Appendix SI

List of sections:

SI-I: Description of the basic model

We construct a compartmental model (1, 2) that couples host and vector dynamics. Mosquitos are assumed to be in one of two states: susceptible to infection (M_S) or infectious (M_I), and the size of the vector population is determined as a function of rainfall ($\lambda_{rainfall}$), while mosquito mortality is assumed to be constant (μ_M).

In the human host population we distinguish between young children under the age of 5 and older children and adults ($1/k$ = 5yrs (3)). We assume that older children and adults gain partial protective immunity following exposure to infection (4-6). This immunity is incomplete in that recovered hosts are still susceptible to future infections, and hence infectious to mosquitoes, but is protective in that it provides resistance from experiencing clinical symptoms. However, these protective effects of immunity are short lasting, and with insufficient re-exposure boosting this immunity, the protection wanes and host can become fully susceptible to clinical illness again after several years. There is therefore a direct dependency between morbidity and the history of infection.

For young children, we consider two possible states: fully susceptible to disease (J) and clinically infected (I_J), and for the rest of the host population we consider four possible states: fully susceptible (S), clinically infected (I_S), recovered with protective immunity (R), and asymptomatically infected (I_R). On average hosts with clinical illness (I_J and I_S) clear infection within $1/\sigma$ days, after which children return to their susceptibility state (J), while the rest of the host population gains short-term protective immunity (R). This short-term protection lasts on average $1/\delta$ years, after which hosts return to being susceptible to clinical disease again (S). However, if during this period hosts are re-exposed to infection, they experience it asymptomatically (I_R) with an average duration of $1/\sigma_R$ days, after which they return to having protective immunity once again (R). Hence, with sufficient re-exposure to infection, hosts can maintain protective immunity to disease indefinitely.

Transmission of infection: Mosquitoes bite human hosts at a constant attack rate (i.e., the total number of bites of a particular mosquito per unit time). Following a biting event, the probability that a susceptible mosquito becomes infected depends both on the rate of contact between susceptible mosquitos to infected hosts (i.e., the levels of M_S, I_J, I_S and I_R), and on the probability of successful transition from host to mosquito (τ_{HM}) (see Figure SI-I-1).

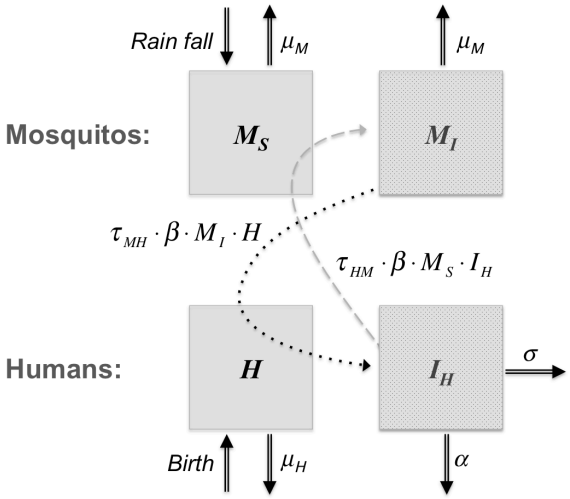


Figure SI-I-1: A sketch of the transmission pathways of infection from: i) infected mosquitos (M_I) to susceptible hosts (H) as a function of τ_{MH}, and from *ii*) infected hosts (I_H) to susceptible mosquitos (M_S) as a function of τ_{HM}. Infected mosquitoes (M_I) remain carriers for life, while infected humans clear infection after a mean period of $1/\sigma$ days. Replenishment of the susceptible vector population is determined as a function of rainfall, while the birth rate of the human population remains constant in size. Mosquito mortality and mortality of the susceptible human population are both constant (μ_M and μ_H, respectively), while symptomatic infection in humans may lead to disease-induced death ($\alpha > \mu_H$).

SI-II: A generalized version of the model with multiple age groups

The generalized model explicitly incorporates multiple-age groups indexed from i =[1,…, n]. Hosts in age group i pass to age group i+1 at a rate $\kappa_{i,i+1}$, but these rates are not necessarily identical, such that $\kappa_{i,i+1}$ may be different from $\kappa_{i+1,i+2}$. This allows additional partitioning if particular age ranges of interest, such as young children (among others, for example, this allows incorporation of maternal immunity of very young infants).

In each age group i, non-vaccinated hosts are either susceptible to clinical infection, $S(i)$, infected with clinical disease, $I(i)$, susceptible only to asymptomatic infection, $R(i)$, or asymptomatically infected, $A(i)$. Infected hosts $I(i)$ and $A(i)$ clear infection at rates $\sigma_{I(i)}$ and $\sigma_{A(i)}$, respectively. Following infection, a majority of the hosts gain protective immunity placing them in class $R(i)$, but this protection can wane a rate δ_i, making them susceptible to clinical infection. $S(i)$, once again. In contrast, we consider the possibility that for some age groups (namely, young children under the age of 5), clinical protection cannot be gained, and following clinical infection, $I(i)$, hosts in these age groups will return to the fully susceptible class, $S(i)$ (see Figure SI-II-1).

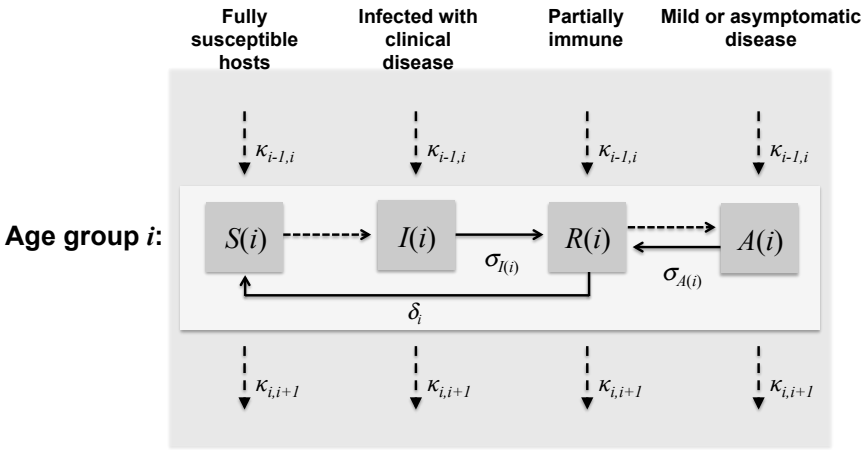


Figure SI-II-1: A sketch demonstrating the dynamics within an age group i, showing the transition between age classes.

Each age group is vaccinated at a certain, but only hosts that are not infected will transition to a vaccinated state (i.e., classes $S(i)$ and $R(i)$ transition to $V_S(i)$ and $V_R(i)$ at rates $\nu_{S(i)}$ and $\nu_{R(i)}$, respectively). Depending on the type of vaccine, vaccinated hosts may still be susceptible to infection, moving them to either classes $V_I(i)$ or $V_A(i)$) depending on their immune protection status. In such cases, this may allow them to also gain and/or maintain (boost) their protective immunity even if they did not have any before being vaccinated. We assume that vaccine protection is not life long, and looses its effect at a rate of $\omega(i)$, while the status of immune protection may still be maintained such that $V_S(i)$ transitions back to $S(i)$, and $V_R(i)$ to $R(i)$ (see Figures SI-II-2 and SI-II-3).

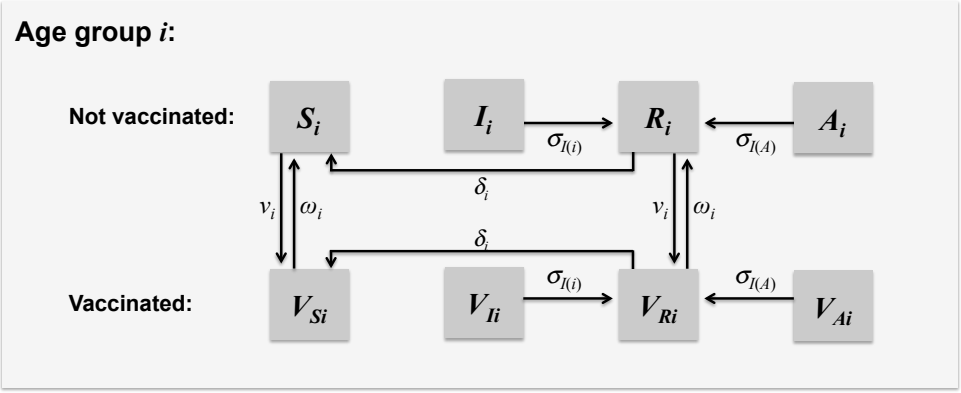


Figure SI-II-2: A sketch demonstrating the transition between non-vaccinated hosts to vaccinated ones within a single age group i.

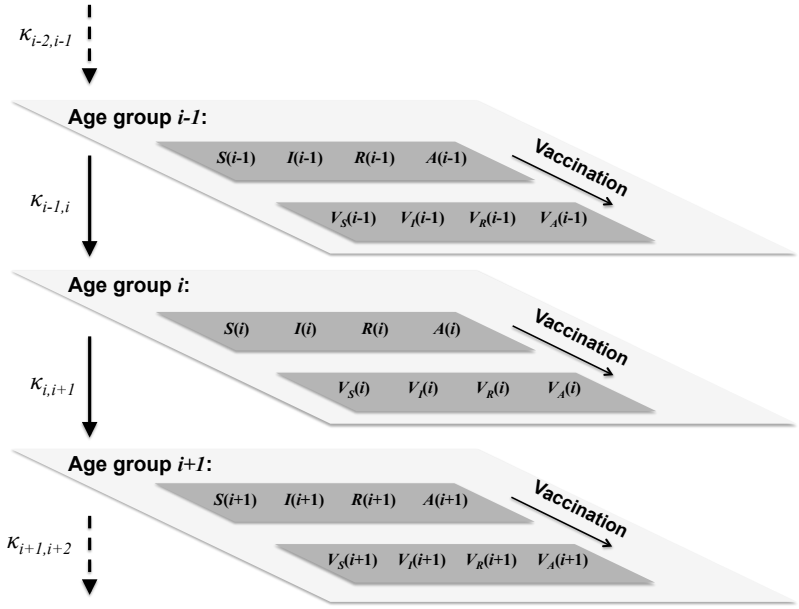


Figure SI-II-3: A sketch demonstrating the general model with transitions between age groups and within age groups.

Model equations:

Non-vaccinated hosts in age group $i = 1 \ldots n$:

$$\begin{cases} \dot{S}(i) = \mathrm{K}_{S(i)} - \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,S(i)} M_I S(i) + (1-\pi_i)\sigma_{I(i)} I(i) - \nu_{S(i)} S(i) + \omega_{S(i)} V_S(i) + \delta_i R(i) \\ \dot{I}(i) = \mathrm{K}_{I(i)} + \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,S(i)} M_I S(i) - \sigma_{I(i)} I(i) \\ \dot{R}(i) = \mathrm{K}_{R(i)} - \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,R(i)} M_I R(i) + \pi_i \sigma_{I(i)} I(i) + \sigma_{A(i)} A(i) - \nu_{R(i)} R(i) + \omega_{R(i)} V_R(i) - \delta_i R(i) \\ \dot{A}(i) = \mathrm{K}_{A(i)} + \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,R(i)} M_I R(i) - \sigma_{A(i)} A(i) \end{cases}$$

Vaccinated hosts in age group $i = 1 \ldots n$:

$$\begin{cases} \dot{V}_S(i) = \mathrm{K}_{V_S(i)} - \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,V_S(i)} M_I V_S(i) + \nu_{S(i)} S(i) - \omega_{S(i)} V_S(i) + \delta_i V_R(i) \\ \dot{V}_I(i) == \mathrm{K}_{V_I(i)} + \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,V_S(i)} M_I V_S(i) - \sigma_{I(i)} V_I(i) \\ \dot{V}_R(i) == \mathrm{K}_{V_R(i)} - \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,V_R(i)} M_I V_R(i) + \sigma_{I(i)} V_I(i) + \sigma_{A(i)} V_A(i) + \nu_{R(i)} R(i) - \omega_{R(i)} V_R(i) - \delta_i V_R(i) \\ \dot{V}_A(i) == \mathrm{K}_{V_A(i)} + \dfrac{\beta}{N_H}(1-b+\varepsilon b)\tau_{MH,V_R(i)} M_I V_R(i) - \sigma_{A(i)} V_A(i) \end{cases}$$

Vector population:

$$\begin{cases} \dot{M}_S = B_M - \left(\mu_M + \zeta\beta b(1-\varepsilon)\right) M_S - \dfrac{\beta}{N_H}(1-b+\varepsilon b) M_S \sum\limits_{j\in\{I,A,V_I,V_A\}} \sum\limits_{i=1}^{n} j(i)\tau_{HM,j(i)} \\ \dot{M}_I = -\left(\mu_M + \zeta\beta b(1-\varepsilon)\right) M_I + \dfrac{\beta}{N_H}(1-b+\varepsilon b) M_S \sum\limits_{j\in\{I,A,V_I,V_A\}} \sum\limits_{i=1}^{n} j(i)\tau_{HM,j(i)} \end{cases}$$

Where:

$$\begin{cases} \text{if } i=1: \mathrm{K}_{S(1)} = B_H - S(1)\left(\kappa_{1,2} + \alpha_{S(1)}\right) \text{ and } \mathrm{K}_{j(1)} = -j(1)\left(\kappa_{1,2} + \alpha_{j(i)}\right) \quad \left[j = I, R, A, V_S, V_I, V_R, V_A\right] \\ \text{if } i=2,\ldots,n-1: \mathrm{K}_{j(i)} = j(i-1)\kappa_{i-1,i} - j(i)\left(\kappa_{i,i+1} + \alpha_{j(i)}\right) \quad \left[j = S, I, R, A, V_S, V_I, V_R, V_A\right] \\ \text{if } i=n: \mathrm{K}_{j(n)} = j(n-1)\kappa_{n-1,n} - j(n)\alpha_{j(n-1)} \quad \left[j = S, I, R, A, V_S, V_I, V_R, V_A\right] \end{cases}$$

Parameter definitions:

B	Birth of children ($\mathrm{B} = \mu_H N_H$)
N_H	Total number of hosts
$365 * 1/\mu_M$	Average life expectancy of mosquitoes (days)
$1/\kappa_{i,i+1}$	Average years in age group i ***In all simulations we assume children under the age of 5yrs do not acquire protective immunity (3), and in the 5-stage model we assume children under the age of 1yr are protected by maternal immunity (7)*
$1/\mu_H$	Average life expectancy of humans (yrs)

$\lambda_{rain\ fall}$	Birth of mosquitos
N_M	Mosquito population size in the absence of insecticides
N^*_M	Effective mosquito population size in the presence of bednets
β	Biting rate of mosquitoes (total number of bites of a particular mosquito per unit time, i.e., the attack rate)
$\tau_{HM,\,j(i)}$	Probability of successful transmission from an infected host in age group *i* to a susceptible mosquito, where $j = I, A, V_I, V_A$
$\tau_{MH,\,j(i)}$	Probability of successful transmission from an infected mosquito to a susceptible host in age group *i*, where $j = S, R, V_S, V_R$
$\sigma_{j(i)}$	Clearance rate of infection in age group *i*, where $j = S, I, R, A$ ***We assumed this spans roughly 30dys to 1yr (4, 5, 8, 9)*
$\alpha_{j(i)}$	Natural death and disease induced death during infection in age group *i*, where $j = S, I, R, A, V_S, V_I, V_R, V_A$ (e.g., in the absence of virulence $\alpha_{j(i)} = \mu_H$) ***In the results we present we assumed no disease induced death, nonetheless, incorporation of $\alpha_{j(i)} > 0$ showed equivalent results*
δ_i	Loss of protective immunity in age group *i* ***We assumed this spans roughly 1 to 2yrs (3-5, 8, 9)*
ε	Vector mobility
b	The fraction of hosts protected by a bednets
ξ	Probability of mosquito mortality following an encounter with a treated net
$\nu_{j(i)}$	Rate of vaccination for age group *i*, where $j = S, R, V_S, V_R$
$\omega_{j(i)}$	Loss of vaccine effect for age group *i,* where $j = S, R, V_S, V_R$ ***We assumed this spans roughly 1 to 2yrs (10)*

SI-III: Intervention: Bednets

In our model we assume a certain fraction of the host population use bednets as a means of protection from mosquito bites. We note as b corresponding to the product of bednet efficiency and the proportion of the host population using bednets (b ranges from 0 to 1). Hence the rate at which a mosquito bites a non-protected host is: $\beta(1+\varepsilon b/(1-b))/N$, where N is the total number of hosts, and ε represents the "efficiency" of mosquitoes to target non protected hosts in contrast to protected ones. Bednets are commonly treated with a repellant, in which case this would be equivalent to setting $\varepsilon > 0$. In our model, this coefficient, ε, is expressed by a Type-II functional response (17) of mosquito foraging, determining the extent to which the mosquito population can successfully locate available blood meals. For $\varepsilon = 0$, mosquitoes invest equal effort in foraging between all hosts, protected or not, but as ε increases, vector preferentially target the non-protected hosts. This implies that when $\varepsilon > 0$, the rate at which non-protected hosts are bitten increases with the level of bednet usage. ε may also be interpreted as representing the degree of vector mobility, such that physical restrictions on the movement of vectors would lead to lower values of ε. Studies are now showing evidence of malaria vectors changing their biological behavior due to the large coverage of bednets. This includes changes in the time of biting activity, and changes in feeding preference (11, 13, 15, 16, 18, 19). In our model this could be interpreted as a selective force favoring higher levels of ε.

In addition to repellent, bednets are also commonly treated with insecticides that are meant to kill the mosquitos landing on them. To incorporate this effect on the vector population, we define ξ as the probability of mosquito mortality following an encounter with a treated net. Hence, the rate at which mosquitoes encounter a treated bednet and then die is $\xi\beta b(1-\varepsilon)$. ξ can take different values depending on the type of nets being used (i.e., whether they are treated or not), the rate at which the nets are re-treated with insecticides (e.g., Insecticide-treated nets, ITNs, loose their efficiency after a period of six months to a year and after a number of washes, in contrast to long-lasting insecticidal mosquito nets, LLINs, that can stay efficient for several

years (20)), the level of mosquito resistance to insecticides, and the type of insecticide being used (e.g., synthetic pyrethroid insecticide such as deltamethrin or permethrin, and others).

Figure SI-III-1 demonstrates the implications of insecticide treatment that repels vs. kills.

With the use of bednets child morbidity is generally found to decrease while adult morbidity primarily increases and may only start decreasing close to the elimination threshold (Eq. 1 in the main text). However, as shown in Figure SI-III-1, when bednets are not insecticide-impregnated (ξ=0), this decrease is minor, even when coverage levels are very high. Notably, bednets treated with relatively mild repellent (ε=0.2) are less effective at the population level, than those that are not treated at all. This indicates that the repulsion of mosquitoes from nets is likely to have a counter-productive effect that significantly suppress their benefits if bednets do not also lead to enhanced mosquito mortality. This can occur as the nets age and the bednet declines in potency, and it emphasizes the superiority of LLINs over ITNs [note that we use ITN to represent both Insecticide-Treated Bednets and Long-Lasting Insecticide-Treated Nets (LLIN's)]. Differences between these are discussed in the *Methods* section of the main text. When the probability of mosquitoes dying from contact with nets decreases, the mosquito population maintains its size leading to an enhancement of the attack-rate on the unprotected hosts, which also increases at higher levels of bednet coverage (11-13). Crucially, the overall community benefits more from mass use of completely untreated nets, than when only a sub-section use treated, but non-fatal repellents. Naturally this introduces a conflict between immediate benefits for individuals on short timescales, and longer-term benefits for both individuals and the community as a whole. In this sense, ITNs in contrast to LLINs, may not always be in the benefit of the public good. This agrees with field studies that have concluded that "optimal LLIN should maximize engagement so as to maximize mortality" (14), and emphasizes the fundamental importance of treating bednets with insecticides that are more likely to kill than to repel, as well as the importance of considering the nature of vector activity when designing control policies (15, 16).

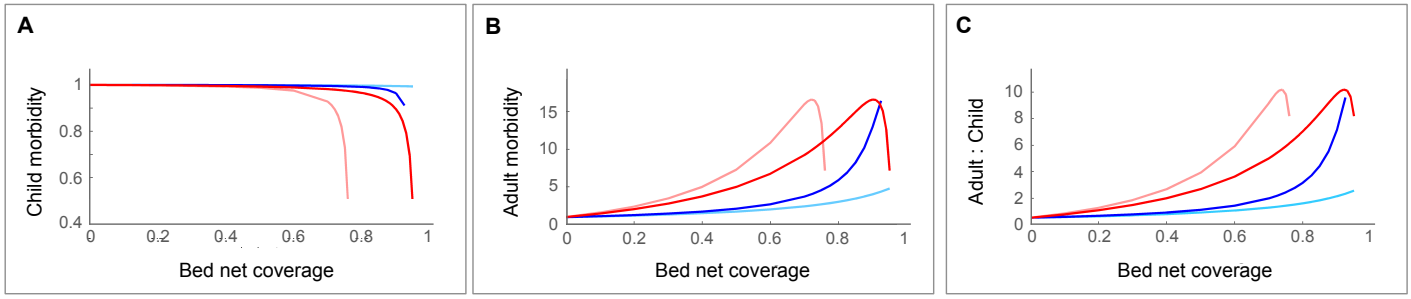


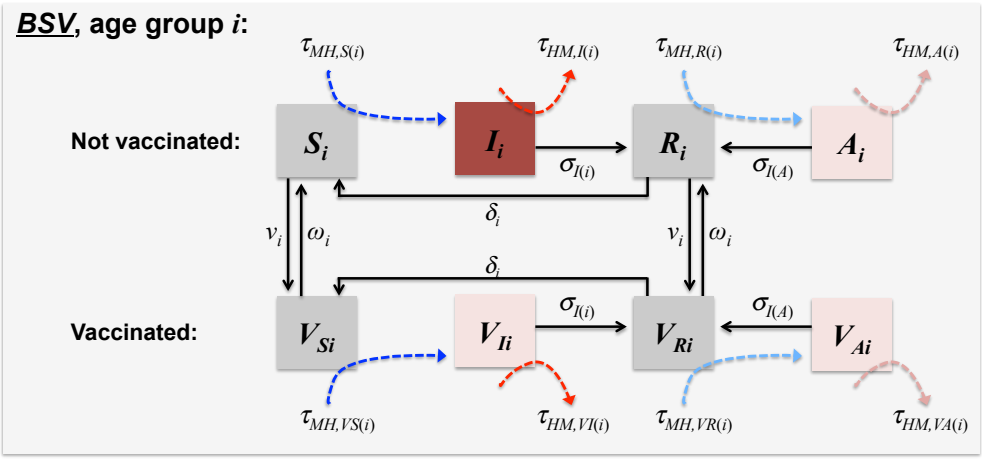
Figure SI-III-1: Change in morbidity with different levels of bednet use. **A-B** show changes children and adults, respectively, calculated by dividing levels of morbidity with intervention to those without it, and **C** shows the ratio between these, demonstrating an increase in pressure on the productive class. Different forms of insecticide treatment of repelling vs. killing are considered: pink: ε=0, ξ=0.2, red: ε=0.2, ξ=0.2, dark blue: ε=0, ξ=0, and light blue: ε=0.2, ξ=0. For all cases, adult morbidity primarily increases, and may only start decreasing close to the point of elimination, while child morbidity always decreases. All parameters are identical to those in Figure 2 of the main text.

SI-IV: Intervention: Vaccination

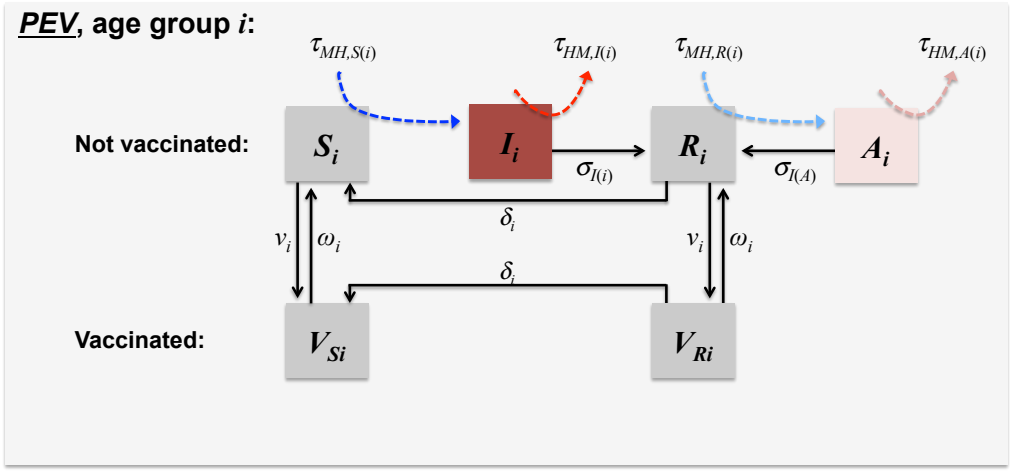
We consider the three major vaccine families currently in development (21, 22):

1) *Blood-stage vaccine (BSV)*: This vaccine provides protection from clinical disease but does not block infection; hence hosts can still become mildly or asymptomatically infected and infectious. The probabilities of successful transmission from an infected vaccinated host to a

susceptible mosquito and from an infected mosquito to a susceptible vaccinated host are therefore positive (i.e., $\tau_{MH,VS(i)}$, $\tau_{MH,VR(i)}$, $\tau_{HM,VI(i)}$ and $\tau_{HM,VA(i)} > 0$), but possibly lowere than for the non vaccinated hosts (i.e., $\tau_{HM,VI(i)} \leq \tau_{HM,I(i)}$, $\tau_{HM,VA(i)} \leq \tau_{HM,A(i)}$, $\tau_{MH,VS(i)} \leq \tau_{MH,S(i)}$ and $\tau_{MH,VS(i)} \leq \tau_{MH,S(i)}$).Vaccine protection lasts $1/\omega(i)$ years on average. Hosts that are infected during this period will acquired or boost their natural immunity, while in the absence of re-infection, they can loose natural immunity they may have already had. This implies that with early vaccination and with sufficient re-exposure, vaccinated hosts can gain and maintain natural immunity without ever experiencing clinical disease throughout their life.



2) *Pre-erythocytic vaccine (PEV)*: This vaccine provides full protection from all forms of infection for an average period of $1/\omega(i)$ years. Therefore the probability of successful transmission from infected mosquito vaccinated human is 0 (i.e., $\tau_{MH,VS(i)} = \tau_{MH,VR(i)} = 0$), and the probability of successful transmission from human to mosquito is not defined (i.e., $\tau_{HM,VI(i)}$ and $\tau_{HM,VA(i)} = n.d.$). This implies that on the host population level, vaccination has the potential to lead to a significant reduction in the general force of infection. On the host individual host level however, even though this vaccine provides protection from clinical disease on the short term, on the longer term vaccinated hosts may be loosing naturally acquired protective immunity, which they may have otherwise been able to maintain by regular boosting.



3) *Transmission-blocking vaccine (TBV)*: This vaccine does not block infection or provide protection from clinical disease, but it significantly reduces the likeliness that infected hosts will cause secondary infections. We therefore define the probability of successful transmission from infected mosquito to susceptible vaccinated human as positive (i.e., $\tau_{MH,VS(i)}$, $\tau_{MH,VR(i)} > 0$), and from infected vaccinated human to susceptible mosquito as significantly reduced (i.e., $\tau_{HM,\ VI(i)}$ and $\tau_{HM,\ VA(i)} \approx 0$). Effects of this vaccine last for an average period of $1/\omega(i)$ years.

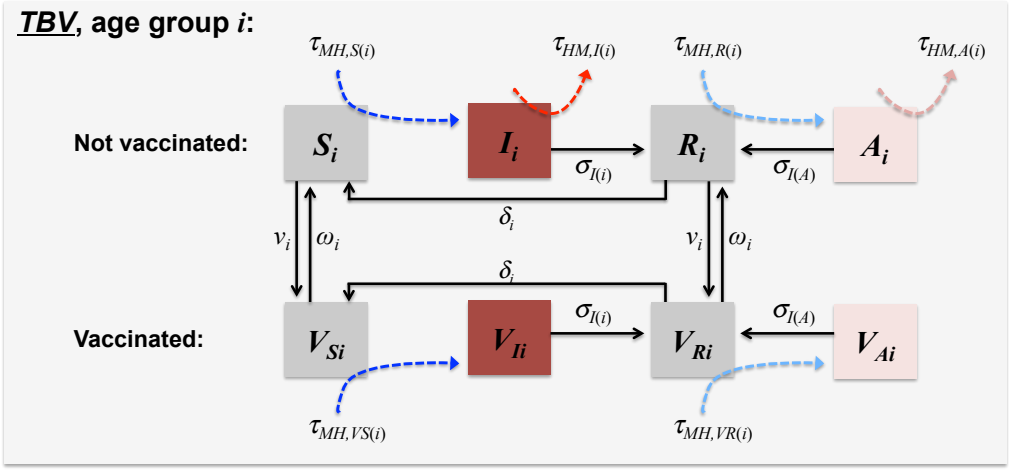


Table SI-IV-1 summarizes the effect each vaccine has on transmission to and from vaccinated hosts, and the on the fraction of the host population we consider as suffering morbidity. Figure SI-IV-2 shows the change in morbidity for different levels of vaccine coverage.

	$\tau_{MH,V}$	$\tau_{HM,V}$	**Hosts with clinical disease**	**Hosts contributing to the force of infection**
BSV	+	+	$I_J + I_S$	$I_J + I_S + I_{V,J} + I_{V,S}$
PEV	0	*n.d.*	$I_J + I_S$	$I_J + I_S$
TBV	+	reduced	$I_J + I_S + I_{V,J} + I_{V,S}$	$I_J + I_S$

Table SI-IV-1: A summary of the effects of each of the vaccines on the transmission cycle between hosts and vectors. $\tau_{MH,V}$ is the probability of successful transmission from an infected vector to a vaccinated host, and $\tau_{HM,V}$ is the probability of successful transmission from an infected vaccinated host to a vector.

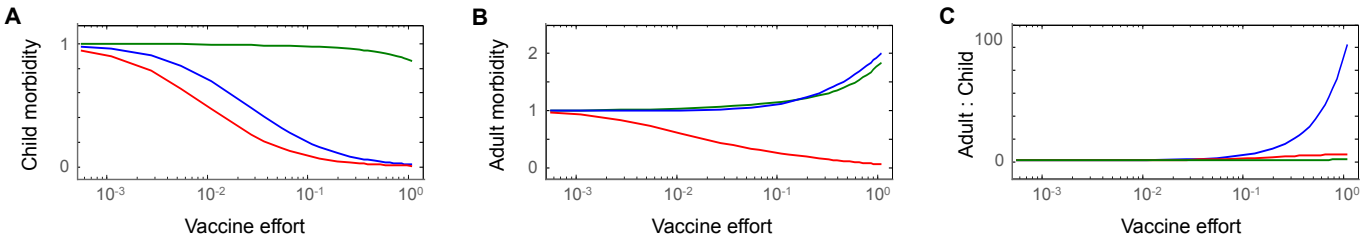


Figure SI-IV-2: Change in morbidity with different levels of vaccine coverage. **A** and **B** show changes for children and adults, respectively, calculated by dividing levels of morbidity with intervention to those without it, and **C** shows

the ratio between these. For all three vaccines (*BSV* in red, *PEV* in blue, and *TBV* in green), as the level of vaccination increases, relative child morbidity decreases. For adults, however, *BSV* leads to a small decrease in morbidity, while the *PEV* and the *TBV* lead to a significant increase in the level of morbidity. For all three vaccines immunity is assumed to wane after $1/\omega$=2 years on average. As in the main text, this example is for the simple version of the model with two age groups: a) young children, and b), older children and adults. Vaccine effort of young children is defined as $\log(v_J)$. For all classes i=J,S,R: $\tau_{MH,i}$=$\tau_{HM,i}$=0.5. For *BSV*: $\tau_{MH,V}$=$\tau_{HM,V}$=0.5, for *PEV* $\tau_{MH,V}$=0, and for *TBV* $\tau_{MH,V}$=0.5, and $\tau_{HM,V}$=0. v_J=v_S/100=v_R/100(yr^{-1}), and ε=0.2 and ξ=0.2. All other parameters are identical to those in Figure 1 of the main text.

SI-V: Model sensitivity

The result presented in the main text and ones obtained using the generalized version of the model with multiple age groups gave equivalent as demonstrated below where we show results for 2-age group and 5-age groups.

In the 2-age group example, at the mean age of 5yr children transition to the older age class, and we assume that only hosts in the second age group can gain clinical immunity. However, the 5-age group allows us to incorporate more complicated scenarios. Here we assumed the mean age of transition from group 1 to 2 was 1yr, from 2 to 3 was 5yr, from 3 to 4 was 10yr, and from 4 to 5 was 20yr. We assumed infants in the first age group (0-1yr) had maternal immunity and did not get infected, and that only host of age group 3 and above could gain clinical immunity.

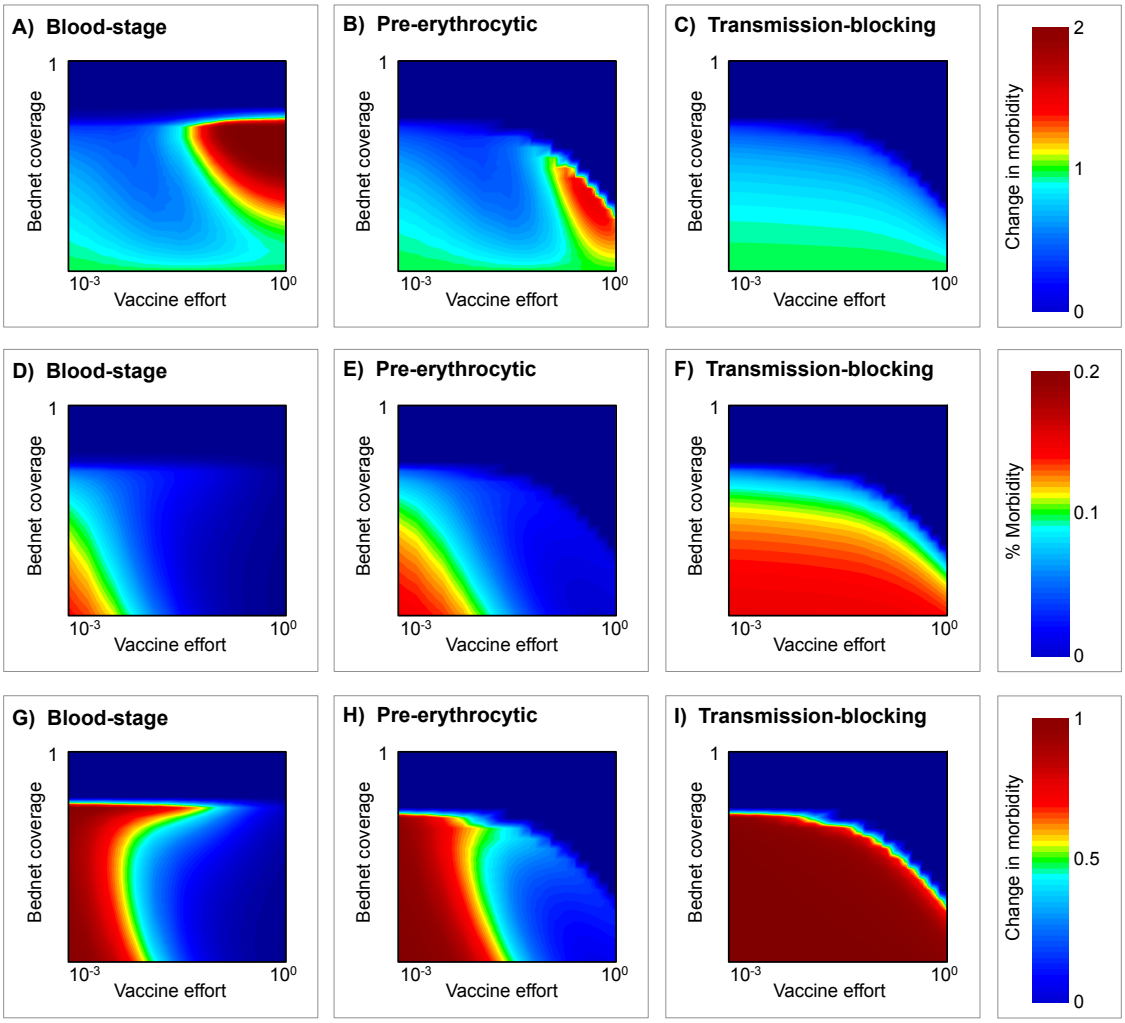


Figure SI-V-1: **2-age groups**: Effects of combined intervention on morbidity following vaccine and bednet use. Contour plots **A-C** show changes in total morbidity calculated by dividing the observed level of morbidity with bednets by its level in their absence. Cold colors show synergistic interactions, and warm colors show antagonistic ones. **D-F** show changes in total morbidity calculated by dividing the observed level of morbidity with vaccine treatment by its level in its absence. **G-I** show the corresponding percent of hosts in the total population suffering clinical disease (morbidity). Vaccine effort is defined as log (v_1), where $v_1=v_2/100$ (yr^{-1}). Parameters: N_H=5000, N_M=5000, β=0.5, ε=0.2, ξ=0.4, $1/\sigma$=60dy, $1/\delta=1/\delta_V$=1yr., $1/\kappa_{1,2}$=5yr, $1/\alpha_J=1/\alpha_S=1/\mu_H$=30yr, $1/\mu_M$=20dy, $\lambda_{rainfall}=N_M\times\mu_M$. For all classes i=1, …, n: $\tau_{MH,S(i)}=\tau_{MH,R(i)}$=0.5, $\tau_{HM,I(i)}=\tau_{HM,A(i)}$=0.5. For *BSV*: $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}=\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0.5, for *PEV*: $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}$=0.5, $\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0, and for *TBV* $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}$=0, $\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0.5.

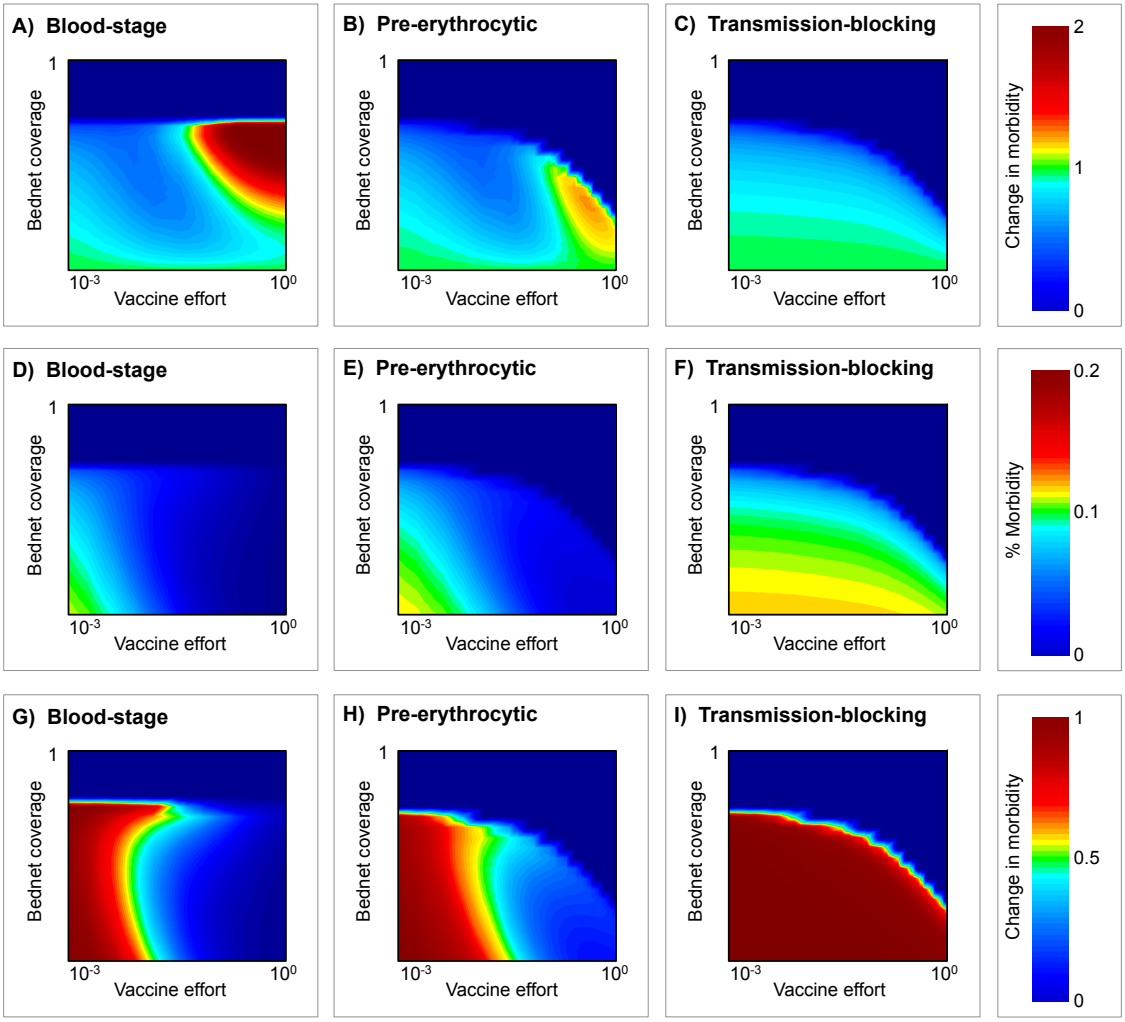


Figure SI-V-2: **5-age groups**: Effects of combined intervention on morbidity following vaccine and bednet use. Contour plots **A-C** show changes in total morbidity calculated by dividing the observed level of morbidity with bednets by its level in their absence. Cold colors show synergistic interactions, and warm colors show antagonistic ones. **D-F** show changes in total morbidity calculated by dividing the observed level of morbidity with vaccine treatment by its level in its absence. **G-I** show the corresponding percent of hosts in the total population suffering clinical disease (morbidity). Parameters: N_H=5000, N_M=5000, $1/\mu_M$=20dys, $\lambda_{rainfall}= N_M\times\mu_M$, β=0.5, ε=0.2, ξ=0.4, and $1/\kappa_{1,2}$=1yr, $1/\kappa_{2,3}$=4yrs, $1/\kappa_{3,4}$=5yrs, $1/\kappa_{4,5}$=10yrs. For all age groups i=1,…,n and for classes j = *S*, *I*, *R*, *A*, V_S, V_I, V_R, V_A: $1/\alpha_{j(i)}$=30yrs , $1/\sigma_{j(i)}$=60dys, $1/\delta_i$=1yr, $1/\omega_{j(i)}$=1yr. Vaccine effort is defined as log(v_1), where for classes j = *S*, *I*, *R*, *A*, V_S, V_I: $v_{j(1)}=v_{j(2)}=v_{j(3)}/100=v_{j(4)}/100=v_{j(5)}/100(yr^{-1})$. For i=1,…,n: $\tau_{MH,S(i)}=\tau_{MH,R(i)}$=0.5, $\tau_{HM,I(i)}=\tau_{HM,A(i)}$=0.5. For *BSV*: $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}=\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0.5, for *PEV*: $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}$=0.5, $\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0, and for *TBV* $\tau_{MH,VS(i)}=\tau_{MH,VR(i)}$=0, $\tau_{HM,VI(i)}=\tau_{HM,VA(i)}$=0.5.

In addition, we also tested sensitivity of our results by considering the following parameter ranges (see summary in Table SI-V-3):

1) Duration of natural immunity ($1/\delta_i$) spanning from on average 1yr to on average 32yrs: We found that only at the extreme case where duration of immunity is on the order of a host's lifetime do our results break down, and for all other values the results were equivalent to the ones presented in the main text.

2) Transmission intensity (β, the total number of bites of a mosquito per unit time), spanning from 0.25 to 1: For all values the results were equivalent to the ones presented in the main text.

3) Infectiousness of asymptomatic hosts ($\tau_{HM,A(i)}$) spanning from 0 to 0.5: For all values the results were equivalent to the ones presented in the main text.

4) Duration of clinical infection ($1/\sigma_{I(i)}$) and duration of asymptomatic infection ($1/\sigma_{A(i)}$), we considered cases where: *i*) the durations remained equal, both spanning from 30 to 720 days, and cases where *ii*) duration of the asymptomatic infection was longer than the duration of clinical infection. For the latter we also considered cases where the infectiousness of asymptomatic hosts was lower of that of the clinical cases ($\tau_{HM,I(i)}>\tau_{HM,A(i)}$): We found that only at extremely long durations of both clinical and asymptomatic infection (both on the ord

Table SI-V-3 provides a summary of parameter ranges and combinations that were tested. All cases were run assuming **5-age groups** with parameters similar to those presented in Figure SI-V-2. The comparison we made was to the results presented in Figure 3 of the main text, where the line marked in red is the case analogous to the case show there, just with 5 age groups vs. 2, as well as assuming maternal immunity up to the age of 1 yr.

Table SI-V-3:

Clinical infection (days)	Asymptomatic infection (days)	Natural immunity (years)	Vaccine protection (years)	Beta	Clinical infectiousness	Asymptomatic infectiousness	BSV	PEV	TBV
Extending natural immunity to the order of a life time and changing beta									
60	60	1	1	0.5	0.5	0.5	equivalent	equivalent	equivalent
60	**60**	**2**	**2**	**0.5**	**0.5**	**0.5**	equivalent	equivalent	equivalent
60	60	4	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
60	60	8	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
60	60	32	2	0.5	0.5	0.5	similar	similar	equivalent
60	60	2	2	0.25	0.5	0.5	equivalent	equivalent	equivalent
60	60	2	2	1	0.5	0.5	equivalent	equivalent	equivalent
Decreasing transmissibility of asymptomatic infection									
60	60	2	2	0.5	0.5	0	equivalent	equivalent	equivalent
60	60	2	2	0.5	0.5	0.1	equivalent	equivalent	equivalent
60	60	2	2	0.5	0.5	0.25	equivalent	equivalent	equivalent
Decreasing duration of infection, extending duration of natural immunity and decreasing transmissibility of asymptomatic infection									
30	30	2	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	30	4	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	30	8	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	30	32	2	0.5	0.5	0.5	similar	similar	equivalent
30	30	2	2	0.5	0.5	0.25	equivalent	equivalent	equivalent
Extending clinical and asymptomatic infection									
120	120	2	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
180	180	2	2	0.5	0.5	0.5	equivalent	equivalent	different
360	360	2	2	0.5	0.5	0.5	similar	similar	different
720	720	2	2	0.5	0.5	0.5	similar	similar	different
Extending asymptomatic infection, extending duration of natural immunity and decreasing transmissibility of asymptomatic infection									
30	180	1	1	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	180	2	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	180	4	2	0.5	0.5	0.5	equivalent	equivalent	equivalent
30	180	8	2	0.5	0.5	0.5	similar	similar	equivalent
30	180	32	2	0.5	0.5	0.5	similar	similar	equivalent
30	180	2	2	0.25	0.5	0.5	equivalent	equivalent	equivalent
30	180	2	2	1	0.5	0.5	equivalent	equivalent	equivalent
30	180	2	2	0.5	0.5	0.25	equivalent	equivalent	equivalent

SI-VI: Trends in data

Changing trends of adult and child mortality in Sub-Saharan African from 1980 to 1989, and from 2006 to 2010

In areas of endemic malaria acquired immunity is generally known to protect adults from clinical disease. In many Sub-Saharan African countries that have been subject to mass intervention over the past decade, there has been a striking epidemiological shift in cases, with increasing proportions of adult mortality relative to young children. There is concern that these patterns reflect, at least in part, shifts in malaria morbidity to older ages due to lower levels of protective immunity, implying a rise in susceptibility of older children and adults. It has been suggested that Pyrethroid insecticide resistance may have been responsible for these patterns, rather than age-dependent changes in immunity profiles. This explanation seems disingenuous as resistance would lead to reduced efficiency of bednets across all age groups, rather than to increased incidences of malaria attacks in older children and adults (23). Unfortunately, insufficient data is available for proving casualty between mass bednets intervention and increased morbidity of adults (24); further studies are needed to assess age shifts in malaria morbidity and mortality after increases in malaria control.

Figure SI-VI below shows the cumulative probability of death due to malaria for children under the age of 5yr., and for older children and adults of over 15yr. for 36 out of 38 countries in Western, Eastern and Southern Sub-Saharan African. The probability is calculated as the number of people out of 1,000 who were likely to die. We focus on two representative periods: 1) 1980 to 1989, a period when mortality was relatively stable, and 2) 2006 to 2010, the period following the 2004 peak of malaria mortality (25), after which mass intervention had been put in place in all these countries (26). The data on global malaria mortality between 1980 and 2010 is from the Institute of Health and Evaluation (IHME) (27).

In Figure SI-VI-1 is the cumulative probability of death of children (thin lines), and of adults (bold lines) divided by its level in 1980, respectively, and in Figure SI-VI-2 is the ratio of adults (>15yr.) to children (<5yr). Although levels of child mortality were relatively high following their peak in the early 2000's, these have rapidly decreased during the half-decade of 2006-2010, and in many countries even reached levels lower than those of the early 1980's. This has been associated with the success of mass intervention, and in particular bednets. In contrast, for adults the cumulative probability of death due to malaria remained significantly higher in 2006-2010 relative to the 1980's, and despite signs of decreasing levels, adult mortality is still relatively high, and the rate of this decline seems to be decelerating in a majority of the countries. In particular, in Figure SI-VI-2 we see that for many of the countries the ratio of adult to children is still climbing.

These asymmetric decreases in malaria among different age groups clearly pose a challenge to control and elimination efforts.

Figure SI-VI – 1

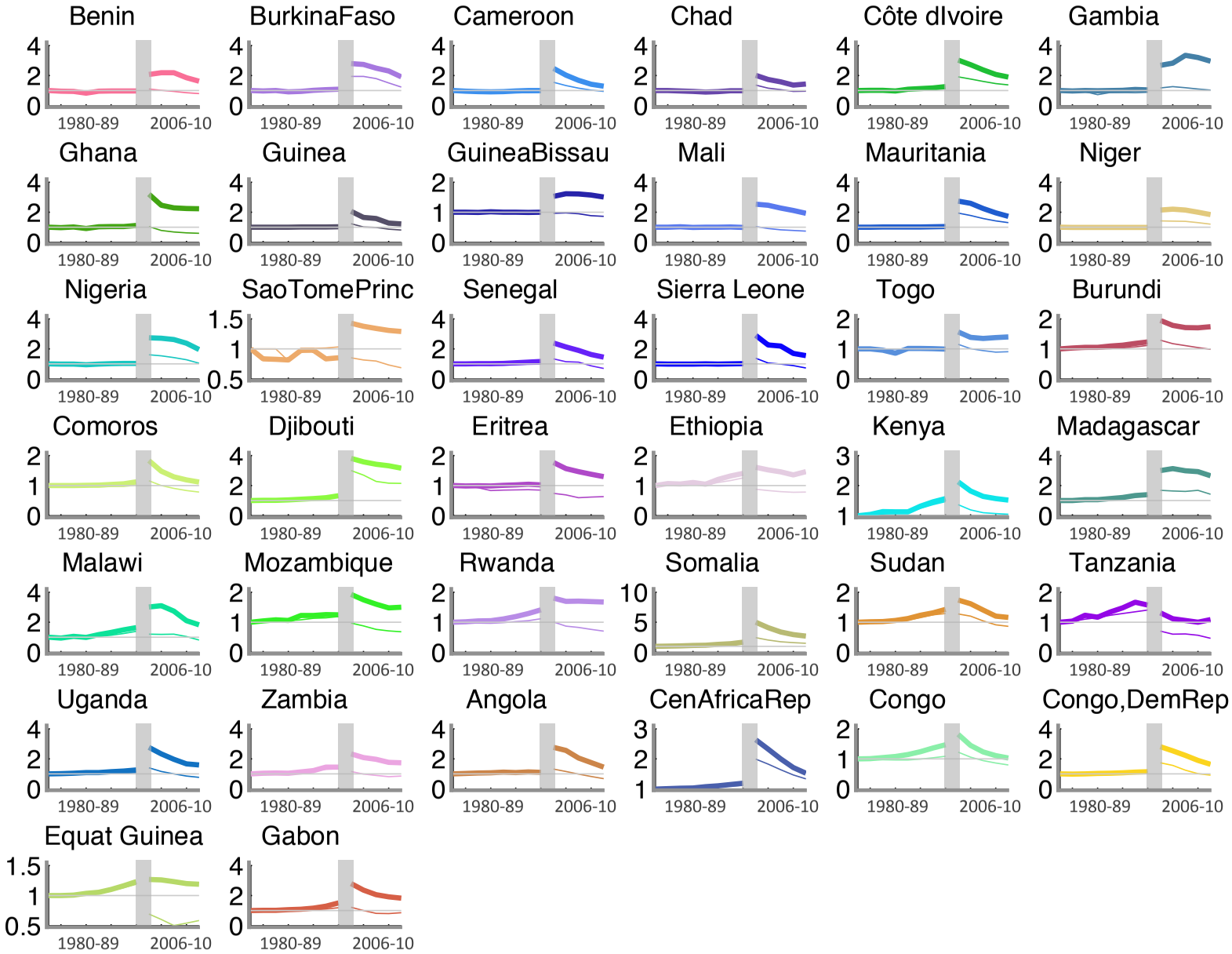
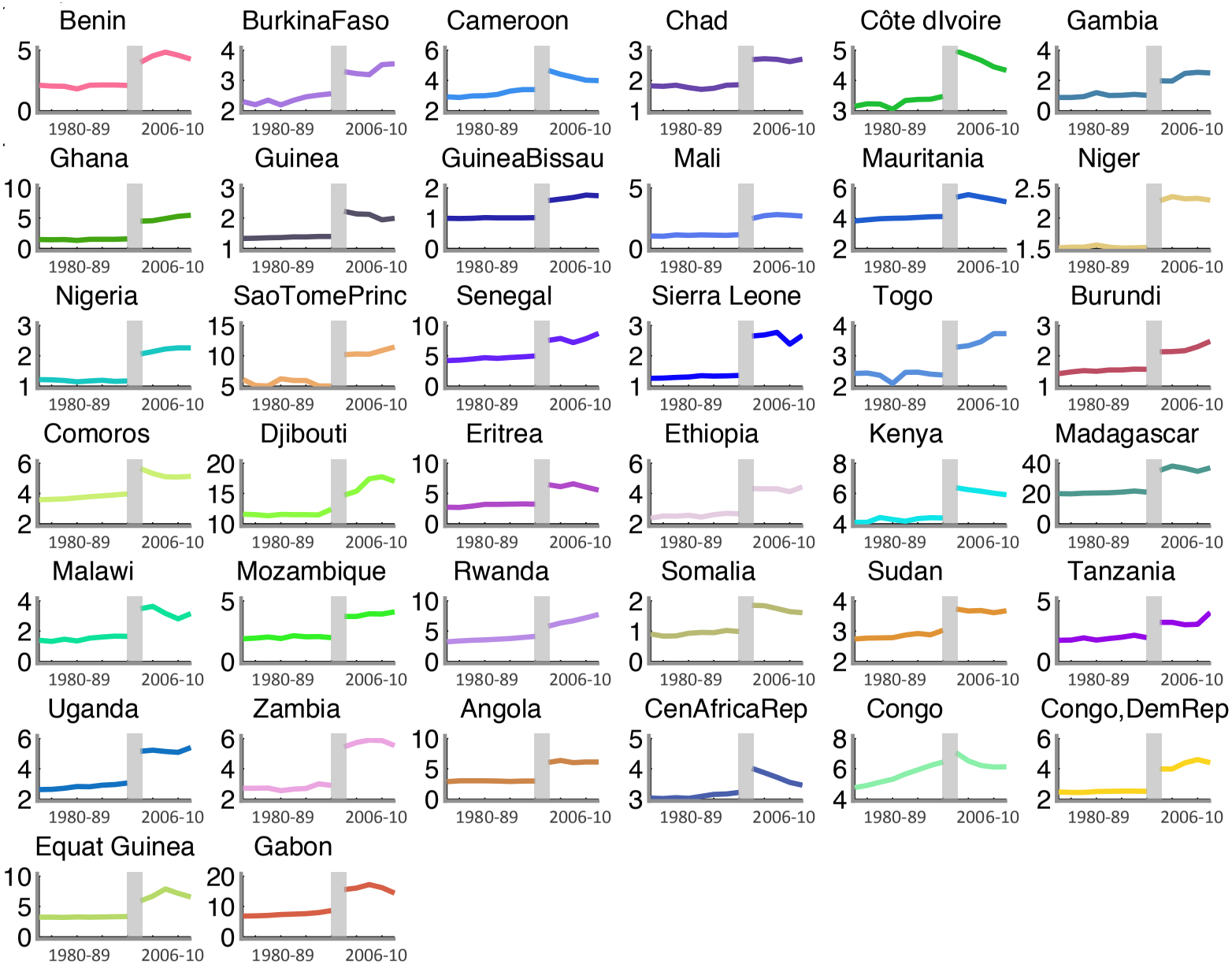


Figure SI-VI – 2



References:

1. Anderson RM & May RM (1991) *Infectious diseases of humans : dynamics and control* (Oxford University Press, Oxford ; New York) pp viii, 757 p.
2. Keeling MJR, P. (2007) *Modeling Infectious Diseases in Humans and Animals* (Princeton University Press).
3. Doolan DL, Dobano C, & Baird JK (2009) Acquired immunity to malaria. *Clinical microbiology reviews* 22(1):13-36, Table of Contents.
4. Artzy-Randrup Y, Alonso D, & Pascual M (2010) Transmission intensity and drug resistance in malaria population dynamics: implications for climate change. *PloS one* 5(10):e13588.
5. Klein EY, Smith DL, Boni MF, & Laxminarayan R (2008) Clinically immune hosts as a refuge for drug-sensitive malaria parasites. *Malaria journal* 7:67.
6. Keegan LT & Dushoff J (2013) Population-level effects of clinical immunity to malaria. *BMC infectious diseases* 13:428.
7. Snow RW*, et al.* (1998) Risk of severe malaria among African infants: direct evidence of clinical protection during early infancy. *The Journal of infectious diseases* 177(3):819-822.
8. Aguas R, White LJ, Snow RW, & Gomes MG (2008) Prospects for malaria eradication in sub-Saharan Africa. *PloS one* 3(3):e1767.
9. Sama W, Owusu-Agyei S, Felger I, Vounatsou P, & Smith T (2005) An immigration-death model to estimate the duration of malaria infection when detectability of the parasite is imperfect. *Statistics in medicine* 24(21):3269-3288.
10. Olotu A*, et al.* (2013) Four-year efficacy of RTS,S/AS01E and its interaction with malaria exposure. *The New England journal of medicine* 368(12):1111-1120.
11. Pates H & Curtis C (2005) Mosquito behavior and vector control. *Annual review of entomology* 50:53-70.
12. Chen-Hussey V*, et al.* (2013) Can topical insect repellents reduce malaria? A cluster-randomised controlled trial of the insect repellent N,N-diethyl-m-toluamide (DEET) in Lao PDR. *PloS one* 8(8):e70664.
13. Moore SJ, Davies CR, Hill N, & Cameron MM (2007) Are mosquitoes diverted from repellent-using individuals to non-users? Results of a field study in Bolivia. *Tropical medicine & international health : TM & IH* 12(4):532-539.
14. Siegert PY, Walker E, & Miller JR (2009) Differential behavioral responses of Anopheles gambiae (Diptera: Culicidae) modulate mortality caused by pyrethroid-treated bednets. *Journal of economic entomology* 102(6):2061-2071.
15. Russell TL, Beebe NW, Cooper RD, Lobo NF, & Burkot TR (2013) Successful malaria elimination strategies require interventions that target changing vector behaviours. *Malaria journal* 12:56.
16. Ferguson HM*, et al.* (2010) Ecology: a prerequisite for malaria elimination and eradication. *PLoS medicine* 7(8):e1000303.
17. Holling CS (1959) The components of predation as revealed by a study of small-mammal predation of the European pine sawfly. *The Canadian Entomologist* 91(5):293–320.
18. Karunamoorthi K (2011) Vector control: a cornerstone in the malaria elimination campaign. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 17(11):1608-1616.
19. Russell TL*, et al.* (2011) Increased proportions of outdoor feeding among residual malaria vector populations following increased use of insecticide-treated nets in rural Tanzania. *Malaria journal* 10:80.
20. WHO (2007) Insecticide-treated mosquito nets: a WHO position statement.
21. Hill AV (2011) Vaccines against malaria. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 366(1579):2806-2814.

22. Crompton PD, Pierce SK, & Miller LH (2010) Advances and challenges in malaria vaccine development. *The Journal of clinical investigation* 120(12):4168-4178.
23. Trape JF*, et al.* (2011) Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. *The Lancet infectious diseases* 11(12):925-932.
24. Killeen GF*, et al.* (2007) Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. *PLoS medicine* 4(7):e229.
25. Murray CJ*, et al.* (2012) Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* 379(9814):413-431.
26. WHO (2008) Roll Back Malaria Partnership, The Global Malaria Action Plan for a Malaria-Free World.
27. http://www.healthmetricsandevaluation.org