals (MIR and MIV) who receive doses of vaccine and thus move into the corresponding MIR1 or MIV1 immunity states. The model tracks individuals that received one or more vaccine doses and did not "take" (i.e., no seroconversion) using the S1, MIR1, and MIV1 states, but does not distinguish individuals according to the number of non-taking doses beyond ≥1.

sd second dose toggle (= 0 for the first RI dose, 1 if vaccine dose represents and RI dose after the first dose)

pd prior dose toggle (= 0 if dose given to any individual without respect to prior dose, 1 if dose given only to individuals who did not receive a prior dose (i.e., individuals in S, MIR, or MIV immunity states, but not in S1, MIR1, or MIV1)

sprelcov relative vaccination coverage in the subpopulation (if included) for age group *a* (note, in the equations below, *sprelcov* =1 for the general population)

f_{new} fraction of the population for which a later-than-first scheduled RI dose reaches individuals who missed the first scheduled RI dose (i.e., 1- f_{new} represents the fraction of individuals who received but did not "take" the first dose who receive this later-than-first dose as such)

$covRI_{a+1}$ RI vaccination coverage (i.e., fraction of the population receiving an RI dose upon aging from age group *a* into age group *a+1*) using the country, age, and year-specific values [1]

f_{SIA_a} fraction of age group *a* in the SIA target age range (same concept used for both pSIA and oSIA)

nd_{SIA} number of days for the SIA (same concept used for both pSIA and oSIA)

$covSIA_a$ pSIA vaccination coverage (i.e., fraction of the target population receiving a pSIA dose in target age group *a*)

$covORI_a$ oSIA vaccination coverage (i.e., fraction of the target population receiving an ORI dose in target age group *a*)

$$fVRI1_{S_a} = Ag_{S_a} covRI_{a+1}(1 - sd)sprelcov$$
$$fVRI_{MIR_a} = Ag_{MIR_a} covRI_{a+1}\big((1 - sd) + f_{new} sd\big)sprelcov$$
$$fVRI_{MIV_a} = Ag_{MIV_a} covRI_{a+1}\big((1 - sd) + f_{new} sd\big)sprelcov$$
$$fVRI2_{S_a} = Ag_{S_a} covRI_{a+1}\ sd\ f_{new} sprelcov$$
$$fVRI2_{S1_a} = Ag_{S1_a} covRI_{a+1}\ sd\ (1 - f_{new})(1 - pd)sprelcov$$
$$fVRI_{MIR1_a} = Ag_{MIR1_a} covRI_{a+1}(1 - f_{new} sd)(1 - pd)sprelcov$$
$$fVRI_{MIV1_a} = Ag_{MIV1_a} covRI_{a+1}(1 - f_{new} sd)(1 - pd)sprelcov$$
$$fVSIA_{S_a} = -\frac{Ln(1-covSIA_a)}{t_{SIA}} f_{SIA_a} S_a sprelcov\ dt$$
$$fVSIA_{MIR_a} = -\frac{Ln(1-covSIA_a)}{t_{SIA}} f_{SIA_a} \mathrm{MIR}_a sprelcov\ dt$$
$$fVSIA_{MIV_a} = -\frac{Ln(1-covSIA_a)}{t_{SIA}} f_{SIA_a} \mathrm{MIV}_a sprelcov\ dt$$
$$fVSIA_{S1_a} = -\frac{Ln(1-covSIA_a)}{t_{SIA}} f_{SIA_a} (\mathrm{S1}_a - \mathrm{PS1}_{\mathrm{SIA}_a}) sprelcov\ dt$$
$$fORI_{S_a} = -\frac{Ln(1-covORI_a)}{t_{SIA}} f_{SIA_a} S_a sprelcov\ dt$$

$$fORI_{MIR_a} = -\frac{Ln(1-covORI_a)}{t_{SIA}} f_{SIA_a} \mathrm{MIR}_a sprelcov\ dt$$
$$fORI_{MIV_a} = -\frac{Ln(1-covORI_a)}{t_{SIA}} f_{SIA_a} \mathrm{MIV}_a sprelcov\ dt$$
$$fORI_{S1_a} = -\frac{Ln(1-covORI_a)}{t_{SIA}} f_{SIA_a} (\mathrm{S1}_a - \mathrm{OS1}_{\mathrm{SIA}_a})(1-pd) sprelcov\ dt$$

Equations for pregnancy related co-flows (f) used to model immunity states of fetuses and to track adverse outcomes related to infections during pregnancy

Equations for new pregnancies (*Preg*) for time step depend on the immunity state and relative fertility of the WCBA in age group *a*. The model uses national fertility data for each of 7 age groups of WCBA: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, and 45-49 years. The model thus implicitly ignores any pregnancies that involve mothers <15 years old or >49 years old. If the model includes both a general population and an under-vaccinated subpopulation, then new pregnancies (and births) are attributed proportional to their relative fractions (not shown).

n_{preg} total number of pregnancies corresponding to the number of births that occur 280 days later

f_{fert_a} fraction of the total number of births in the year that starts 280 days later attributable to WCBA in age group *a*

$$Preg_{S_a} = n_{preg}\, f_{fert_a} (S_a + S1_a)/N_a dt$$
$$Preg_{I0to20_a} = n_{preg}\, f_{fert_a} (E_{1_a} + E_{2_a} + I_{1_a} + I_{2_a})/N_a dt$$
$$Preg_{R_a} = n_{preg}\, f_{fert_a} R_a/N_a dt$$
$$Preg_{V_a} = n_{preg}\, f_{fert_a} (VRI1_a + VRI2_a + VSIA_a + VORI_a)/N_a dt$$

Equations for flow (*f*) of pregnancies of women in S and S1 (i.e., PIS = PS) in pregnancy stage *j* (see Figure 2) due to infection during pregnancy

$$f_{inPregS_j} = \lambda_{a_m} PS_j\ dt$$

Total flow of new rubella infections in pregnancy (RIP) of susceptible WCBA that occur 0 to <20 weeks since LMP for the time step (i.e., new pregnancies of infected women at the time of becoming pregnant for all age groups of WCBA plus new infections of already pregnant fully susceptible women <20 weeks since LMP)

$$f_{RIP} = \sum Preg_{I0to20_a} + f_{PS_1}$$

Equation for fetal aging (*FAg*) out of pregnancy immunity state (PIS) for stage j per time step (j=1, 2, or 3, corresponding to 0to<20wk, 20to<39wk, wk 39, see Figure 2), which equals aging into the next pregnancy immunity state for j=1,2 or birth upon aging out of j=3)

$$FAg_{PIS_j} = \zeta_j PIS_j dt$$

Equation for excess losses of pregnancies due to the maternal infection with virus *v* early in the pregnancy (all assumed to occur at the point of the pregnancy aging from stage j=1 (i.e., 0 to 20 weeks) into stage j=2 (i.e., 20 to 39 weeks) for virus *v*

$$f_{induced_v} = FAg_{PI_{0to20_v}} f_{indterm_v}$$

$f_{spont_v} = FAg_{PI_{0to20_v}} \mathrm{f}_{sponterm_v}$
$f_{stillborn_v} = FAg_{PI_{0to20_v}} \mathrm{f}_{fetdeath_v}$
$f_{infantmort_v} = FAg_{PI_{0to20_v}} \mathrm{f}_{infmort_v}$
Estimated CRS cases as a fraction of all rubella infections of susceptible WCBA in 0 to 20 weeks since LMP
$f_{CRScase} = FAg_{PI_{0to20}} \mathrm{f}_{CRS}$

Flow of excess pregnancy losses for j=1
$f_{loss_1} = FAg_{PI\,0to20_1}(f_{indterm} + f_{sponterm} + f_{fetdeath} + f_{infmort})$

Equation to correct excess losses of pregnancies (based on births of surviving infants) to adjust for infant mortality and other pregnancy losses
$Loss_v = \frac{f_{induced_v} + f_{spont_v} + f_{stillborn_v} + f_{infantmort_v}}{1 - pregloss(t)}$

Equations used for updating immunity state values for each age group a at each time step using the flow equations

Immunity states

Note: for *a*=1, $Ag_{IS_{a-1}}$=0, B_{IS_a}>0
$\Delta \mathrm{E}1_a = Ag_{E1_{a-1}} + f_{E1_a} - f_{E2_a} - Ag_{E1_a} - D_{E1_a}$
$\Delta \mathrm{E}2_a = Ag_{E2_{a-1}} + f_{E2_a} - f_{I1_a} - Ag_{E2_a} - D_{E2_a}$
$\Delta \mathrm{I}1_a = B_{I1_a} + Ag_{I1_{a-1}} + f_{I1_a} - f_{I2_a} - Ag_{I1_a} - D_{I1_a}$
$\Delta \mathrm{I}2_a = Ag_{I2_{a-1}} + f_{I2_a} - f_{R_a} - Ag_{I2_a} - D_{I2_a}$
$\Delta \mathrm{R}_a = B_{R_a} + Ag_{R_{a-1}} + f_{R_a} - Ag_{R_a} - D_{R_a}$

Equations involving vaccination also require consideration of vaccine take rates
tr take rate for first dose of vaccine
trsd take rate for second dose of vaccine

$\Delta \mathrm{PS1}_{\mathrm{SIA}a} = Ag_{PS1_{SIA_{a-1}}} + fVSIA_{S_a}(1 - tr) + fVSIA_{S1_a}(1 - trsd) - Ag_{PS1_{SIA_a}} - D_{PS1_{SIA_a}}$
$\Delta \mathrm{OS1}_{\mathrm{SIA}a} = Ag_{OS1_{SIA_{a-1}}} + fVORI_{S_a}(1 - tr) + fORI_{S1_a}(1 - trsd) - Ag_{OS1_{SIA_a}} - D_{OS1_{SIA_a}}$

For age groups with infants (i.e., age groups *a* = 1 to <8)
$\Delta \mathrm{MIR}_a = B_{MIR_a} + Ag_{MIR_{a-1}} - fVRI_{MIR_{a-1}} - fVSIA_{MIR_a} - fORI_{MIR_a} - Ag_{MIR_a} - W_{MIR_a}$
$\Delta \mathrm{MIV}_a = B_{MIV_a} + Ag_{MIV_{a-1}} - fVRI_{MIV_{a-1}} - fVSIA_{MIV_a} - fORI_{MIV_a} - Ag_{MIV_a} - W_{MIV_a}$
$\Delta \mathrm{MIR1}_a = Ag_{MIR1_{a-1}} + fVRI_{MIR_{a-1}} + fVSIA_{MIR_a} + fORI_{MIR_a} - Ag_{MIR1_a} - W_{MIR1_a}$
$\Delta \mathrm{MIV1}_a = Ag_{MIV1_{a-1}} + fVRI_{MIV_{a-1}} + fVSIA_{MIV_a} + fORI_{MIV_a} - Ag_{MIV1_a} - W_{MIV1_a}$
$\Delta \mathrm{S}_a = B_{S_a} + Ag_{S_{a-1}} + W_{MIR_a} + W_{MIV_a} - f_{SE1_a} - fVRI1_{S_{a-1}} - fVRI2_{S_{a-1}} - fVSIA_{S_a} - fORI_{S_a} - Ag_{S_a}$

$$\Delta S1_a = Ag_{S1_{a-1}} + W_{MIR1_a} + W_{MIV1_a} - fVRI2_{S1_{a-1}}trsd + fVRI1_{S_{a-1}}(1-tr) + fVRI2_{S_{a-1}}(1-trsd) - f_{S1E_{1_a}} + (fVSIA_{S_a} + fORI_{S_a})(1-tr) - (fVSIA_{S1_a} - fORI_{S1_a})(1-trsd) - Ag_{S1_a}$$

$$\Delta VRI1_a = Ag_{VRI1_{a-1}} + fVRI1_{S_{a-1}}tr - Ag_{VRI1_a}$$

$$\Delta VRI2_a = Ag_{VRI2_{a-1}} + (fVRI2_{S_{a-1}} + fVRI2_{S1_{a-1}})trsd - Ag_{VRI2_a}$$

$$\Delta VSIA_a = Ag_{VSIA_{a-1}} + fVSIA_{S_a}tr + fVSIA_{S1_a}trsd - Ag_{VSIA_a}$$

$$\Delta VORI_a = Ag_{VORI_{a-1}} + fVORI_{S_a}tr + fVORI_{S1_a}trsd - Ag_{VORI_a}$$

For one-year olds (i.e., age group a =8)

$$\Delta S_a = Ag_{S_{a-1}} + Ag_{MIR_{a-1}} + Ag_{MIV_{a-1}} - fVRI1_{S_{a-1}} - fVRI2_{S_{a-1}} - fVRI_{MIR_{a-1}} - fVRI_{MIV_{a-1}} - fVSIA_{S_a} - fORI_{S_a} - f_{SE_{1_a}} - Ag_{S_a} - D_{S_a}$$

$$\Delta S1_a = Ag_{S1_{a-1}} + Ag_{MIR1_{a-1}} + Ag_{MIV1_{a-1}} + (fVRI1_{S_{a-1}} + fVRI_{MIR_{a-1}} + fVRI_{MIV_{a-1}})(1-tr) + fVRI2_{S_{a-1}}(1-trsd) - (fVRI2_{S1_{a-1}} + fVRI_{MIR1_{a-1}} + fVRI_{MIV1_{a-1}})trsd - f_{S1E_{1_a}} + (fVSIA_{S_a} + fORI_{S_a})(1-tr) - (fVSIA_{S1_a} + fORI_{S1_a})trsd - Ag_{S1_a} - D_{S1_a}$$

$$\Delta VRI1_a = Ag_{VRI1_{a-1}} + (fVRI1_{S_{a-1}} + fVRI_{MIR_{a-1}} + fVRI_{MIV_{a-1}})tr - Ag_{VRI1_a} - D_{VRI1_a}$$

$$\Delta VRI2_a = Ag_{VRI2_{a-1}} + (fVRI2_{S_{a-1}} + fVRI2_{S1_{a-1}} + fVRI_{MIR1_{a-1}} + fVRI_{MIV1_{a-1}})trsd - Ag_{VRI2_a} - D_{VRI2_a}$$

$$\Delta VSIA_a = Ag_{VSIA_{a-1}} + fVSIA_{S_a}tr + fVSIA_{S1_a}trsd - Ag_{VSIA_a} - D_{VSIA_a}$$

$$\Delta VORI_a = Ag_{VORI_{a-1}} + fVORI_{S_a}tr + fVORI_{S1_a}trsd - Ag_{VORI_a} - D_{VORI_a}$$

For individuals over one year old (i.e., age groups a >8)

$$\Delta S_a = Ag_{S_{a-1}} - fVRI1_{S_{a-1}} - fVRI2_{S_{a-1}} - fVSIA_{S_a} - fORI_{S_a} - f_{SE_{1_a}} - Ag_{S_a} - D_{S_a}$$

$$\Delta S1_a = Ag_{S1_{a-1}} + fVRI1_{S_{a-1}}(1-tr) + fVRI2_{S_{a-1}}(1-trsd) - fVRI2_{S1_{a-1}}trsd - f_{S1E_{1_a}} + (fVSIA_{S_a} + fORI_{S_a})(1-tr) - (fVSIA_{S1_a} + fORI_{S1_a})trsd - Ag_{S1_a} - D_{S1_a}$$

$$\Delta VRI1_a = Ag_{VRI1_{a-1}} + fVRI1_{S_{a-1}}tr - Ag_{VRI1_a} - D_{VRI1_a}$$

$$\Delta VRI2_a = Ag_{VRI2_{a-1}} + (fVRI2_{S_{a-1}} + fVRI2_{S1_{a-1}})trsd - Ag_{VRI2_a} - D_{VRI2_a}$$

$$\Delta VSIA_a = Ag_{VSIA_{a-1}} + fVSIA_{S_a}tr + fVSIA_{S1_a}trsd - Ag_{VSIA_a} - D_{VSIA_a}$$

$$\Delta VORI_a = Ag_{VORI_{a-1}} + fVORI_{S_a}tr + fVORI_{S1_a}trsd - Ag_{VORI_a} - D_{VORI_a}$$

Pregnancies and fetal states

The model maintains the stocks for pregnancy immunity states such that the number of pregnancies aging out of stage j=3 equals the number of births of surviving infants. The model sets the initial size of the PIS stocks by assuming fully susceptible WCBA and assigning all pregnancies to PS with the number of births attributable to each WCBA age group divided by ζ_j.

$$\Delta PS_{1_a} = Preg_{S_a} - f_{inPregS_{1_a}} - FAg_{PS_{1_a}}$$

$$\Delta PI_{0to20_{1_a}} = Preg_{I0to20_a} + f_{inPregS_{1_a}} - FAg_{PI_{0to20_{1_a}}}$$

$\Delta PI_{20plus_{1_a}} = 0$ (for stage j=1, no flow into PI_{20plus})

$$\Delta PR_{1_a} = Preg_{R_a} - FAg_{PR_{1_a}}$$

$$\Delta \mathrm{PV}_{1_a} = Preg_{V_a} - FAg_{PV_{1_a}}$$
$$\mathrm{PTot}_{2_a} = \mathrm{PS}_{2_a} + \mathrm{PR}_{2_a} + \mathrm{PV}_{2_a}$$
$$\Delta \mathrm{PS}_{2_a} = FAg_{PS_{1_a}} - f_{inPregS_{2_a}} - FAg_{PS_{2_a}} + f_{loss_{1_a}}(\mathrm{PS}_{2_a}/\mathrm{PTot}_{2_a})$$
$$\Delta \mathrm{PI}_{0\mathrm{to}20_{2_a}} = (FAg_{PI_{0to20_{1_a}}} - f_{loss_{1_a}})f_{FI1} - FAg_{PI_{0to20_{2_a}}}$$
$$\Delta \mathrm{PI}_{20\mathrm{plus}_{2_a}} = f_{inPregS_{2_a}} f_{FI2} - FAg_{PI_{20plus_{2_a}}}$$
$$\Delta \mathrm{PR}_{2_a} = FAg_{PR_{1_a}} - (FAg_{PI_{0to20_{1_a}}} - f_{loss_{1_a}})(1 - f_{FI1}) + f_{inPregS_{2_a}}(1 - f_{FI2}) - FAg_{PR_{2_a}} + f_{loss_{1_a}}(\mathrm{PR}_{2_a}/\mathrm{PTot}_{2_a})$$
$$\Delta \mathrm{PV}_2 = FAg_{PV_{1_a}} - FAg_{PV_{2_a}} + f_{loss_{1_a}}(\mathrm{PV}_{2_a}/\mathrm{PTot}_{2_a})$$
$$\Delta \mathrm{PS}_3 = FAg_{PS_{2_a}} - f_{inPregS_{3_a}} f_{FI3} - FAg_{PS_{3_a}}$$
$$\Delta \mathrm{PI}_{0\mathrm{to}20_3} = FAg_{PI_{0to20_{2_a}}} - FAg_{PI_{0to20_{3_a}}}$$
$$\Delta \mathrm{PI}_{20\mathrm{plus}_3} = FAg_{PI_{20plus_{2_a}}} + f_{inPregS_{3_a}} f_{FI3} - FAg_{PI_{20plus_{3_a}}}$$
$$\Delta \mathrm{PR}_3 = FAg_{PR_{2_a}} - FAg_{PR_{3_a}}$$
$$\Delta \mathrm{PV}_3 = FAg_{PV_{2_a}} - FAg_{PV_{3_a}}$$

Summing over all 7 fertility age groups (a=f1-f7), yields the values for FIS for each time step, separately for M and R).

$$\mathrm{FS}_M = \sum_{a=f1}^{f7} \mathrm{PS}_{3_{\mathrm{a,M}}}$$
$$\mathrm{FI}_M = \sum_{a=f1}^{f7} \mathrm{PI}_{20\mathrm{plus}_{3_{\mathrm{a,M}}}}$$
$$\mathrm{FR}_M = 0$$
$$\mathrm{FMIR}_M = \sum_{a=f1}^{f7} (\mathrm{PR}_{3_{\mathrm{a,M}}} + \mathrm{PI}_{0\mathrm{to}20_{3_{\mathrm{a,M}}}})$$
$$\mathrm{FMIV}_M = \sum_{a=f1}^{f7} \mathrm{PV}_{3_{\mathrm{a,M}}}$$
$$\mathrm{FS}_R = \sum_{a=f1}^{f7} \mathrm{PS}_{3_{\mathrm{a,R}}}$$
$$\mathrm{FI}_R = \sum_{a=f1}^{f7} (\mathrm{PI}_{0\mathrm{to}20_{3_{\mathrm{a,R}}}} \mathrm{f}_{CRI_{0to20}} + \mathrm{PI}_{20\mathrm{plus}_{3_{\mathrm{a,R}}}} \mathrm{f}_{CRI_{20plus}})$$
$$\mathrm{FR}_R = \sum_{a=f1}^{f7} (\mathrm{PI}_{0\mathrm{to}20_{3_{\mathrm{a,R}}}}(1 - \mathrm{f}_{CRI_{0to20}}) + \mathrm{PI}_{20\mathrm{plus}_{3_{\mathrm{a,R}}}}(1 - \mathrm{f}_{CRI_{20plus}}))$$

$$\mathrm{FMIR}_R = \sum_{a=f1}^{f7} \mathrm{PR}_{3_a,\mathrm{R}}$$

$$\mathrm{FMIV}_R = \sum_{a=f1}^{f7} \mathrm{PV}_{3_a,\mathrm{R}}$$

Thresholds used for die out, importations, and outbreak response dynamics

$EPI_{a,v}$(t) effective proportion infectious in age group a for virus v
$EPIM_{m,v}$(t) effective proportion infectious in mixing age group a_m for virus v
EPI^* effective proportion infectious below which we assume 0 force-of-infection (i.e., the transmission threshold)

If $EPI_{a,v}$(t) < EPI* then the model sets $\lambda_{a,v}(t)$ and transmission can die out
If $EPI_{a,v}$(t) > EPI* then the model sets $\lambda_{a,v}(t)$ = EPI*, which implies frequent importations
For countries maintaining or near elimination, if the number of new infections in the current time step minus the number in the prior time step divided by the number of infections in the prior time step exceeds the outbreak threshold (assumed to be 0.001), then this triggers an oSIA that begins 30 days later if the model assumes that the country performs ORI. For countries maintaining elimination, a single case triggers an ORI activity. For the retrospective analysis, we assume that the model captures all off the SIAs (preventive (pSIAs) and ORI (oSIAs)) as reported SIAs.[1] The model includes the capability to detect outbreaks in endemic countries for potential use in triggering ORI for prospective modeling, but we do not use this for the retrospective analysis.

Expressions for characterizing force of infection and population immunity considering age and subpopulation heterogeneity in mixing

Using expressions similar to those described elsewhere for a dynamic model for poliovirus transmission,[2-4] we develop the concepts required to account for age-heterogeneous mixing and heterogeneous mixing between subpopulations for the measles and rubella dynamic model.

To model age-heterogeneous mixing in a single spatially homogeneous population we define the following notation:
n_{a_m}= number of mixing age groups (the model includes 35 age groups, but we assume that preferential mixing occurs within 3 mixing age groups: 0-<5 yrs, 5-<15 yrs, ≥15 yrs)
S_{a_m}= number of susceptible people in a_m
I_{a_m}= number of infected individuals in a_m
N_{a_m}= total number of people in a_m
$f_{N_{a_m}}$= proportion of all people in a_m (N_{a_m}/N)
$f_{S_{a_m}}$= proportion susceptible in a_m (S_{a_m}/N_{a_m})
$f_{I_{a_m}}$= proportion infectious in a_m (I_{a_m}/N_{a_m})
RC_{a_m} = relative number of contacts for individuals in a_m

The force-of-infection for mixing age group w equals:

$$\lambda_w = \beta \sum_{x=1}^{n_{a_m}} M(w,x) f_{I_x}$$

where M(w,x) is the normalized preferential mixing matrix that describes the relative contact rate for individuals in mixing age group w to individuals in mixing age group *x*:[5, 6]

$$M(w,x) = \kappa(w) 1_{\{w=x\}} + \frac{\big(1-\kappa(w)\big)\big(1-\kappa(x)\big) RC_x N_x}{\sum_{c=1}^{n_{a_m}} N_c RC_c \big(1-\kappa(c)\big)}$$

where κ(w) is the proportion of contacts by individuals in mixing age group *w* reserved for other individuals in mixing age group *w*, and the indicator function $1_{\{condition\}}$=1 if condition is true, and 0 otherwise.

Given that N_{a_m} depends on time, we recalculate the mixing matrix at each time step. If κ does not depend on the mixing age group (i.e., the same preferential mixing occurs for each mixing age group) as we assume in this model, then κ(w) = κ and $M(w,x) = \kappa 1_{\{w=x\}} + (1-\kappa) RC_x f_{N_x}$.

In a homogeneous mixing model, each infection generates on average $R_n = R_0 \times f_{S_{a_m}}$ secondary infections, where R_n is the net reproductive number. By definition, R_0 equals R_n if the entire population is fully susceptible (i.e., $f_{S_{a_m}}$=1). Similarly, for a model with age-heterogeneous mixing, we define the effective susceptibility matrix as:
$PS(w,x) = M(w,x)\, f_{S_w}$

PS(w,x) represents a measure of the susceptibility of mixing age group *w* to mixing age group *x,* taking into account the immunity of mixing age group *w* and the relative contact rates from mixing age group *w* to mixing age group *x*. If κ does not depend on the mixing age group, then the matrix for $PS(w,x) = \kappa 1_{\{w=x\}} + (1-\kappa) f_{N_x} f_{S_w}$.

Analogous to homogeneous mixing, the net reproductive matrix for age-heterogeneous mixing equals: $R_n(w,x) = R_0 \times PS(w,x) = R_0 \times M(w,x) \times f_{S_w}$.

When the entire population is fully susceptible (i.e., f_{S_w} =1 for all *w*), then $R_n(w,x)$ represents the next-generation matrix and the dominant eigenvalue of this matrix equals R_0.[7] By analogy, we define:
PS_A = dominant eigenvalues of PS(w,x) = age-mixing-adjusted susceptible proportion in the population
$EIP_A = 1 - PS_A$ = age-mixing-adjusted effective immune proportion (i.e., the effective population immunity)
If PS_A stays below its threshold PS^* (i.e., $PS^* = 1/R_0$), or equivalently if EIP_A stays above its threshold EIP^* (i.e., $EIP^* = 1 - 1/R_0$), then the infection will eventually die out.

To extend the age mixing-adjusted PS_A and EIP_A to also include mixing between subpopulations, we define:
m = number of conceptual mixing subpopulations of size N/m, where N is the total size of all *m* subpopulations

nsp = number of modeled subpopulations with potentially different levels of immunization = 2
sp = 0 = index of the under-vaccinated subpopulation, with size N/m
sp = 1 = index of the general subpopulation, with size N×(1-1/m)
$f_{S_{a_m,sp}}$= proportion susceptible in mixing age group *a* and subpopulation *sp*
$f_{I_{a_m,sp}}$= proportion infectious in mixing age group *a* and subpopulation *sp*
p_{within} = proportion of contacts of individuals in the under-vaccinated subpopulation reserved for other individuals of the same subpopulation

The age-specific force-of-infection for the under-vaccinated subpopulation equals:

$$\lambda_{w,0} = \left(\beta \sum_{x=1}^{n_{a_m}} M(w,x) f_{I_{x,0}}\right) p_{within} + \left(\beta \sum_{x=1}^{n_{a_m}} M(w,x) f_{I_{x,1}}\right)(1 - p_{within})$$

The force-of-infection for the general subpopulation equals:(2)

$$\lambda(a,1) = \left(\beta \sum_{x=1}^{n_{a_m}} M(w,x) f_{I_{x,0}}\right)(1 - p_{within})/(m-1) + \left(\beta \sum_{x=1}^{n_{a_m}} M(w,x) f_{I_{x,1}}\right)((1 - p_{within})(m-2)/(m-1) + p_{within})$$

We build the net reproductive matrix (size nsp x na by nsp x na) for the model with two subpopulations and age-heterogeneous mixing from four components $R_{sp0,sp1}$ (size na x na each):

$$R = \begin{bmatrix} R_{00}(w,x) & R_{01}(w,x) \\ R_{10}(w,x) & R_{11}(w,x) \end{bmatrix}$$

$R_{sp0,sp1}$(w,x) represents the number of secondary infections in subpopulation 0 and mixing age group *w* resulting from 1 infection in subpopulation 1 and mixing age group *x*. Following the expressions above for the force-of-infection, we define sub-matrix $R_{sp0,sp1}$ as:

$$\begin{aligned} R_{sp0,sp1}(w,x)(t) &= R_0 \times M_{sp2}(w,x) \times f_{S_{w,sp}} \\ &\times \left(p_{within} 1_{\{sp0=sp1=0\}} + (1 - p_{within}) 1_{\{sp0=0,sp1=1\}} \right. \\ &+ \frac{(1 - p_{within})}{(m-1)} 1_{\{sp0=1,sp1=0\}} \\ &\left. + \left(p_{within} + \frac{(m-2)}{(m-1)} (1 - p_{within}) \right) 1_{\{sp0=\, sp1=1\}} \right) \end{aligned}$$

Dividing by R_0 yields the effective susceptibility matrix for the two-subpopulation model with age-heterogeneous mixing:

$$
\begin{aligned}
SP_{sp0,sp1}(w,x)(t) &= R_{sp0,sp1}(w,x)(t)/R_0 \\
&= M_{sp1}(a,b) \times \mathrm{f}_{S_{w,sp}} \\
&\times \Bigg(p_{within} 1_{\{sp0=sp1=0\}} + (1-p_{within}) 1_{\{sp0=0,sp1=1\}} \\
&+ \frac{(1-p_{within})}{(m-1)} 1_{\{sp0=1,sp1=0\}} \\
&+ \left(p_{within} + \frac{(m-2)}{(m-1)} (1-p_{within}) \right) 1_{\{sp0=\, sp1=1\}} \Bigg)
\end{aligned}
$$

Finally, the subpopulation and age-mixing adjusted measures of population susceptibility and immunity equal:
PS_{AS} = dominant eigenvalues of $PS_{sp0,sp1}(a,b)$ = subpopulation- and age-mixing-adjusted effective susceptible proportion in the population
EIP_{AS} =1-PS_{AS} = subpopulation- and age-mixing-adjusted effective immune proportion in the population
If PS_{AS} stays below the threshold $PS^*=1/R_0$, or equivalently if EIP_{AS} stays above its threshold $EIP^*=1-1/R_0$, then the infection will eventually die out.

We use the power iteration algorithm to determine the largest eigenvalue of the square ESP matrix:

1. Start with an initial, random vector $\mathbf{b_0}$ with the same length as the dimension of **A**.
2. Compute the next iteration of **b** as: $\mathbf{b_{k+1}} = \mathbf{A}\,\mathbf{b_k}/||\mathbf{A}\,\mathbf{b_k}||$, where the denominator represents the norm of the vector $\mathbf{A}\,\mathbf{b_k}$, i.e., $(\mathbf{A}\,\mathbf{b_k})^T(\mathbf{A}\,\mathbf{b_k})$.
3. Repeat step 2 for k iterations. The sequence, which results in $\mathbf{b_k}$, converges to the dominant eigenvector of **A** (unless by chance the initial vector $\mathbf{b_0}$ coincides with a non-dominant eigenvector of A, which remains highly unlikely given that we use random real numbers for $\mathbf{b_0}$).
4. Assuming that $\mathbf{b_K}$ represents a sufficiently close approximation of the dominant eigenvalue of **A**, compute the corresponding dominant eigenvalue of **A** using the Rayleigh quotient
   $\mathbf{b_K}^T\,\mathbf{A}\,\mathbf{b_K} / \mathbf{b_K}^T\,\mathbf{b_K}$.

Algorithm for fitting national inputs

We developed an algorithm to match the patterns observed in the time series incidence data. The algorithm runs the model over a large range of the inputs that we allow to vary by country (i.e., κ, R_0, amplitude of seasonality, and the number of years used to initially equilibrate the model). Figure A1 shows the ranges and the increments that we used for the inputs, with the rubella-related inputs conditional on the measles fit (i.e., same κ and lower R_0 with initial R_0 based on available serology data,[8] and relative values used for global polio modeling, which depend on World Bank Income Level[9, 10]). The evaluation algorithm includes two major steps. First, the algorithm finds the set of local minima and maxima in both sets of data, and normalizes their heights against the global maximum of the set. We consider a point a peak if its value exceeds at least 1,000 cases more than either of its neighbors, and a trough its value falls 1,000 below either

of its neighbors (with the threshold of 1,000 selected such that small changes in reporting coverage do not appear as significant). Figure A1 shows sample code for the peak detection algorithm (Algorithm 1). Once we find the peaks and troughs, we used the distance function in Algorithm 2 to assess fit based on the locations and relative heights of the peaks. Algorithm 2 indicates peaks using positive heights and troughs using negative heights, with distance assessed between the peak/trough. For each peak or trough found in the model data, if the same feature appears in the same place in the time series of incidence data, the distance measure increases by the difference between the relative heights of the peaks. If a peak in the model data occurs in the same location as a trough in the time series incidence data or vice versa, the distance increases by 2 plus the relative distance between the peak and the trough (i.e., the fit incurs a penalty). If a peak or trough in either data set occurs in the same location as a flat slope, the algorithm adds a penalty of 1 to the distance. The fit(s) with the minimum distance then provide the starting point for further analysis and consideration of missing data (e.g., incomplete time series of incidence data, potentially missing SIAs or outbreak response activities) or other data (e.g., results of serological studies). We fit the models without the presence of an under-vaccinated subpopulation, because prior to the adoption of immunization the entire population remains unvaccinated. We then run the model with the heterogeneous subpopulation as needed to consider the implications of such groups and the impacts of importations.

For countries with available serological data,[8] we checked the model fit against the serological evidence. Due to the non-standardized reporting of serological data (i.e., different age groups and target populations at different snap shots in time) this required manual checks using weighted averages for serological data that corresponded to age categories that spanned different model age categories. Uncertainty about the quality of some of the estimates of reported coverage of SIAs led us to revise some of the coverage estimates downward to better reflect the incidence and serological data. The fitting process required judgment, particularly for countries with limited and low-quality data, and while other model inputs may provide an equally good or better fit, we recognize that the uncertainty about the quality of the data remains a significant limitation. However, we ultimately seek to identify a model fit that provides behavior consistent with all of the available historical evidence to support prospective analyses, for which we will use the virus-specific and country-specific inputs (that do not vary with time) estimated using during the retrospective analysis to explore the health and economic outcomes of different immunization inputs over time associated with different policies.

Figure A1: Overview of process used to identify national inputs consistent with the reported time series of incidence

Algorithm 1 Peak Detection

Inputs: A set of time series data, $A = \{(0, a_0), ..., (n-1, a_{n-1})\}$, which does not necessarily contain data for every time index. The maximum value of a point in A, $a_{\max}$.
Outputs: A set of points, $PEAK$, with peaks normalized onto $(0, 1]$ and troughs on $[-1, 0)$.

function PEAKDETECT($A, a_{\max}$):
  $PEAK \leftarrow \emptyset$ ▷ $PEAK$ begins as an empty set
  for $i \leftarrow 1$ to $n-2$ **do** ▷ iterate through all interior points
    if $i-1, i, i+1$ are indices in A **then** ▷ if 3 adjacent points exist
      if $a_i > a_{i+1} + 1000$ and $a_i > a_{i-1} + 1000$ **then**
        Add $\left(i, \frac{a_i}{a_{\max}}\right)$ to $PEAK$ ▷ if a_i is a maximum, add it to $PEAK$
      else if $a_i < a_{i+1} - 1000$ and $a_i < a_{i-1} - 1000$ **then**
        Add $\left(i, -1 + \frac{a_i}{a_{\max}}\right)$ to $PEAK$ ▷ if a_i is a minimum, add it to $PEAK$
      end if
    end if
  end for
return $PEAK$
end function

Algorithm 2 Distance Evaluation

Inputs: Two sets of normalized peaks and troughs, $A = \{(t_0, a_{t_0}), ..., (t_{n-1}, a_{t_{n-1}})\}$ and $B = \{(t_0, b_{t_0}), ..., (t_{n-1}, b_{t_{n-1}})\}$. Peaks are represented with positive values of a and b, while troughs are represented by negative values.
Outputs: A numerical distance between the sets, d.

function DISTANCE(A, B)
  $d \leftarrow 0$ ▷ Distance starts at 0, and is added to
  for $t \leftarrow 0$ to t_n **do**
    if $(t, c) \in A$ and $(t, d) \in B$ **then** ▷ Peaks and troughs in the same location
      if $c \cdot d < 0$ **then** ▷ A peak opposite a trough
        $d \leftarrow d + 2 + |c - d|$ ▷ Distance increases a lot for peak opposite trough
      else ▷ Two peaks in the same location
        $d \leftarrow d + |c - d|$ ▷ Distance increase depends on relative heights
      end if
    else if $(t, c) \in A$ or $(t, d) \in B$ **then** ▷ Features not present in one set
      $d \leftarrow d + 1$
    end if
  end for
return d
end function

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