Malaria Elimination Transmission and Costing in the Asia-Pacific: a multi-species dynamic transmission model

Supplementary File 1: Mathematical model description

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This document provides a description of the methodology, equations and parameters underlying the mathematical model for *P. falciparum* and *P. vivax* malaria transmission.

Plasmodium falciparum sub-model

We use a compartmental model for the transmission of *P. falciparum* malaria. It's structure is similar to previously published models [1-6]. There are four infection classes in this model representing infections that are: severe; clinical; asymptomatic and detectable by microscopy; asymptomatic and undetectable by microscopy. Each infection class has a distribution of parasitaemia associated with it that is used to estimate the sensitivity of various diagnostic tests. Each infection class also has an infectiousness associated with it based on infectivity data. The probability of individuals entering each class of infection is dependent on their immunity status. We assume that untreated individuals will transition from higher to lower severity infection classes as they recover and that they can be boosted to higher severity classes on superinfection. We assume that treated individuals test positive for HRP2 after clearance of asexual parasitaemia for different durations depending on the detection limit of the test used. We use a spatially explicit version of this model to estimate the relative contribution of spatially heterogeneous interventions in a spatially heterogeneous transmission setting. The population is divided into a number of interconnected patches with each patch having its own transmission intensity. The patches are connected spatially such that the risk of infection of an individual in a particular patch from an individual in another patch is negatively correlated with the distance between the villages and positively correlated with the population size of the village. This connectivity between villages is used as a proxy for population movement between villages.

The system is depicted in Figure 1 and described by the following set of ordinary differential equations with compartment descriptions in Table 1:

$$\frac{dS}{dt} = \mu P(t) - \mu S - \Lambda(t)S + \omega R$$

$$\frac{dI_n}{dt} = -\mu I_n + p_{sn}(1-p_s)\Lambda(t)S - r_n I_n + r_a I_a - (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_n + p_{rn}(1-p_r)\Lambda(t)(R+H)$$

$$\frac{dI_a}{dt} = -\mu I_a + (1-p_{sn})(1-p_s)\Lambda(t)S + (1-p_{sev})r_c I_c - r_a I_a + (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_a + (1-p_{rn})(1-p_r)\Lambda(t)(R+H) + ptf(1-ptfc)r_t(T_o+T_v+T_h)$$

$$\frac{dI_c}{dt} = -\mu I_c + (1-\tau)p_s\Lambda(t)S + (1-\tau_{sev})(1-\theta_1)r_s I_s - (1-p_{sev})r_c I_c \ - p_{sev}r_c I_c + p_r(1-\tau)\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(1-ptftr)r_t(T_o+T_v+T_h)$$

$$\frac{dI_s}{dt} = -\mu I_s - (1-\tau_{sev})r_s I_s - \tau_{sev}r_Q I_s + p_{sev}r_c I_c$$

$$\frac{dT_o}{dt} = -\mu T_o + \tau_o p_s\Lambda(t)S - (1-ptf)r_t T_o + p_r\tau_o\Lambda(t)(I_n+I_a+R+H)$$

$$\frac{dT_v}{dt} = -\mu T_v + \tau_v p_s\Lambda(t)S - (1-ptf)r_t T_v + p_r\tau_v\Lambda(t)(I_n+I_a+R+H)$$

$$\frac{dT_h}{dt} = -\mu T_h + \tau_h p_s\Lambda(t)S - (1-ptf)r_t T_h + p_r\tau_h\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(ptftr)r_t(T_o+T_v+T_h)$$

$$\frac{dR}{dt} = -\mu R + r_n I_n - \Lambda(t)R - \omega R + \chi H$$

$$\frac{dH}{dt} = -\mu H + (1-ptf)r_t(T_o+T_v+T_h) + \tau_{sev}(1-\theta_2)r_Q I_s - \Lambda(t)H - \chi H$$

where

$$P = S + I_n + I_a + I_c + I_s + T_o + T_v + T_h + R + H$$

$$\Lambda(t) = (1/\lambda(t) + 1/\gamma_h + 1/\gamma_m)^{-1}$$

$$\lambda(t) = seas(t)\frac{b^2\epsilon_h\epsilon_m\frac{M}{P(t)}I(t)}{(b\epsilon_h\frac{M}{P(t)} + \delta_m)(\frac{\gamma_m}{\gamma_m+\delta_m})}$$

$$I(t) = \frac{\zeta_n I_n(t) + \zeta_a I_a(t) + I_c(t) + I_s(t)}{P(t)}$$

$$seas(t) = 1 + eln * a * \ cos(2\pi(t-\phi))$$

$$\tau = \tau_o + \tau_v + \tau_h$$

where eln is the Bivariate ENSO (El Niño southern oscillation) index time series standardised between 0 and 1 and smoothed with a running median to estimate effect size. (Accessible at: http://www.esrl.noaa.gov/psd/data/climateindices/).

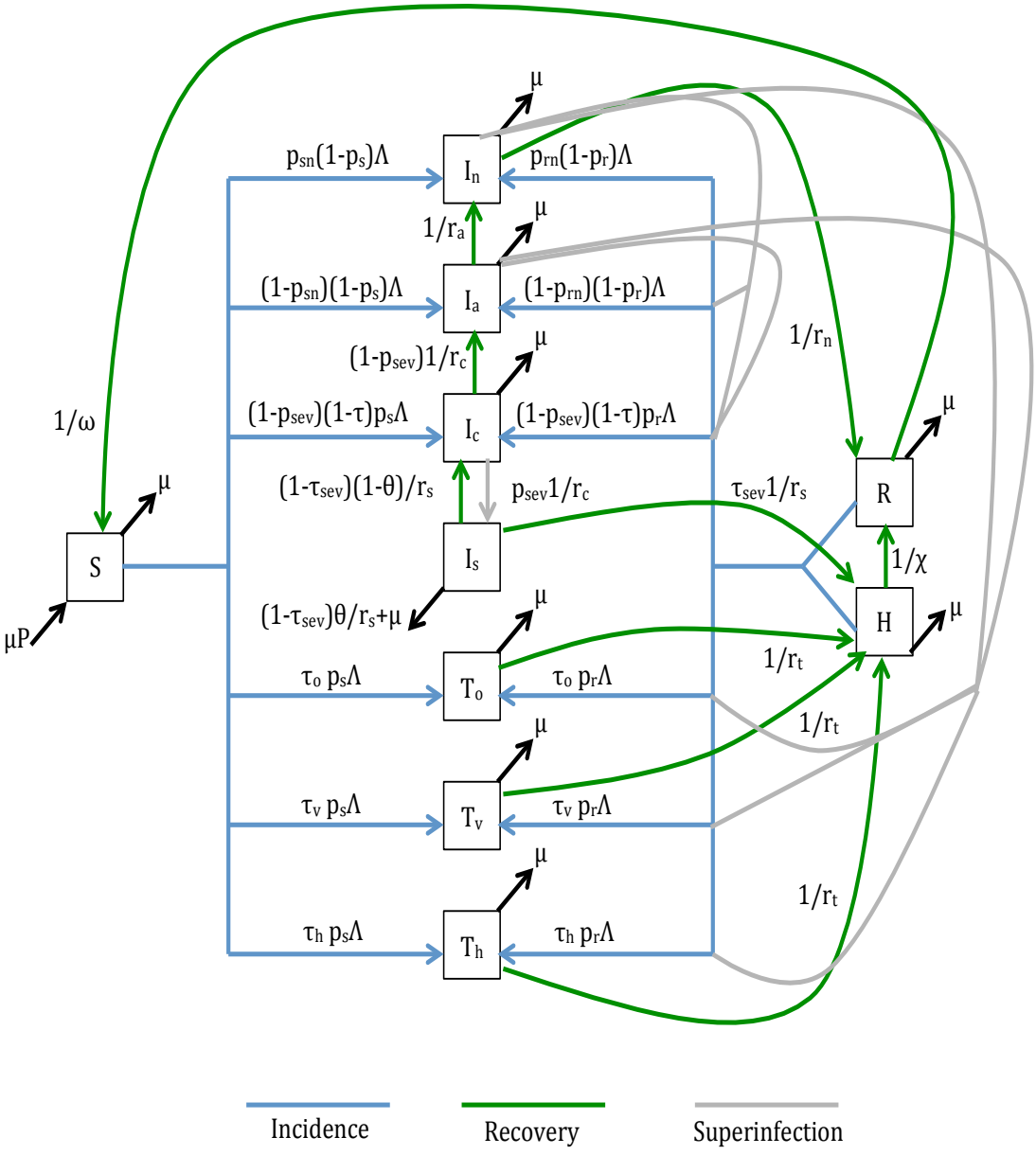

Figure 1 *Plasmodium falciparum* model flow diagram

Plasmodium vivax sub-model

We also use a compartmental model for the transmission of *P. vivax* malaria. Its structure is similar to the *P. falciparum* model with respect to the four infection classes, though there are key differences between the two model structures. *P. vivax* infections are characterized by relapses of malaria arising from persistent liver stages of the parasite (hypnozoites). We assumed that infections may clear with the persistence of hypnozoites in the liver (dependent on a probability) and that these hypnozoites may trigger relapses of infection. The relationship between Glucose 6-phosphate dehydrogenase deficiency (G6PDd) and *P. vivax* malaria is captured in the following manner. The distribution of G6PDd in each patch is determined by available data [7]. The probability of individuals entering each class of infection is dependent on their immunity status. The G6PDd proportion of the population has a reduced probability of clinical infection compared to the non-G6PDd proportion of the population. When primaquine treatment is introduced, those diagnosed with P. vivax can receive a test for G6PDd and are given Primaquine depending on the test outcome subject to test sensitivity. As with the *P. falciparum* model, we assume that untreated individuals will transition from higher to lower severity infection classes as they recover and that they can be boosted to higher severity classes on superinfection. The model is also spatially explicit with interconnected patches representing geographic areas of interest.

The system is depicted in Figure 2 and described by the following set of ordinary differential equations with compartment descriptions in Table 1:

Dependencies between P. vivax and P. falciparum models

The *P. vivax* and *P. falciparum* models are independent models for the same population. The models are entangled together at each time step to incorporate interactions and dependencies between the two species in the following manner:

1. Dual treatment (Treatment of mixed infection)

The untreated population infected with *P. falciparum* malaria who are simultaneously infected with and being treated with a drug for *P. vivax* malaria that is also effective against *P. falciparum* malaria (e.g. ACT, Chloroquine), will also be cured of their *P. falciparum* malaria. Likewise, treatment for a *P. falciparum* infection such as ACT, will also cure a *P. vivax* infection, though hypnozoites may persist in the liver after infection. [8, 9]

2. Triggering

It has been observed in many studies that clinical *P. falciparum* infections are often followed by *P. vivax* infection [10-12]. It has been hypothesized that the subsequent appearance of *P. vivax* implies that a *P. falciparum* episode reactivates *P. vivax* hypnozoites [10]. This is incorporated into the model with the population experiencing a clinical *P. falciparum* infection having a higher probability of *P. vivax* relapse compared to the rest of the population.

3. Radical cure

Primaquine is currently the only available drug that prevents relapse of *P. vivax* malaria. However, Primaquine is dangerous for individuals with G6PD deficiency and should not used as radical cure for *P. vivax* infections without knowledge of G6PD status [13]. The model assumes that the population is screened for G6PDd and only those who test as G6PD normal (subject to test sensitivity) are given Primaquine.

$$\frac{dS}{dt} = \mu P(t) - \mu S - \Lambda(t)S + \omega R + \kappa L$$

$$\frac{dI_n}{dt} = -\mu I_n + p_{sn}(1-p_s)\Lambda(t)S - r_n I_n + r_a I_a - (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_n + p_{rn}(1-p_r)p_{rel}\nu L + p_{rn}(1-p_r)\Lambda(t)(R+L)$$

$$\frac{dI_a}{dt} = -\mu I_a + (1-p_{sn})(1-p_s)\Lambda(t)S + (1-p_{sev})r_c I_c - r_a I_a + (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_a + (1-p_{rn})(1-p_r)p_{rel}\nu L + (1-p_{rn})(1-p_r)\Lambda(t)(R+L) + p_{tf}(1-ptfc)r_t(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD})$$

$$\frac{dI_c}{dt} = -\mu I_c + (1-\tau)p_s\Lambda(t)S + (1-\tau_{sev})(1-\theta_1)r_s I_s - (1-p_{sev})r_c I_c + p_r(1-\tau)\Lambda(t)I_a - p_{sev}r_c I_c + p_r(1-\tau)\Lambda(t)I_n + p_r(1-\tau)p_{rel}\nu L + p_r(1-\tau)\Lambda(t)(R+L) + p_{tf}(1-ptftr)(ptfc)r_t(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD})$$

$$\frac{dI_s}{dt} = -\mu I_s - (1-\tau_{sev})r_s I_s - \tau_{sev}r_Q I_s + p_{sev}r_c I_c$$

$$\frac{dT_o}{dt} = -\mu T_o + (1-p_{gd})\tau_o p_s\Lambda(t)S - (1-p_{tf})r_t T_o + (1-p_{gd})p_r\tau_o\Lambda(t)(I_n+I_a+R+L) + (1-p_{gd})p_r\tau_o p_{rel}\nu L$$

$$\frac{dT_v}{dt} = -\mu T_v + (1-p_{gd})\tau_v p_s\Lambda(t)S - (1-p_{tf})r_t T_v + (1-p_{gd})p_r\tau_v\Lambda(t)(I_n+I_a+R+L) + (1-p_{gd})p_r\tau_v p_{rel}\nu L$$

$$\frac{dT_h}{dt} = -\mu T_h + (1-p_{gd})\tau_h p_s\Lambda(t)S - (1-p_{tf})r_t T_h + (1-p_{gd})p_r\tau_h\Lambda(t)(I_n+I_a+R+L) + (1-p_{gd})p_r\tau_h p_{rel}\nu L + p_{tf}(ptftr)(ptfc)r_t(T_o+T_v+T_h)$$

$$\frac{dT_{oGD}}{dt} = -\mu T_{oGD} + p_{gd}\tau_o p_s\Lambda(t)S - (1-p_{tf})r_t T_{oGD} + p_{gd}p_r\tau_o\Lambda(t)(I_n+I_a+R+L) + p_{gd}p_r\tau_o p_{rel}\nu L$$

$$\frac{dT_{vGD}}{dt} = -\mu T_{vGD} + p_{gd}\tau_v p_s\Lambda(t)S - (1-p_{tf})r_t T_{vGD} + p_{gd}p_r\tau_v\Lambda(t)(I_n+I_a+R+L) + p_{gd}p_r\tau_v p_{rel}\nu L$$

$$\frac{dT_{hGD}}{dt} = -\mu T_{hGD} + p_{gd}\tau_h p_s\Lambda(t)S - (1-p_{tf})r_t T_{hGD} + p_{gd}p_r\tau_h\Lambda(t)(I_n+I_a+R+L) + p_{gd}p_r\tau_h p_{rel}\nu L + p_{tf}(ptftr)(ptfc)r_t(T_{oGD}+T_{vGD}+T_{hGD})$$

$$\frac{dR}{dt} = -\mu R + (1-p_h)(1-p_{tf})r_t(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD}) + (1-p_h)\tau_{sev}(1-\theta_2)r_Q I_s + r_n I_n - \Lambda(t)R - \omega R$$

$$\frac{dL}{dt} = -\mu L + p_h(1-p_{tf})r_t(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD}) + p_h\tau_{sev}(1-\theta_2)r_Q I_s - p_{rel}\nu L - \Lambda(t)L - \kappa L$$

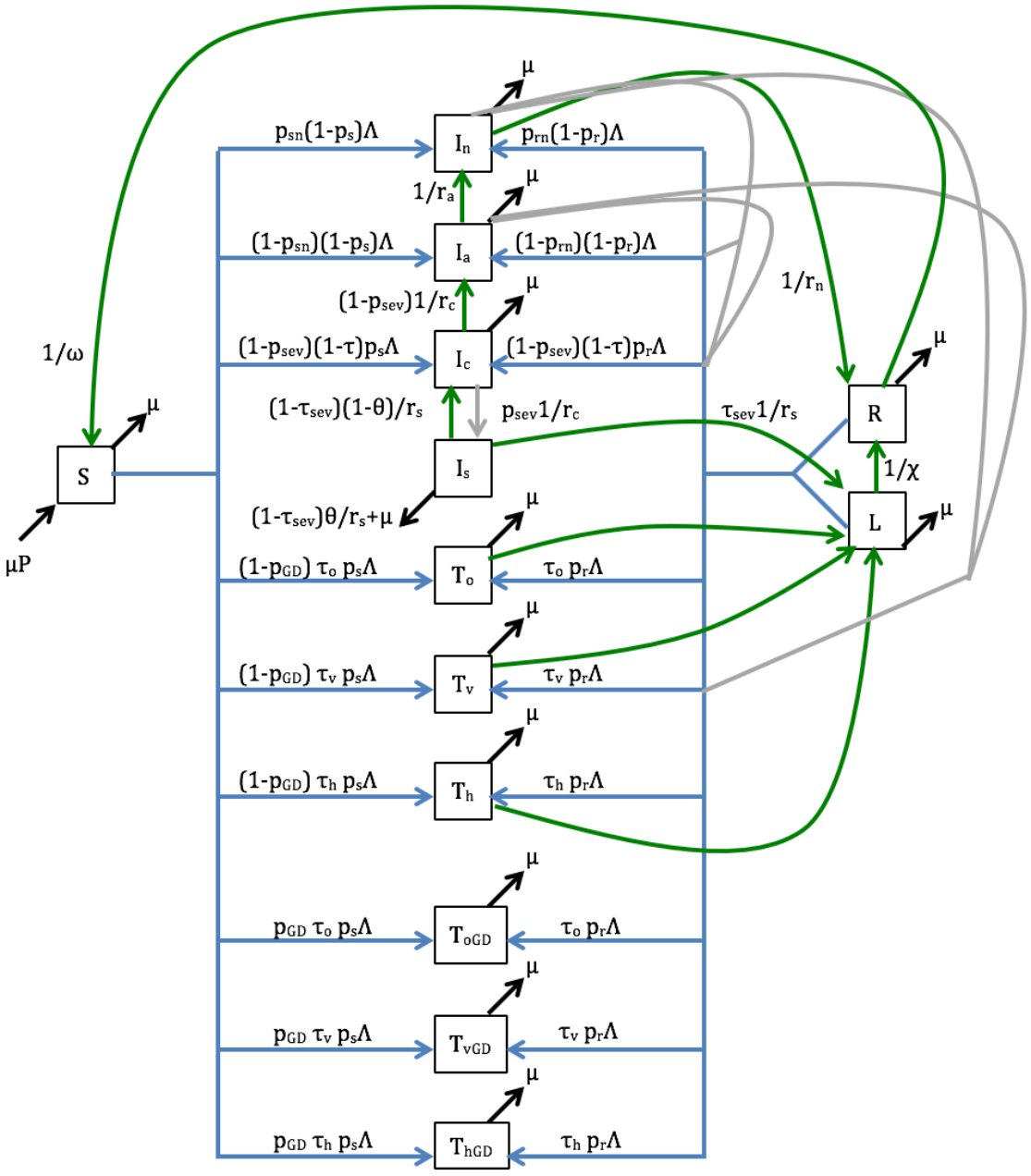

Figure 2 *Plasmodium vivax* model flow diagram

4. Masking

Different brands of Rapid Diagnostic Tests (RDT) have different targets and hence it may be the case that *non-falciparum* malaria is masked by *falciparum* malaria [14]. A comparison of RDTs that are designed to differentiate *falciparum* malaria from *non-falciparum* malaria but cannot differentiate between *non-falciparum* species nor identify *non-falciparum* malaria species within a mixed infection suggested that 11% - 22% of microscopy-confirmed *non-falciparum* cases are missed, with approximately 25% of these cases being declared as positive for *falciparum*. RDTs targeted to detect *P. vivax* specifically, whether alone or part of a mixed infection, were more accurate with tests missing less than 5% of *P. vivax* cases [14]. To account for this it is assumed that 5% of *P. vivax* cases are treated as *P. falciparum* cases and will not be candidates for radical cure in the model.

5. Competition between species

Experiments on patients with mixed infections have suggested that different malaria parasites interact or antagonize each other in the host [15]. The nature of these interactions is not always clearly understood with conflicting clinical results. It appears that though the different malaria species do engage in mutual parasite suppression, which species suppresses which remains unclear. In the case of *P. falciparum* and *P. vivax*, there is evidence for both directions of suppression [16, 17]. With respect with cross immunity, Maitland (1997) suggested the existence of an anti-toxic cross immunity between *P. falciparum* and *P. vivax* while Jeffery (1966) found no evidence for cross immunity [17, 18]. Other studies suggest that mixed infections could be associated with more severe disease [[15]. In light of this evidence the model does not account for mutual suppression and cross immunity.

6. Protective effect of G6PDd against malaria

The results of studies examining the risk of malaria for different G6PD-deficient genotypes are not consistent and the nature of protective effect itself is not clearly understood [7, 19]. Leslie (2010) found that study participants with reduced Mediterranean-type G6PD levels were approximately one-fifth as likely to develop *P. vivax* malaria as those with normal G6PD levels while Louicharoen (2009) found that the Mahidol^{487A} variant reduces *vivax*, but not *falciparum* parasite density in humans while having no effect on the number of clinical cases reported [20, 21]. Ruwende et al. (1995) found a reduction in risk for severe falciparum malaria in both males and females deficient in the A- G6PD variant while Guindo et al. (2007) found a similar effect in males, but none in females [22, 23]. In light of this evidence the model does not include a protective effect for the G6PDd proportion of the population.

Table 1 Model Variables

Symbol	Definition
	***Falciparum* Variables**
S	Uninfected and non-immune population
H	Uninfected and immune population who test positive by RDT
R	Uninfected and immune population
$\mathbf{I_N}$	Infected and asymptomatic malaria population undetectable by microscopy
$\mathbf{I_A}$	Infected and asymptomatic malaria population detectable by microscopy
$\mathbf{I_C}$	Infected and clinical malaria population
$\mathbf{I_S}$	Infected and severe malaria population
$\mathbf{T_0}$	Population under effective treatment by other means (E.g. Private care)
$\mathbf{T_V}$	Population under effective treatment by Village Malaria Worker
$\mathbf{T_H}$	Population under effective treatment through Health Information System
	***Vivax* Variables**
S	Uninfected and non-immune population
L	Uninfected and immune population with hypnozoites
R	Uninfected and immune population without hypnozoites
$\mathbf{I_N}$	Infected and asymptomatic malaria population undetectable by microscopy
$\mathbf{I_A}$	Infected and asymptomatic malaria population detectable by microscopy
$\mathbf{I_C}$	Infected and clinical malaria population
$\mathbf{I_S}$	Infected and severe malaria population
$\mathbf{T_0}$	Population under effective treatment by other means (E.g. Private care)
$\mathbf{T_V}$	Population under effective treatment by Village Malaria Worker
$\mathbf{T_H}$	Population under effective treatment through Health Information System
$\mathbf{T_{0,GD}}$	Population under effective treatment by other means (E.g. Private care) with G6PDd
$\mathbf{T_{V,GD}}$	Population under effective treatment by Village Malaria Worker with G6PDd
$\mathbf{T_{H,GD}}$	Population under effective treatment through Health Information System with G6PDd

Table 2 Model Parameters

Symbol	Definition	Value	Units	Sim Range	Source
	Common Parameters				
M	Maximum populations of mosquitoes		num		estimated from data
ϕ	Month of peak transmission	(1, 12)	month		estimated from data
a	Amplitude of seasonal variation	1	na	(0,1)	assumption
δ_m	Average life expectancy of mosquito	14	days	(10,20)	[24, 25]
b	Number of mosquito bites per human per day	1/3	day^{-1}	(0.1,0.5)	[26, 27]
ε_m	Probability that a bite from an infectious mosquito will result in infection	50	%	(20,50)	[27-29]
$1/\gamma_M$	Duration of latent period in mosquitoes	10	days	(5, 15)	[13, 24, 30-33]
eff_{IRS}	Effectiveness of indoor residual spraying	25	%	(0, 50)	estimated from data
eff_{ITN}	Effectiveness of bednets	25	%	(0, 50)	estimated from data
hl_{NET}	Half-life of bednets	1.5	year	(1, 2)	[34]
eff_{VMW}	Effectiveness of Village Malaria Worker	60	%	(50, 70)	Expert opinion
eff_{HIS}	Effectiveness of Health Information System	25	%	(10,30)	estimated from data
eff_{OTH}	Effectiveness of other treatment systems	10	%	(5, 15)	estimated from data
$1/\mu$	Average life expectancy of the population	72	year	(68,75)	[35]
eln	Smoothing parameter of el niño effect	21			estimated
	Falciparum Parameters				
p_S	Proportion of non-immune individuals expected to develop clinical malaria after infection	90	%	(80,100)	[31, 36]
p_R	Proportion of immune individuals expected to develop clinical malaria after infection	10	%	(0,77)	[37]
p_{SN}	Proportion of non-immune individuals expected to develop sub-patent infection upon challenge	10	%	(0,20)	assumption
p_{RN}	Proportion of immune individuals expected to develop sub-patent infection upon challenge	50	%	(30,70)	assumption
$1/r_S$	Duration of symptoms in an untreated severe infection	10	day	(5,15)	[38, 39]
$1/r_C$	Duration of symptoms in an untreated clinical infection	10	days	(5,15)	[38, 39]
$1/r_A$	Duration of symptoms in an untreated asymptomatic infection	130	days	(60, 200)	[40-42]
τ_{SEV}	Proportion of severe malaria that is treated	80	%	(0, 100)	assumption

p_{sev}	Proportion of clinical infections that become severe	3	%	(5,25)	[43, 44]
ζ_A	Relative infectiousness of asymptomatic infection compared to clinical infection	12.6/27	na	(0,0.50)	[45]
ζ_N	Relative infectiousness of sub-patent infection compared to clinical infection	3.9/27	na	(0., 0.25)	[46]
$1/\omega$	Duration of immunity in an individual without challenge	1	year	(0.5,10)	[41]
θ_1	Probability that untreated severe malaria progresses to death	70	%	(50,80)	[44]
θ_2	Probability that treated severe malaria progresses to death	22	%	(15,30)	[47-49]
ε_h	Probability that a bite from an infectious human will result in infection	50	%	(7,64)	[30, 50]
$1/\gamma_H$	Incubation period and time to gametocytemia in humans	21	days	(14,24)	[30-33, 51]
$1/\chi$	Period of HRP2 detectability by RDT	28	days	(21,37)	[52-54]
$1/r_T$	Time taken to clear asexual parasites after treatment	3	day	(3,7)	[55]
$1/r_Q$	Recovery time with quinine for severe infections	6	days	(4,8)	[56]
ptf	Baseline probability of treatment failure on ACT	5	%	(1,10)	assumption
ptfc	Probability of being clinical after treatment failure	0.75	%	(0.5, 0.9)	assumption
ptftr	Probability of seeking trt if clinical, after treatment failure	0.27	%	(0.1, 0.4)	Estimated from data
	Vivax Parameters				
p_S	Proportion of non-immune individuals expected to develop clinical malaria after infection	90	%	(80,100)	[57]
p_R	Proportion of immune individuals expected to develop clinical malaria after infection	10	%	(0,30)	[58]
p_{SN}	Proportion of non-immune individuals expected to develop sub-patent infection upon challenge	10	%	(0,20)	[57]
p_{RN}	Proportion of immune individuals expected to develop sub-patent infection upon challenge	17	%	(10,40)	[59]
$1/r_S$	Duration of symptoms in an untreated severe infection	5	day	(2,10)	assumption
$1/r_C$	Duration of symptoms in an untreated clinical infection	20	days	(2,60)	[60, 61]
$1/r_A$	Duration of symptoms in an untreated asymptomatic infection	130	days	(60, 200)	[60, 62-64]
τ_{SEV}	Proportion of severe malaria that is treated	80	%	(0, 100)	assumption
p_{sev}	Proportion of clinical infections that become severe	3	%	(5,25)	[44, 65]

ζ_A	Relative infectiousness of asymptomatic infection compared to clinical infection	1	na	(0,0.1)	[66]
ζ_N	Relative infectiousness of sub-patent infection compared to clinical infection	1	na	(0, 1)	[66]
$1/\omega$	Duration of immunity in an individual without challenge	1	year	(0.5,10)	assumption
θ_1	Probability that untreated severe malaria progresses to death	20	%	(5,70)	[44, 67]
θ_2	Probability that treated severe malaria progresses to death	0.02	%	(5,70)	[49, 68-70]
ε_h	Probability that a bite from an infectious human will result in infection	23	%	(7,40)	[13, 28, 71]
$1/\gamma_M$	Duration of latent period in mosquitoes	12	days	(5, 15)	[72, 73]
$1/\gamma_H$	Incubation period and time to gametocytemia in humans	17	days	(15,20)	[13, 51, 74]
$1/r_T$	Time taken to clear asexual parasites in uncomplicated *Pf* infection with treatment	3	day	(3,7)	[55]
$1/r_Q$	Recovery time with quinine for severe infections	6	days	(4,8)	[56]
ptf	Baseline probability of treatment failure on ACT	5	%	(1,10)	assumption
ptfc	Probability of being clinical after treatment failure	0.75	%	(0.5, 0.9)	assumption
ptftr	Probability of seeking trt if clinical, after treatment failure	0.27	%	(0.1, 0.4)	Estimated from data
ptfp	Probability of treatment failure on Primaquine	10	%	(5, 15)	[75-77]
adhp	Non-adherence to 14-day self-administered treatment of primaquine	15	%	(10,30)	[78]
$1/r_P$	Duration of Primaquine treatment	14	day	(12,16)	[8, 79]
$1/\kappa$	Hypnozoite death rate	400	day	(330, 500)	[13, 28, 73]
psens	Sensitivity of Carestart v2 G6PDd RDT	97	%	(95-100)	[80]
pgd	Probability of a clinical infection if G6PDd	30	%	(0, 100)	[21]
mask	Proportion of *P. Vivax* cases masked as *P. falciparum* cases	5	%	(5, 25)	[14]
prel	Probability of relapse	25	%	(14,29)	[11, 81]
Incprel	Probability of relapse due to triggering from a treated *P. falciparum* case	35	%	(20,47)	[11, 81]
$1/\nu$	Time to first relapse	45	day	(21,50,150)	[13, 28, 73, 82]
ph	Probability of recovering with hypnozoites under ACT	68	%	(50,80)	[13, 83]
phprim	Probability of recovering with hypnozoites under Primaquine	13	%	(10,30)	[13, 83]

Sub-patent infection and diagnostics

We assume that parasitaemia (parasites per µl) within each infection class (sub-patent, asymptomatic and clinical) is log-normally distributed as described in [84]. We also use a mixture model approach to obtain the distribution for severe infection using the data from [85].

The following table summarises the model parameters and their sources:

Description	Unit	Pf Value	Ref	Pv Value	Ref
Geometric mean parasitaemia for sub-patent infections (mn_N)	μl^{-1}	5	[86]	5	[86, 87]
Geometric mean parasitaemia for asymptomatic infections(mn_A)	μl^{-1}	5158	[86]	750	
Geometric mean parasitaemia for clinical infections(mn_C)	μl^{-1}	25000	[85, 88]	5000	[89]
Geometric mean parasitaemia for severe infections(mn_S)	μl^{-1}	350000	[85]	20000	[90]
Log standard deviation of log-normal parasite distribution for sub-patent infections	-	0.75		0.75	
Log standard deviation of log-normal parasite distribution for asymptomatic infections	-	1.5	[88, 91]	1.5	[85, 88]
Log standard deviation of log-normal parasite distribution for clinical infections	-	1.3	[85, 88]	1.3	[25, 85]
Log standard deviation of log-normal parasite distribution for severe infections	-	0.26	[85]	4	[25]

The following table describes the detection limits also described in [84]:

Description	Units	Pf Value	Ref
Detection limit for conventional RDT	μl^{-1}	200	[92]
Detection limit for microscopy	μl^{-1}	100	[92]
Detection limit for proposed RDT	μl^{-1}	5	[93, 94]
Detection limit for conventional qPCR	μl^{-1}	0.2	[95]

Test sensitivity:

The parameters above are used to compute diagnostic sensitivity. For each disease class, i, the sensitivity of a test, x, with detection limit, d_T, is given by the formula:

$$sens_{i,x} = 1 - \frac{1}{2}\left[1 + erf\left(\frac{d_T - \mu_i}{\sigma_i \sqrt[2]{2}}\right)\right]$$

Where μ_i and σ_i are the log-mean and the log-standard deviation of the log-normal distribution of parasitaemia for disease class i ε {sub-patent, asymptomatic, clinical, severe).

Test specificity:

It has been shown that treated individuals remain positive by conventional RDT for approximately 28 days after successful clearance of asexual parasites [52-54]. An H compartment (individuals recently recovered who are not infected but test positive by RDT) has therefore been included in the model in order to simulate this. The duration of time spent in the H compartment is dependent on the sensitivity of the RDT to detect HRP2 which is assumed to be linearly correlated with its asexual parasite detection limit.

Duration in each infection class:
For severe, clinical and asymptomatic infection the duration of infection is well documented. For sub-patent infection, we assume that the duration of sub-patent infection, δ_N, can be extrapolated from the duration of infection of asymptomatic infection, δ_A, and an assumption of log-linear decline in parasitaemia using the following formula:

$$\delta_N = \delta_A \frac{\mu_N - d_0}{\mu_A - \mu_N}$$

Where μ_N is the log-mean of the log-normal distribution of parasitaemia for sub-patent infection, μ_A is the log-mean of the log-normal distribution of parasitaemia for asymptomatic infection and d_0 is the detection limit of the most sensitive test (qPCR).
Using the parameters above, we would expect sub-patent infection to be detectable by qPCR for 75 days.

Force of infection and Seasonality

The force of infection on humans, λ is derived by assuming that mosquito dynamics of an SEI model are at a steady state resulting in the following:

$$\Lambda(t) = (1/\lambda(t) + 1/\gamma_h + 1/\gamma_m)^{-1}$$

$$\lambda(t) = seas(t)\frac{b^2\epsilon_h\epsilon_m\frac{M}{P(t)}I(t)}{(b\epsilon_h\frac{M}{P(t)} + \delta_m)(\frac{\gamma_m}{\gamma_m+\delta_m})}$$

$$I(t) = \frac{\zeta_n I_n(t) + \zeta_a I_a(t) + I_c(t) + I_s(t)}{P(t)}$$

$$seas(t) = 1 + eln * a * \ cos(2\pi(t - \phi))$$

where eln is the Bivariate ENSO (El Niño southern oscillation) index time series standardised between 0 and 1 and smoothed with a running median to estimate effect size. (Accessible at: http://www.esrl.noaa.gov/psd/data/climateindices/).

Spatial heterogeneity

A spatially explicit version of this multi-species model can be formulated in a metapopulation framework. This enables the estimation of the relative contribution of spatially targeted interventions in a spatially heterogeneous transmission setting. The area/population of interest is divided into a number of interconnected patches with each patch representing a country/sub-population having its own transmission intensity. The patches are connected spatially such that the risk of infection of an individual in a particular patch from an individual in another patch is negatively correlated with the distance between the patches.

The probability of an individual from patch i being in patch j, σ_{ij}, is assumed to be given by:

$$\sigma_{ij} = \left(\frac{1}{1 + het\ h_{ij}}\right) \Big/ \sum_{j=1}^{N} \frac{1}{1 + het\ h_{ij}}$$

Where h_{ij} is the Euclidian distance between the centroids of patches i and j and N is the number of patches. The parameter, het, is a measure of the level of spatial heterogeneity where het=0 simulates uniform mixing between patches and het=∞ simulates no mixing between patches.

Then $\sum_{j=1}^{N}(\sigma_{ji}\ P_j)$ becomes the "augmented population" of patch i, meaning the population of patch i combined with the parts of the populations of the other patches which are mixing with patch i.

The force of infection on humans, λ, in patch i can be derived by considering a susceptible human from patch i visiting patch j and being bitten there by an infected mosquito and infected before returning to patch i:

$$\lambda = \sum_{j=1}^{N} \sigma_{ij} seas_j \left(\frac{b^2 \epsilon_h \epsilon_m \frac{M_j}{P_j}}{(b\epsilon_h \frac{M_j}{P_j} + \delta_m)(\frac{\gamma_m}{\gamma_m + \delta_m})} \times \frac{\zeta_n I_{nj} + \zeta_a I_{aj} + I_{cj} + I_{sj}}{\sum_{j=1}^{N} \sigma_{ij} P_j} \right)$$

Model Interventions

The table below summarises the impact that each of the interventions modelled has on model parameters/equations.

Intervention	Description	Model Impact
Passive treatment	Treatment probabilities (τ) for different avenues of treatment (v, h, o) dependent on coverage (cov), treatment-seeking and treatment effectiveness (*eff*) and diagnostic sensitivity (*sens*)	See below
$\tau_v = cov_v \times eff_v \times sens_v$ $\tau_h = (1 - cov_v eff_v) \times eff_h \times sens_h$ $\tau_o = (1 - cov_v eff_v - (1 - cov_v eff_v) eff_h) \times eff_o \times sens_o$		
Long Lasting Insecticide-treated Nets	Net distribution as a proportion of the population at risk (*itn*) and the half-life of the net (*hlnet*) are used to compute cumulative coverage (itncov). This, together with usage and ability to prevent	See below

	transmission (*itneff*) is used to decrease the transmission function λ	
$itncov_t = itn_t + 0.5itncov_{t-1}e^{-\frac{1}{12}/(hlnet)}$ $\lambda_t^* = (1 - itncov_t \times itneff) \times \lambda_t$		
Indoor residual spraying	Number of people protected by IRS as a proportion of the population at risk (*irs*) and the half-life of the insectide (*hlspray*) are used to compute cumulative coverage (irscov). This, together with ability to prevent transmission (*irseff*) is used to decrease the transmission function λ	See below
$irscov_t = irs_t + 0.5irscov_{t-1}e^{-\frac{1}{12}/(hlspray)}$ $\lambda_t^* = (1 - irscov_t \times irseff) \times \lambda_t$		
Injectable artesunate	Switching from treatment of severe infections with quinine to injectable artesunate	Parameters decreased: $1/r_Q$ – recovery time pmort – probability of death of treated severe infections
Single dose P.v. treatment	Switching from a 14 day regimen of Primaquine to a 1 day regimen of new treatment.	Parameters affected $1/r_p$ = recovery time adhr = adherance
New P.f. drug	Switching to a new drug against Pf	Parameter reduced: ptf – probability of treatment failure
Mass Drug Administration	Implementing mass treatment at a coverage (*mcov*) over a duration of implementation of a single round (*mdur*) to form a rate of *mrate*: $mrate = -\ln\left(\frac{1 - \text{mcov}}{\text{mdur}}\right)$ The protective duration of the drug is given by $1/mrec$.	See below
Addition of the following differential equations to the model structure: $\frac{dSm_f}{dt} = mrate \times S_f - (mrec + \mu)Sm_f$ $\frac{dTm_f}{dt} = mrate \times (P_f - (S_f + H_f + R_f)) - ptf \times mrec \times Tm_f - (1 - ptf)r_t Tm_f - \mu Tm_f$ $\frac{dHm_f}{dt} = mrate \times H_f + (1 - ptf)r_t Tm_f - (mrec + \mu)Hm_f$ $\frac{dRm_f}{dt} = mrate \times R_f - (mrec + \mu)Rm_f$ $\frac{dSm_v}{dt} = mrate \times S_v - (mrec + \mu)Sm_v$ $\frac{dTm_v}{dt} = mrate \times (P_v - (S_v + L_v + R_v)) - ptf \times mrec \times Tm_v - (1 - ptf)r_t Tm_v - \mu Tm_v$		

$$\frac{dLm_v}{dt} = mrate \times L_v + p_h(1-ptf)r_t Tm_v - (mrec + \mu)Lm_v$$
$$\frac{dRm_v}{dt} = mrate \times R_v + (1-p_h)(1-ptf)r_t Tm_v - (mrec + \mu)Rm_v$$

Model calibration

The model was initially calibrated to the reported annual incidence data from the World Malaria Reports using a pseudo Likelihood maximisation approach based on parameter sets being drawn randomly from the simulation ranges specified in Table 2 and with parameter sets with the highest likelihood being selected for the model. The extent of the data were such that while reported distribution of LLINs and IRS were included in the model to inform changes in incidence, there was no data available on health system advances between 2000 and 2015 such as the introduction of community malaria workers etc. These were imputed based on observed changes in reported incidence.

Thus the model was further calibrated to the estimated burden of disease separately for *P. falciparum* and *P. vivax* malaria to capture the variability in the treatment seeking and completeness rates detailed in Maude, Riley [96], Riley and Maude [97].

Figures 3 and 4 depict the observed clinical burden against the model predicted clinical burden for *P. falciparum* and *P. vivax* malaria respectively. While the model captures the general trend of incidence well, it is unsurprising that the historic data is not always replicated. In addition to the limitations described above, the data were collected at a time when a large proportion of malaria cases reported were suspected, rather than confirmed cases and many countries were still using rapid diagnostic tests that were unable to distinguish between malaria species. In light of this, the authors placed more weight on replicating the most recent data well compared to historic data.

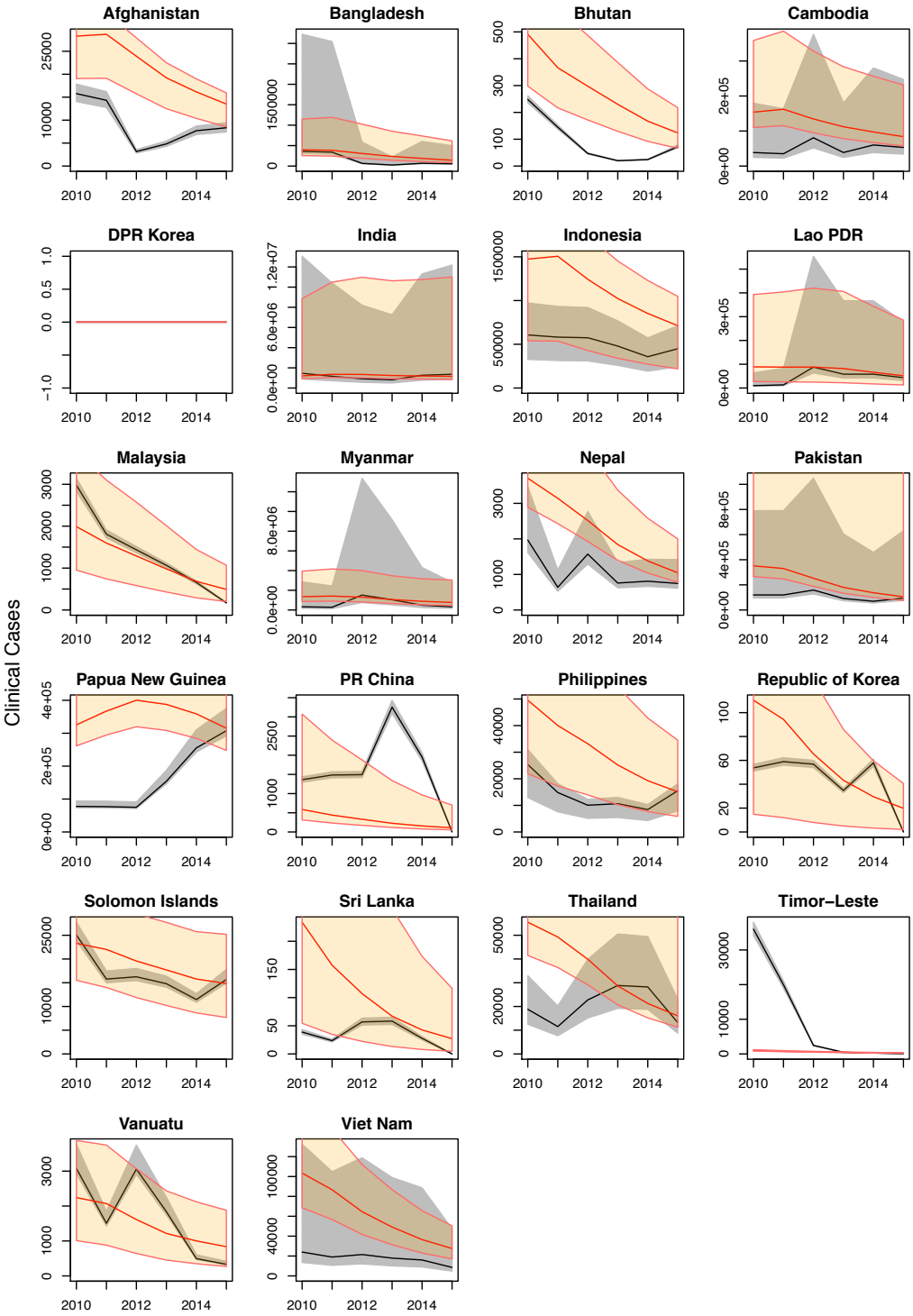

Figure 3 Calibration: *P. falciparum* estimated clinical burden (grey) with predicted clinical burden (red)

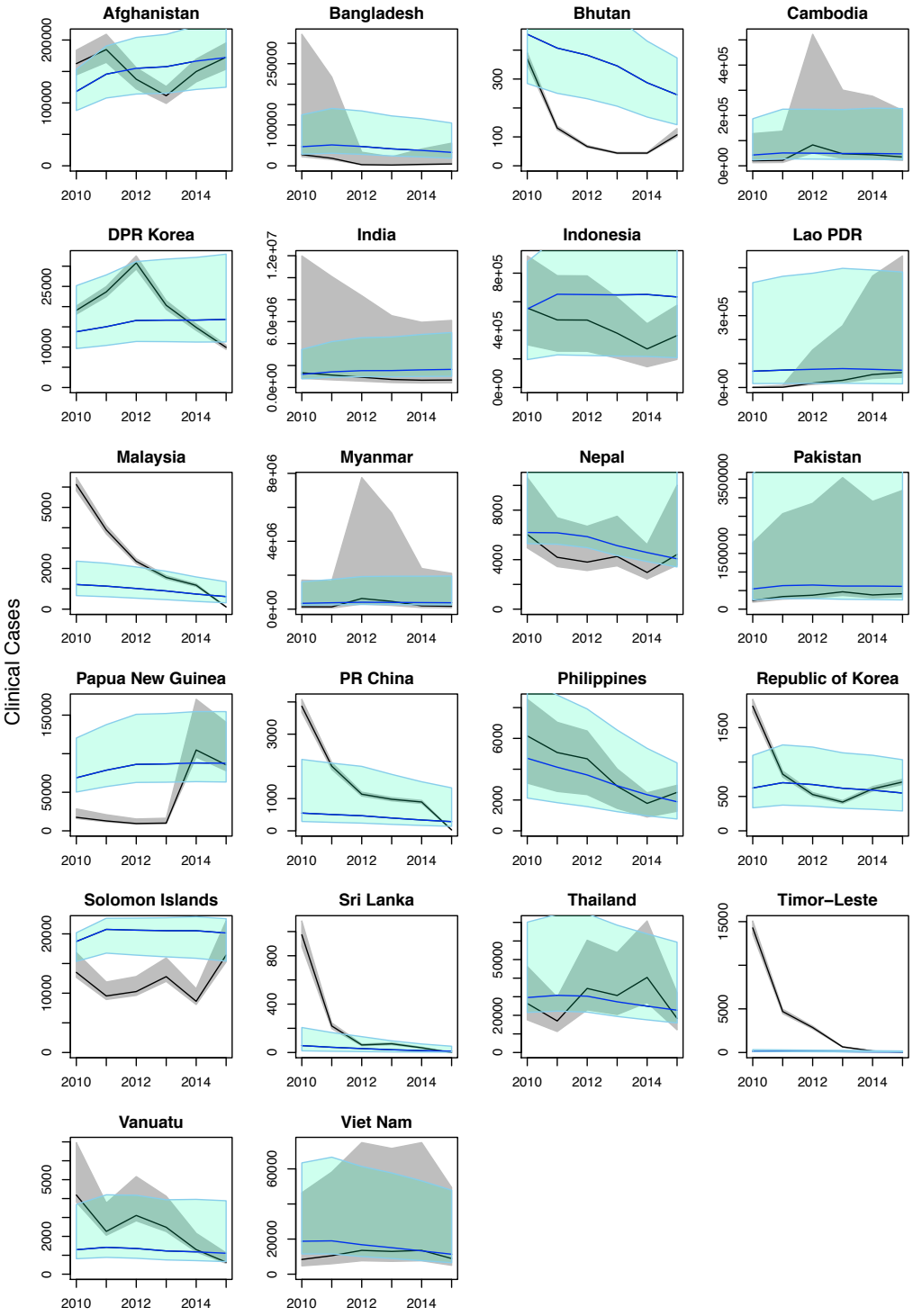

Figure 4 Calibration: *P. vivax* estimated clinical burden (grey) with predicted clinical burden (blue)

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