Modeling strategies to increase population immunity and prevent poliovirus transmission in the high-risk area of northwest Nigeria

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Expressions for population immunity

Thompson et al. (2013)[17] provide expressions for the effective susceptible proportion (ESP) and the effective immune proportion (EIP) in the homogeneous mixing model with partial infectibility by weighing each individuals in each immunity state by their (potential) relative contribution to fecal-oral and oropharyngeal transmission (i.e., the product or relative susceptibility, relative infectiousness, and relative duration of infectiousness compared to fully susceptible individuals). We extend the concept to account for age-heterogeneous mixing and heterogeneous mixing between subpopulations.

We start with the case of age-heterogeneous mixing in a single spatially homogeneous population, which corresponds to the model for the analyses in this paper. We first define the following notation [6] (Duintjer Tebbens RJ, Kalkowka DA, Wassilak SGF, et al, in preparation) for further detail on these and their use in the model):
ni = number of immunity states (including recent and historic states); i=0 represents the fully susceptible state
na = number of mixing age groups (the model includes 8 age groups, but we assume that preferential mixing occurs only between 3 mixing age groups)
ns = number of infection stages (only the infectious (i.e., non-latent) stages matter here)
ne = number of transmission modes (i.e., fecal-oral and oropharyngeal)
R_0 = overall basic reproduction number (may vary over time)
μ = mortality rate, averaged over all age groups
S(a,i) = number of people in mixing age group *a* and immunity state *i* (i.e., this excludes LPV-infected people)
I(a,i,e,s) = individual in mixing age group *a* from immunity state *i* in infection stage *s* for transmission mode *e*
N(a) = total number of people in mixing age group *a*
n(a) = proportion of all people in mixing age group *a*
p(e) = proportion of transmissions via transmission mode *e*
σ(i) = relative susceptibility of immunity state *i*
γ(i,e) = duration of infectiousness for immunity state *i* with respect to transmission mode *e*
π(i,e,s) = relative infectiousness with respect to transmission mode *e* of an individual from immunity state *i* in infection stage *s* (i.e., equals 0 for the latent stages of infection)
$\pi(i,e) = \sum_{s=1}^{ns} \pi(i,e,s)$ = relative infectiousness with respect to transmission mode *e* of an individual from immunity state *i*
$ESP(a) = (\frac{1}{N(a)}) \sum_{i=1}^{ni} \sigma(i) \sum_{e=1}^{ne} \sum_{s=1}^{ns} p(e)S(a,i)\pi(i,e)\gamma(i,e)/\gamma(o,e)$ = effective susceptible proportion in mixing age group *a*
$EPI(a,e) = \sum_{i=1}^{ni} \sum_{s=1}^{ns} I(a,i,e,s)\pi(i,e,s)/N(a)$ = effective proportion infectious in mixing age group *a* with respect to excretion mode *e*

The force-of-infection to mixing age group *a* equals [6] (Duintjer Tebbens RJ, Kalkowka DA, Wassilak SGF, et al, in preparation):

$$\lambda(a) = \sum_{e=1}^{ne} (1/\gamma(0,\mathrm{e}) + \mu) R_0 \sum_{b=1}^{na} M(a,b) EPI(b,e)$$

Where M(a,b) is the normalized preferential mixing matrix that describes the relative contact rate from individuals in mixing age group *a* to individuals in mixing age group *a* [18,19]:

$$M(a,b) = \kappa(a) 1_{\{a=b\}} + \frac{\big(1-\kappa(a)\big)\big(1-\kappa(b)\big)N(b)}{\sum_{c=0}^{n} N(c)\big(1-\kappa(c)\big)}$$

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

Given that N(a) depends on time, we recalculate the mixing matrix at each time step. If κ does not depend on the mixing age group (as in most uses of the model, [6] (Duintjer Tebbens RJ, Kalkowka DA, Wassilak SGF, et al, in preparation) including the analyses from this paper), then κ(a) = κ and $M(a,b) = \kappa 1_{\{a=b\}} + (1-\kappa)n(b)$.

The term $(1/\gamma(0,\mathrm{e}) + \mu)$ represents the average duration of infection by excretion mode *e* for a typical fully susceptible individuals, taking into account the mortality rate for a typical fully susceptible individual. The duration of infectiousness remains much shorter than the mortality rate of any mixing age groups used in the model, and therefore small changes in mortality exert negligible impact of the force-of-infection. Therefore, using the average mortality rate instead of the age-specific rate and also ignoring the effect of multiple infection stages subject to the same background mortality rate on the average duration of infectiousness [20] leads to negligible error. In a homogeneous mixing model, each infection generates on average $R_{net}=R_0 \times ESP$ secondary infections, where R_{net} is the net reproductive number. By definition, R_0 equals R_{net} if the entire population is fully susceptible (i.e., ESP=1). Similarly, for a model with age-heterogeneous mixing, we define the effective susceptibility matrix as:

$ESP(a,b) = M(a,b) \times ESP(a)$

ESP(a,b) represents a measure of how susceptible mixing age group *a* is to mixing age group *b*, taking into account the immunity profile of mixing age group *a* and the corresponding inherent potential to contribute to transmission, as well as the relative contact rates from mixing age group *a* to mixing age group *b*. If κ does not depend on the mixing age group, then $ESP(a,b) = (\kappa 1_{\{a=b\}} + (1-\kappa)n(b)) \times ESP(a)$.

Analogous to homogeneous mixing, the net reproductive matrix for age-heterogeneous mixing equals:

$R_{net}(a,b) = R_0 \times ESP(a,b) = R_0 \times M(a,b) \times ESP(a)$

When the entire population is fully susceptible (i.e., ESP(a)=1 for all *a*), then $R_{net}(a,b)$ represents a simplified next-generation matrix (NGM), and the dominant (i.e., largest) eigenvalue of this matrix equals R_0.[21] The simplification occurs because it does not account for the effect of mortality on the average duration of infectiousness in which infection involves multiple latent

and infectious stages,[20,21] but the effect remains very small because without exception the duration of infectiousness remains much shorter than the mortality rate of any mixing age groups used in the model.

By analogy, we define:
ESPM = dominant eigenvalues of ESP(a,b) = age-mixing-adjusted effective susceptible proportion in the population
EIPM =1-ESPM = age-mixing-adjusted effective immune proportion
If ESPM stays below its threshold ESP^*, or equivalently if EIPM stays above its threshold EIP^*, then the infection will eventually die out, where:
$ESP^* = 1/R_0$
$EIP^* = 1- 1/R_0$

To extend the mixing-adjusted ESP and EIP to also include mixing between subpopulations, as used in some situations (e.g., northern India, NW Nigeria, and the Netherlands [6] (Duintjer Tebbens RJ, Kalkowka DA, Wassilak SGF, et al, in preparation)), we define:
nsp = number of modeled subpopulations = 2
m = number of conceptual subpopulations of size N/m, where N is the total size of all *m* subpopulations
sp = 0 = index of the under-vaccinated subpopulation, with size N/m
sp = 1 = index of the general subpopulation, with size Nx(1-1/m)
ESP(a,sp) = effective susceptible proportion in mixing age group *a* and subpopulation *sp*
EPI(a,e,sp) = effective proportion infectious in mixing age group *a* and subpopulation *sp* with respect to excretion mode *e*
p_{within} = proportion of contacts of individuals in the under-vaccinated subpopulation reserved for other individuals of the same subpopulation
$M_{sp}(a,b)$= mixing matrix M(a,b) using population by age for subpopulation *sp* instead of N(a) in the expression for M(a.b)

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

$$\lambda(a,0) = \left(\sum_{e=1}^{ne}(1/\gamma(0,\mathrm{e})+\mu)R_0\sum_{b=1}^{n}M(a,b)EIP(b,e,0)\right)p_{within} + \left(\sum_{e=1}^{ne}(1/\gamma(0,\mathrm{e})+\mu)R_0\sum_{b=1}^{n}M(a,b)EIP(b,e,1)\right)(1-p_{within})$$

The force-of-infection for the general subpopulation equals:[6]

$$\lambda(a,1) = \left(\sum_{e=1}^{ne}(1/\gamma(0,\mathrm{e})+\mu)R_0\sum_{b=1}^{n}M(a,b)EIP(b,e,0)\right)(1-p_{within})/(m-1) + \left(\sum_{e=1}^{ne}(1/\gamma(0,\mathrm{e})+\mu)R_0\sum_{b=1}^{n}M(a,b)EIP(b,e,1)\right)((1-p_{within})(m-2)/(m-1)+p_{within})$$

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 blocks $R_{sp1,sp2}$ (size na x na each):

$$R = \begin{bmatrix} R_{00}(a,b) & R_{01}(a,b) \\ R_{10}(a,b) & R_{11}(a.b) \end{bmatrix}$$

Following the expressions above for the force-of-infection and rewriting it as a single expression using indicator functions, we define sub-matrix $R_{sp1,sp2}$ as:

$$\begin{aligned} R_{sp1,sp2}(a,b)(t) \\ &= R_0 \times M_{sp2}(a,b) \times ESP(a,sp1) \\ &\times \Bigg(p_{within} 1_{\{sp1=sp2=0\}} + (1-p_{within}) 1_{\{sp1=0,sp2=1\}} \\ &+ \frac{(1-p_{within})}{(m-1)} 1_{\{sp1=1,sp2=0\}} \\ &+ \left(p_{within} + \frac{(m-2)}{(m-1)} (1-p_{within}) \right) 1_{\{sp1=\, sp2=1\}} \Bigg) \end{aligned}$$

$R_{sp1,sp2}$(a,b) represents the number of secondary infections in subpopulation sp1 and mixing age group *a* resulting from 1 infection in subpopulation sp2 and mixing age group *b*. Dividing by R_0 yields the effective susceptibility matrix for the two-subpopulation model with age-heterogeneous mixing:

$$\begin{aligned} ESP_{sp1,sp2}(a,b)(t) = R_{sp1,sp2}(a,b)(t)/R_0 \\ &= M_{sp2}(a,b) \times ESP(a,sp1) \\ &\times \Bigg(p_{within} 1_{\{sp1=sp2=0\}} + (1-p_{within}) 1_{\{sp1=0,sp2=1\}} \\ &+ \frac{(1-p_{within})}{(m-1)} 1_{\{sp1=1,sp2=0\}} \\ &+ \left(p_{within} + \frac{(m-2)}{(m-1)} (1-p_{within}) \right) 1_{\{sp1=\, sp2=1\}} \Bigg) \end{aligned}$$

Finally, the subpopulation and age-mixing adjusted measures of population susceptibility and immunity equal:

ESPM = dominant eigenvalues of $ESP_{sp1,sp2}$(a,b) = subpopulation- and age-mixing-adjusted effective susceptible proportion in the population

EIPM =1-ESPM = subpopulation- and age-mixing-adjusted effective immune proportion in the population

If ESPM stays below the threshold $ESP^*=1/R_0$,or equivalently if EIPM stays above its threshold $EIP^*=1-1/R_0$, then the infection will eventually die out.

We use the power iteration algorithm[22] to determine the largest eigenvalue of the square ESP matrix.

For any given square matrix **A**, we carry the algorithm out in the following steps:

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., $(\mathbf{A}\,\mathbf{b_k})^T(\mathbf{A}\,\mathbf{b_k})$.

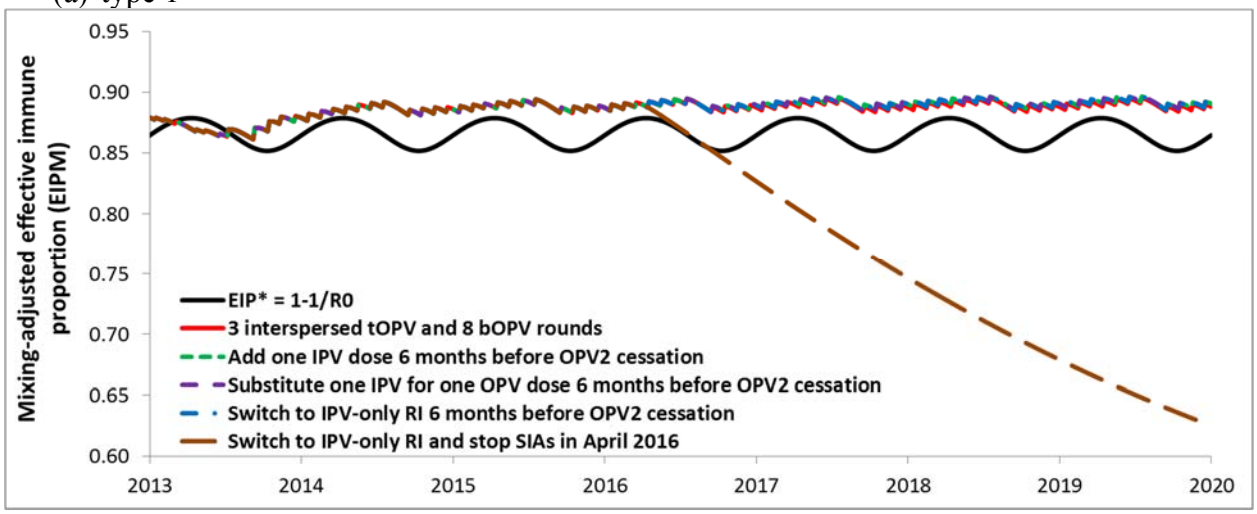
3. Repeat step 2 for some pre-specified number of iterations K. The sequence $\mathbf{b_k}$ converges to the dominant eigenvector of **A** (unless by chance the initial vector $\mathbf{b_0}$ coincides with a non-dominant eigenvector of A, which remains highly unlikely given that we use random real numbers 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
$\mathbf{b_K}^T \mathbf{A}\, \mathbf{b_K} / \mathbf{b_K}^T \mathbf{b_K}$.

Additional results

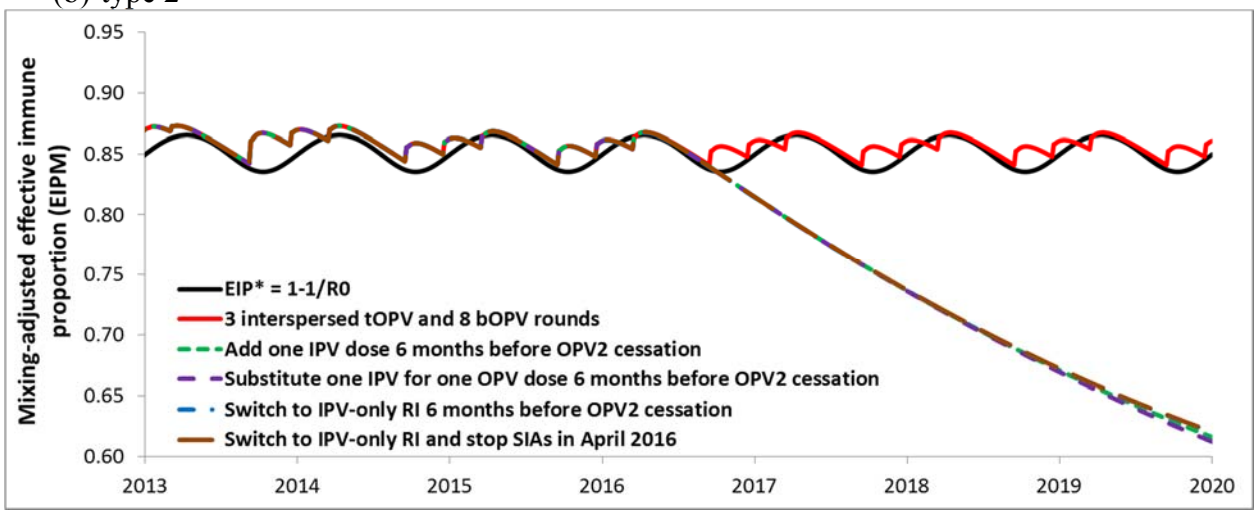
Figure A1 shows the results for all three serotypes for the scenarios shown in Figure 2d. Figure A2 shows the results for all three serotypes for the scenarios shown in Figure 3b. Figure A3 shows the results for all three serotypes for the scenarios shown in Figure 3c. Figure A4 shows EIPM of reference case compared to the threshold EIP* for both areas for all three serotypes.

Figure A1: The impact of the strategies to manage cVDPV2 risks on population immunity in northwestern Nigeria:

(a) type 1



(b) type 2



(c) type 3

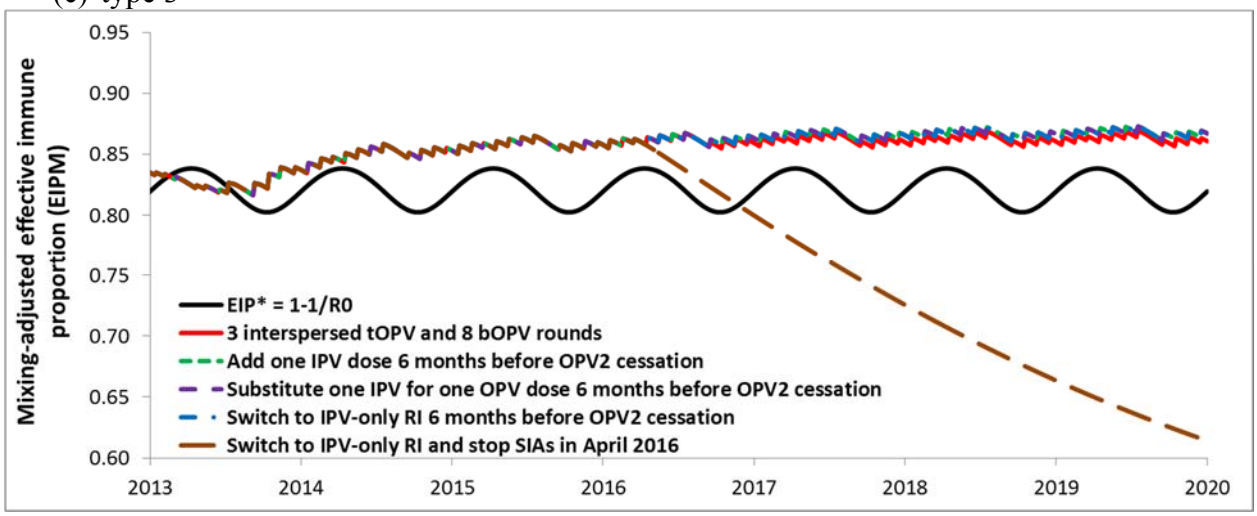
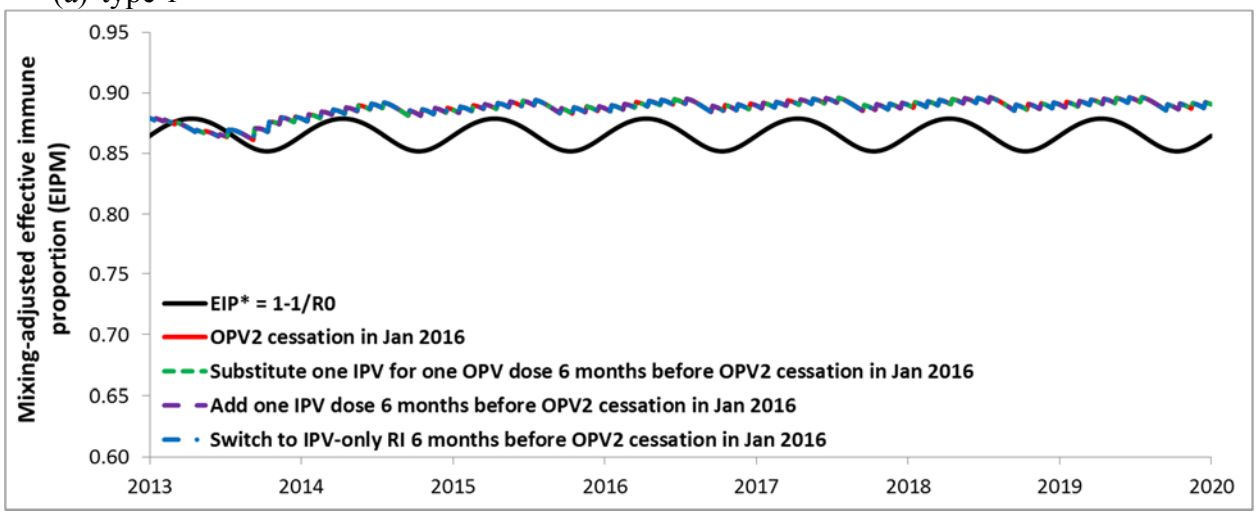
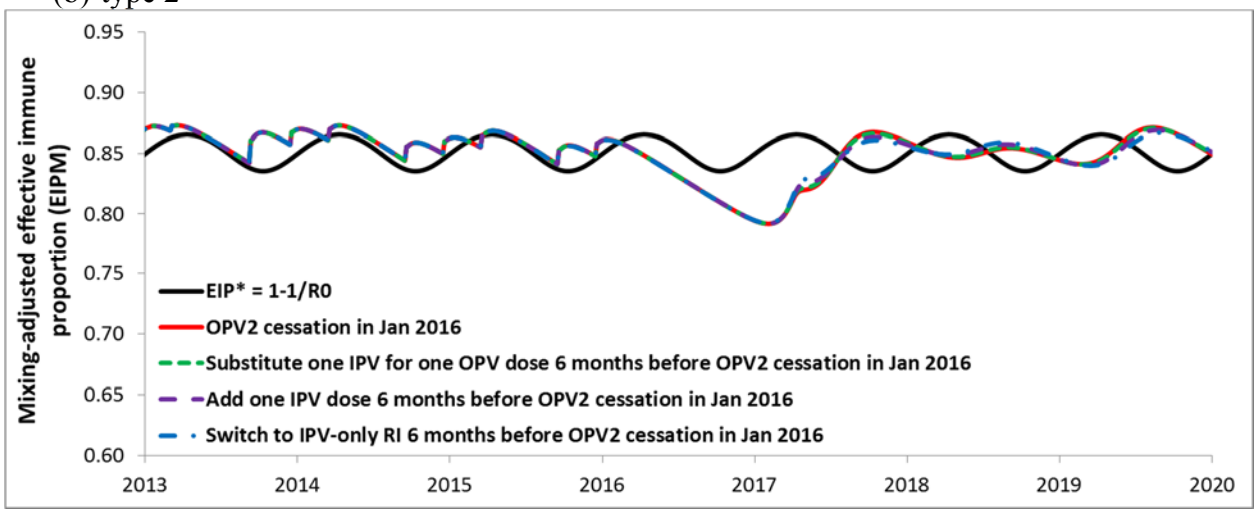

Mixing-adjusted effective immune proportion (EIPM)
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
2013
2014
2015
2016
2017
2018
2019
2020
EIP* = 1-1/R0
3 interspersed tOPV and 8 bOPV rounds
Add one IPV dose 6 months before OPV2 cessation
Substitute one IPV for one OPV dose 6 months before OPV2 cessation
Switch to IPV-only RI 6 months before OPV2 cessation
Switch to IPV-only RI and stop SIAs in April 2016

Figure A2: The impact of the strategies to manage cVDPV risks on population immunity in northwestern Nigeria:

(a) type 1



(b) type 2



(c) type 3

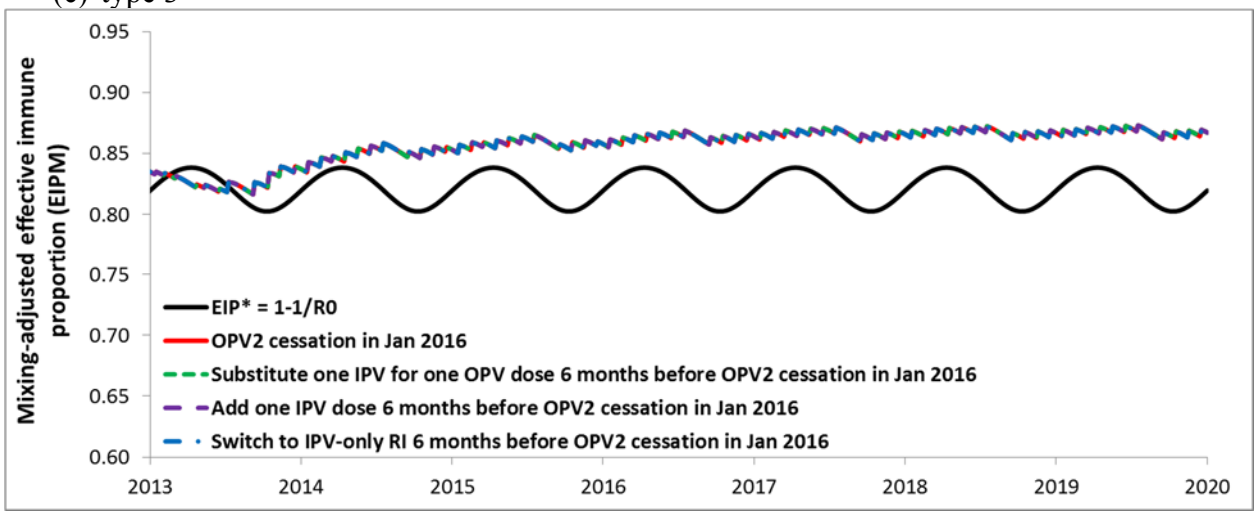
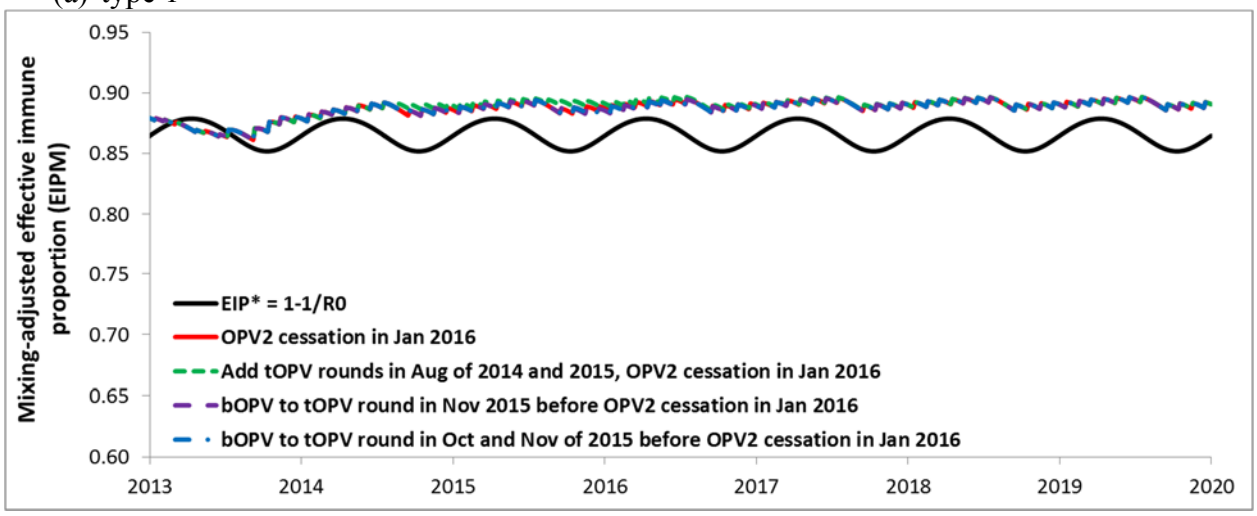
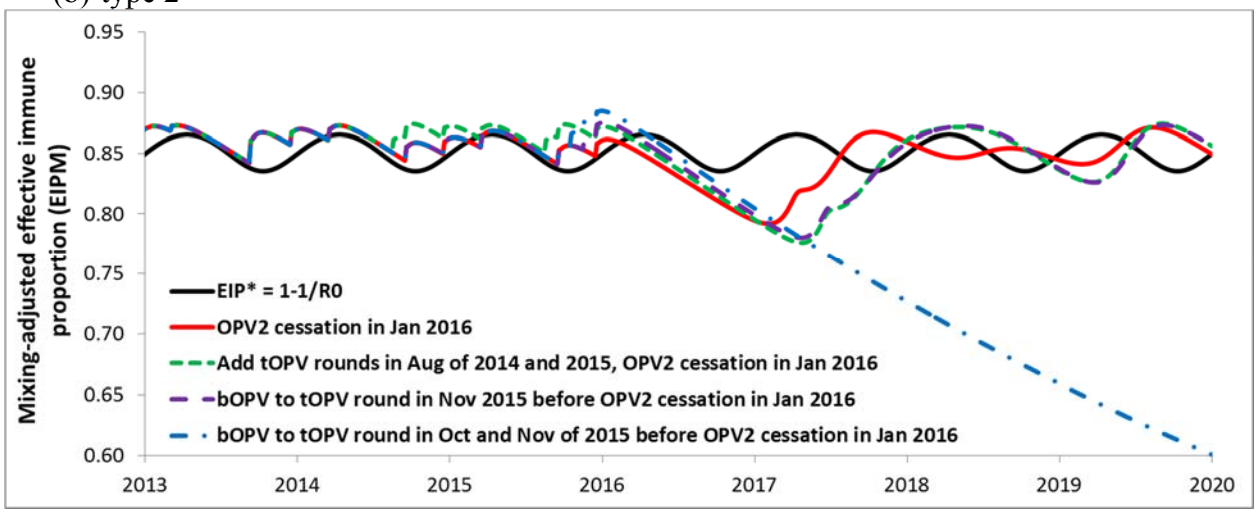


Figure A3: The impact of the strategies to manage cVDPV risks on population immunity in northwestern Nigeria:

(a) type 1



(b) type 2



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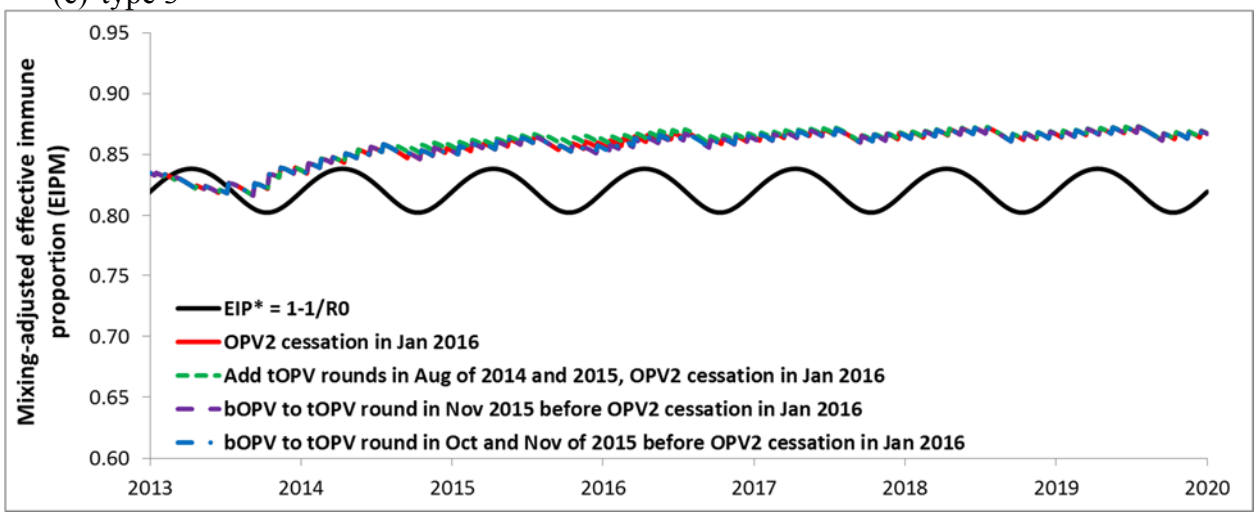
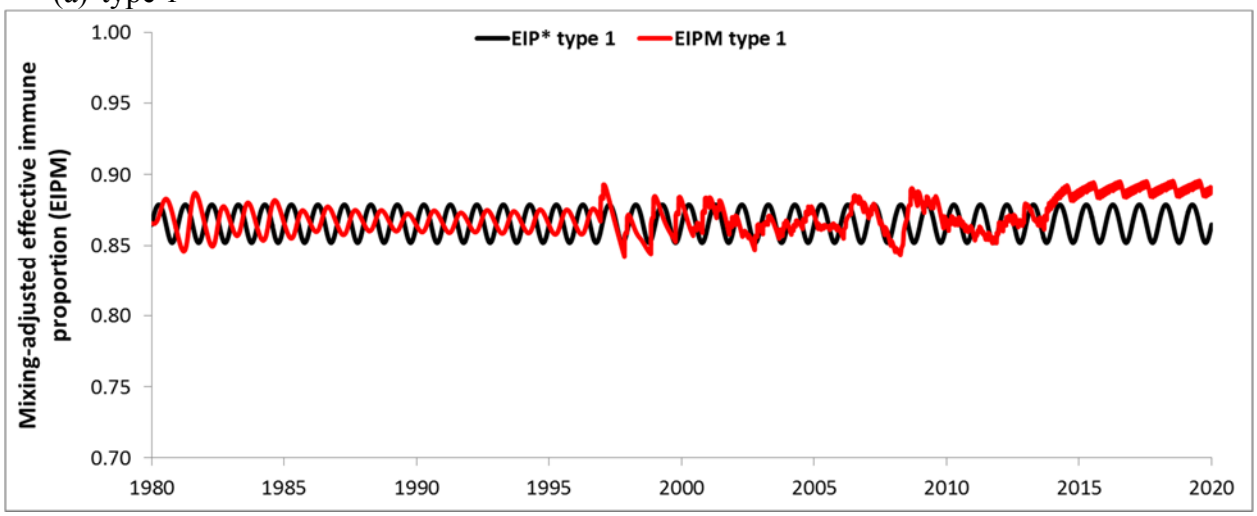
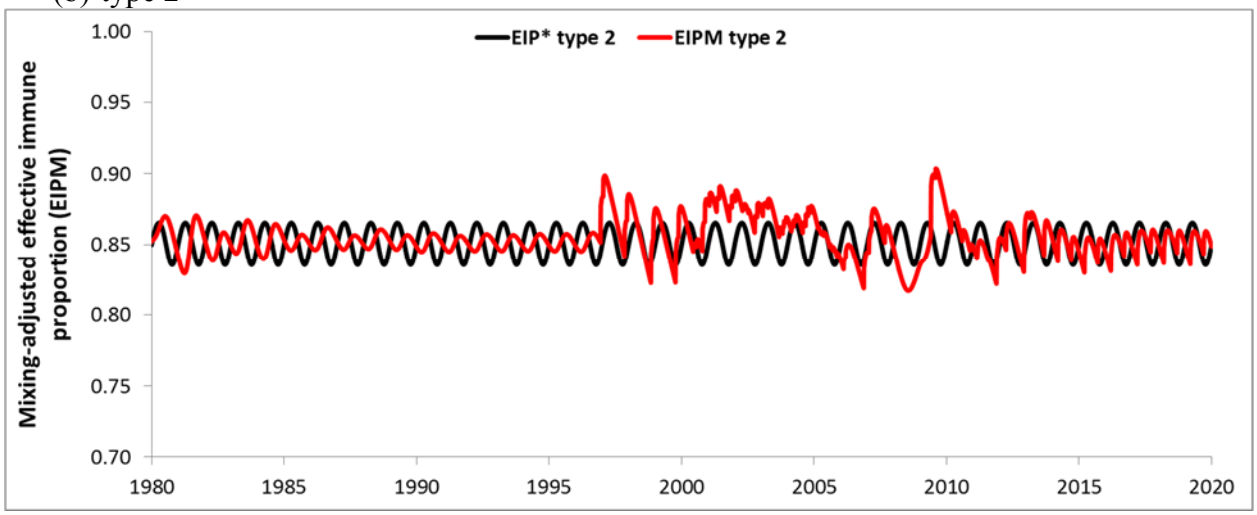


Figure A4: Effective immunity proportion (EIPM) of reference case compared to the threshold (EIP*) for northwestern Nigeria, continued status quo after 2013:

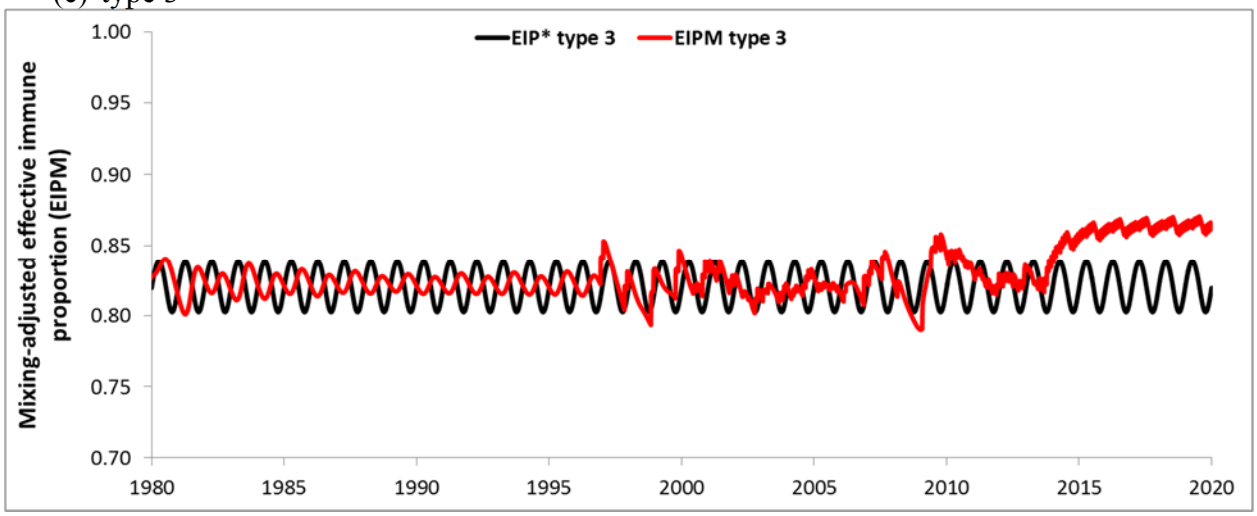
(a) type 1



(b) type 2



(c) type 3



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