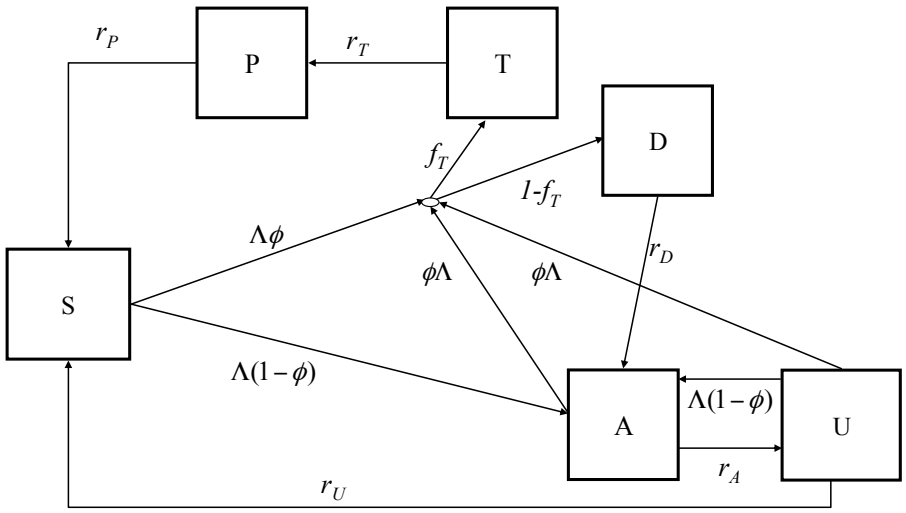
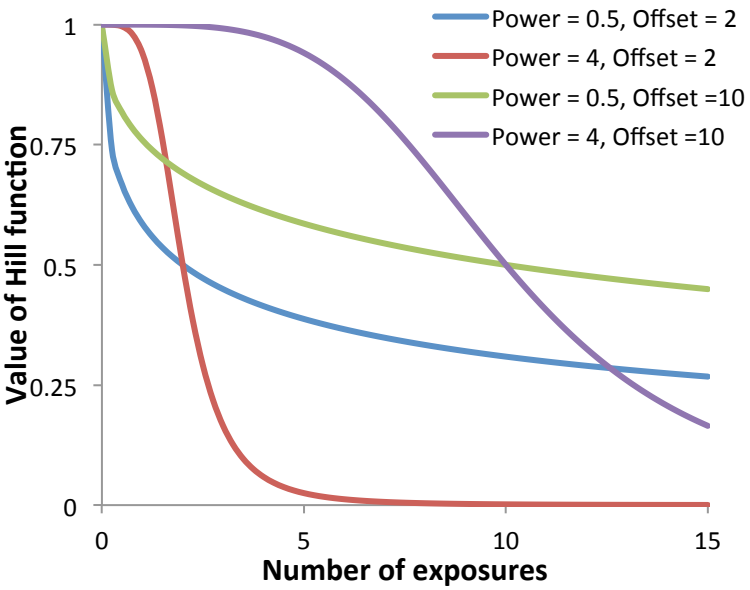
The development of immunity to malaria in pregnancy and its implications for the success of prevention strategies: a model-based analysis

Patrick GT Walker, Jamie T Griffin, Matt Cairns, Stephen J Rogerson, Anna M van Eijk, Feiko ter Kuile, Azra C Ghani.

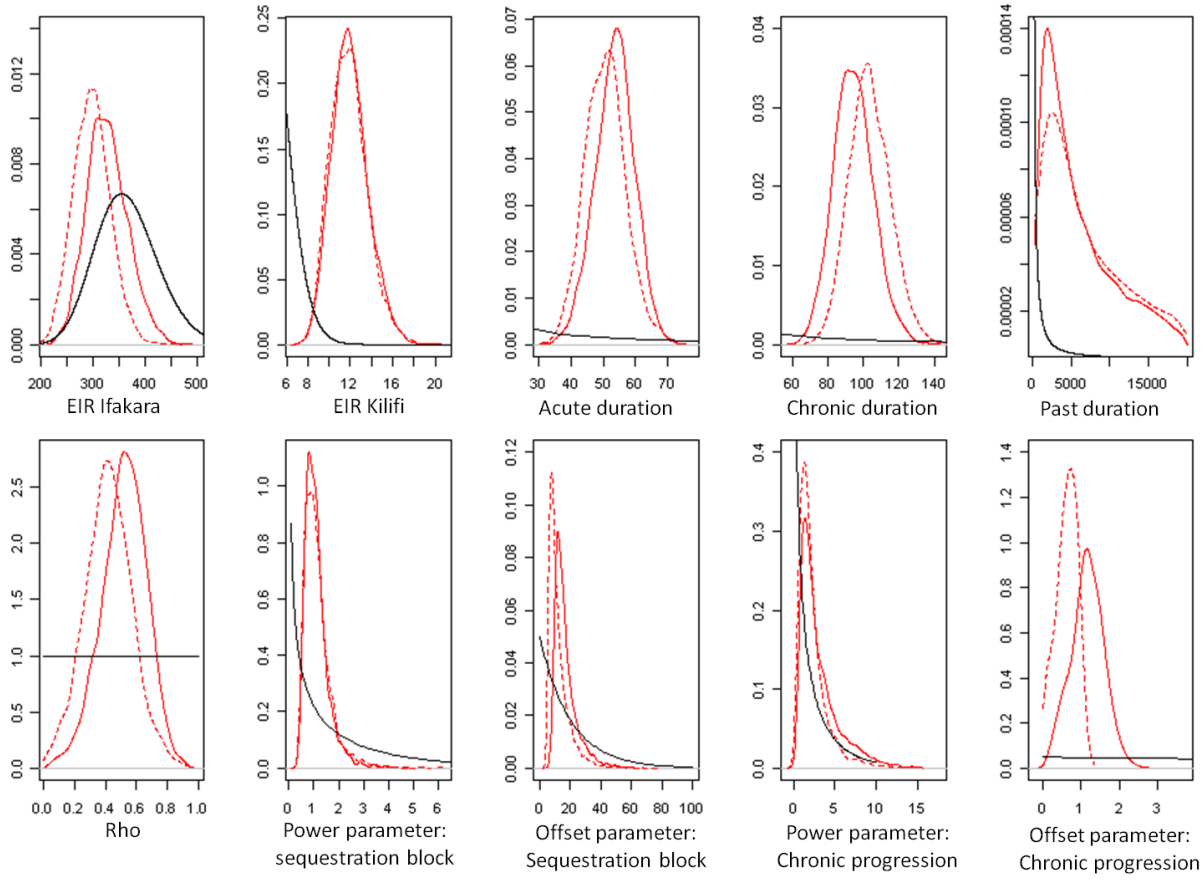
Supplementary Figures



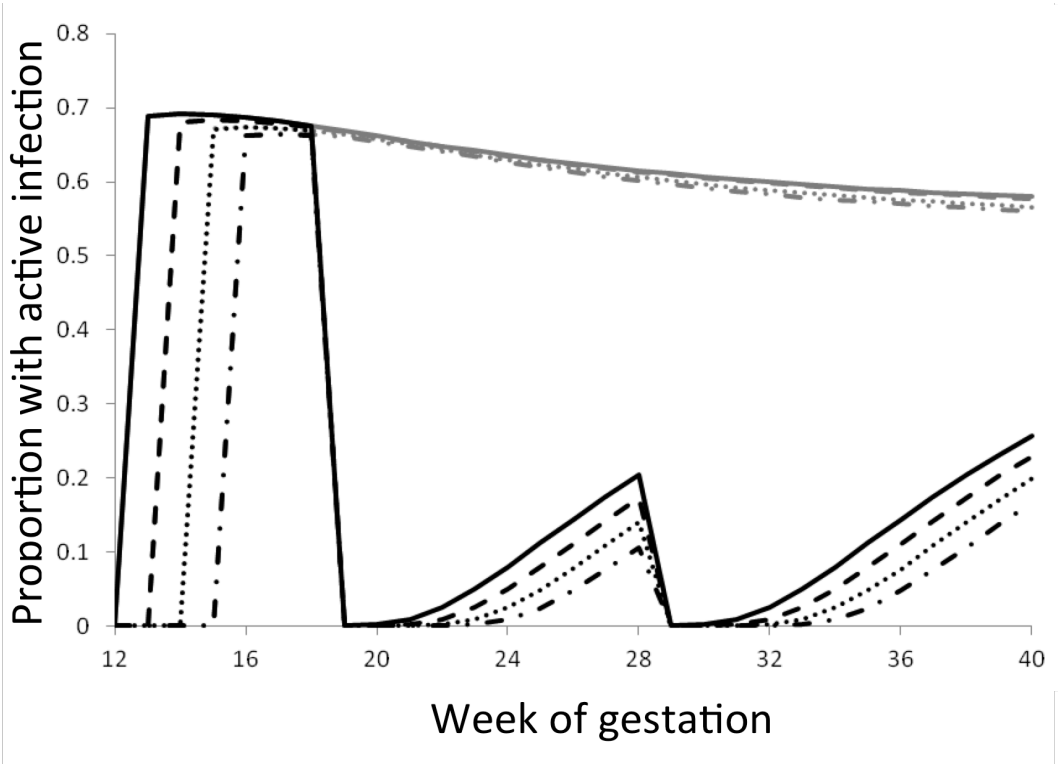
Supplementary Figure S1| Flow diagram for human stages of the general population model (taken from Griffin et al.[42])



Supplementary Figure S2| Different effects of Hill function parameters



Supplementary Figure S3| Posterior distributions of the two final models relative to their priors. Posterior distributions for the final models are shown in red with solid lines for the infection-specific model and dashed lines for the infected-pregnancy-specific model. Prior distributions are indicated with black lines.



Supplementary Figure S4| The effect of IPTp with different durations between infection and sequestration. Figure shows the prevalence of placental infection by week of gestation in the absence of IPTp (grey lines) and when IPTp with a Gamma-distributed subsequent period of prophylaxis, $P \sim \Gamma(4,5)$, is administered at 18 and 28 weeks (black lines) when the duration between infection and sequestration is 0 (solid lines), 7 (dashed lines), 14 (dotted lines) and 21 days (dashed and dotted line).

Supplementary Tables

Supplementary Table S1 Fitted parameters and prior and posterior distributions for the the parameters from the general population model fitted for the analysis

Parameter	Description (units)	Prior distribution [median (95% interval)]	Posterior Median (with 95% credible interval)
b_{MAX}	Probability of human infection from an infectious bite with no immunity	Beta(2,2) † [0.61 (0.20,0.93)]	0.93 (0.84-0,98)
b_{MIN}	Probability of human infection from an infectious bite with full immunity	Uniform(0,1)† [0.27 (0.01,0.76)]	0.006 (0.004,0.01)
I_{B0}	Infection blocking immunity scale parameter	[758 .0 (0.004,2887.3)]	1072.1 (916.3, 1231.5)
κ_b	Infection blocking immunity shape parameter	Gamma(1,2) [1.68 (0.24,5.57)]	6.05 (5.17, 7.21)
τ	Rate of acquisition of Infection blocking immunity power scaling parameter	[0.002 (1.8E-16,4.2)]	0.21 (0.17-0.24)
I_{C0}	Protection from clinical disease scale parameter	[30.7 (1.6-178.6)]	53.03 (41.65,66.64)
κ_c	Protection from clinical disease shape parameter	Gamma(1,2) [1.68 (0.24,5.57)]	2.01 (1.54,2.80)
P_{CM}	Immunity level of newborn relative to mother	Uniform(0,1) [0.5 (0.025,0.975)]	0.53 (0.25,0.88)
d_M	Decay parameter for maternal immunity	Gamma(2,5) [205.1 (101.7-362.4)]	230.4 (143.9,348.0)
$1/r_U$	Duration of sub-patent infection	Weibull(0.0137,4.14) [67 (30, 100)]	107.9 (92.3-122.8)
σ^2	Variance of log of heterogeneity in biting rates	Log-normal(0.483,0.244) [1.62 (1.00, 2.61)]	1.04 (0.83-1.27)

† b_{MAX} and b_{MIN} were subject to the constraint $b_{MAX} > b_{MIN}$ so have 95% prior intervals which differ from their pre-specified distributions.

Supplementary Table S2 Summary of clinical incidence studies included in the model fitting.

Country	*Location*	*Study reference*	*Case detection method*	*Age range for incidence (years)*	*Age range for parasite prevalence (years)*	*EIR estimate (infectious bites per year)*	*EIR reference*
Burkina Faso	Nouna	[45]	Weekly ACD	6 m to 5 yrs	-	230	[46]
Cameroon	Ebolakonou, Koundou	[47]	Daily ACD	All	All	17.7; 176.1	[48]
Ghana	Kassena-Nankana	[49]	PCD	2 m to 2 yrs	-	418	[50]
Ivory Coast	Northern savannah	[51]	Daily ACD	All	All	158; 139; 155	[51]
Kenya	Chonyi, Ngerebya	[52]	Weekly ACD	All	0 to 10	38; 10	[52]
Mali	Doneguebougou, Sobuta	[53]	Weekly ACD	0 to 20	0 to 20	142; 8	[53]
Mozambique	Manhica	[54]	Weekly ACD	0 to 11	All	15	[55]
Mozambique	Matola	[56]	Daily ACD	All	All	12	[56]
Mozambique	Manhica	[57]	PCD	0 to 15	-	38	[58]
Senegal	Dakar Central; South	[58,59]	Weekly ACD	All; 0 to 15	All	0.05	[58,60]
Senegal	Dielmo, Ndiop	[61]	Daily ACD	All	-	200; 20	[61]
Tanzania	Ifakara	[62]	PCD	0 to 6	0 to 6	100	[46,63]
Tanzania	Ifakara	[64]	Weekly ACD	0 to 5	0 to 5	100	[46,63]
Tanzania	Mgome, Ubiri, Magamba	[65]	PCD	0 to 20	0 to 20	163; 3.9; 0.2	[66,67]

ACD- Active case detection, PCD- Passive case detectio

Supplementary Table S3| Deviance Information Criterion values calculated for fitted models using different assumptions about the mechanism of immmunity. Values shown are the median posterior deviance, the complexity *pD* (otherwise known as the effective number of parameters) calculated on the basis of the posterior median of each parameter (as some of the individual posterior distributions appeared non-Normal).

Assumed mechanism of parity-dependent immunity	**Infection-dependent immunity**			**Infected-pregnancy-dependent immunity**		
	Deviance	*pD*	DIC	Deviance	*pD*	DIC
None	4350.3	2.7	4353.0	4350.3	2.7	4353.0
Sequestration-blocking (SB)	4305.3	5.5	4310.9	4320.4	4.6	4325.0
Faster clearance of acute stage	4296.3	5.5	4301.9	4313.2	5.7	4318.9
Faster clearance of chronic stage	4233.3	5.9	4239.2	4235.6	5.6	4241.3
Faster clearance of past stage	4350.5	2.9	4353.4	4350.4	2.8	4353.2
SB and faster clearance of chronic	4222.8	6.9	4229.7	4225.2	6.8	4232.0

Supplementary Table S4| Sensitivity analysis of the percentage of infections able to sequester within the placenta. Results shown are for the infection-specific-immunity model.

Percentage of infections able to sequester	**Fitted EIR for Ifakara Town, Tanzania**	**Fitted EIR for Kilifi District, Kenya**	**DIC**
100%	307	12.0	4229.7
90%	331	13.3	4242.72
75%	406	16.4	4268.86
50%	699	24.9	4372.4

Supplementary Table S5| Posterior means of the final fitted placental malaria models using different durations between infection and sequestration

Time spent infected before placental sequestration occurs	τ_A	τ_C	τ_P	ν	ξ	ψ_C	π_C	ρ
Infection-specific model								
0 days	0.018	0.010	0.0004	1.15	14.46	2.96	1.26	0.54
7 days	0.019	0.011	0.0004	1.31	14.09	2.67	1.2	0.51
14 days	0.020	0.011	0.0003	1.20	15.15	3.01	1.30	0.50
21 days	0.021	0.011	0.0004	1.46	14.51	2.96	1.26	0.54
Infected-pregnancy-specific model								
0 days	0.019	0.010	0.0003	1.09	11.57	2.16	0.70	0.42
7 days	0.020	0.010	0.0003	1.14	12.02	2.40	0.71	0.39
14 days	0.021	0.010	0.0004	1.44	11.06	2.40	0.68	0.42
21 days	0.022	0.010	0.0003	1.48	10.67	2.45	0.71	0.39

Supplementary Notes

Supplementary Note 1

Model of P.falciparum malaria within the general population

Aside from an alteration to the functional form of the acquisition of infection-blocking immunity which is outlined below, the model formulation of the underlying transmission dynamics of *P.falciparum* within the general population is identical to that described by Griffin et al.[42] Here we give a brief description of the model's key features (the stages of infection, forms of acquisition of immunity and dynamics within mosquitoes), details of the parameters fitted for this analysis and the ways in which this model is linked to the model of placental malaria.

The model is structured as a deterministic, compartmental model with individuals moving through six different infectious states: susceptible (S), untreated clinical disease (D), treated clinical disease (T) and protected due to prophylaxis from prior treatment (P), asymptomatic patent infection (A), and sub-patent asymptomatic infection (U). Individuals move through these stages according to the rates shown in Supplementary Figure S1.

The model is further subdivided into age- and biting-intensity-specific categories with immunity acting in an age- and exposure-specific way to reduce the force of infection Λ, the probability of an infection leading to clinical disease ϕ and the mean duration of time spent within the patent infection state, $\frac{1}{r_A}$.

Contemporary countrywide estimates of the proportion of clinical cases effectively treated in Tanzania and Kenya are relatively high (53% for Tanzania in 1998 [68] and 65% for Kenya in 2000 [69] respectively) and the level of chloroquine consumption within the Ifakara Town population at the time of the study was reported to be high [4]. As a result, for both countries the fraction of clinical cases effectively treated, f_t, was set to 0.6.

Infection-blocking immunity. This is assumed to increase in proportion to the time- and age-dependent entomological inoculation rate, $EIR(a,t)$, raised to the power τ, a model parameter to be estimated. It is assumed to wane at a fixed rate $1/d_b$:

$$\frac{\partial I_B}{\partial t} + \frac{\partial I_B}{\partial a} = EIR(a,t)^{\tau} - \frac{I_B}{d_b}. \quad [S1]$$

The age-dependent probability of infection then follows a Hill function:

$$b(a) = b_{MIN} + \frac{b_{MAX} - b_{MIN}}{1 + (I_B(a)/I_{B0})^{\kappa_b}} \quad [S2]$$

where b_{MIN}, b_{MAX}, I_{B0} and κ_b are parameters to be estimated. This then results in the force of infection

$$\Lambda(a,t) = EIR(a,t)çb(a) \quad [S3]$$

where ς is a measure of the relative biting rate experienced by an individual according to the level of heterogeneity in biting rates amongst the population. This is Log-Normally distributed with mean 1 such that:

$$\log(\varsigma) \sim N(-\sigma^2/2, \sigma^2), \qquad \text{[S4]}$$

where the variance σ^2 is estimated during the model fitting. As the model is compartmental, this heterogeneity was incorporated by dividing the population into 5 heterogeneity categories, with the overall biting rates and proportion of individuals in each heterogeneity category for a given σ^2 distributed according to Gauss-Hermite abscissas and weights.

Protection from clinical disease. This is the sum of maternally acquired protection, I_{CM} and that acquired by exposure to infection I_{CA}. The latter depends upon the age-dependent force of infection and a constant decay rate $1/d_c$ thus:

$$\frac{\partial I_{CA}}{\partial t} + \frac{\partial I_{CA}}{\partial a} = \Lambda(\mathrm{a}, \mathrm{t}) - \frac{I_{CA}}{d_C}, \qquad \text{[S5]}$$

which constitutes the mean rate of increase in protection from clinical disease when immunity increases with each infection. Maternally-acquired immunity to clinical disease was assumed to be proportional to the level of immunity acquired by young adult women within the same location $\left(I_{CA}(20,t)\right)$ and to decay at a constant rate, $1/d_M$, following birth:

$$\frac{\partial I_{CM}}{\delta t} + \frac{\partial I_{CM}}{\delta a} = -\frac{I_{CM}}{d_M}, \qquad I_{CM}(0,t) = P_{CM} I_{CA}(20,t), \qquad \text{[S6]}$$

where P_{CM} is the level of immunity maternally-acquired relative to the level of immunity of a mother.

The probability of experiencing clinical disease following infection is then given by a second Hill function:

$$\phi(a) = \frac{1}{1 + (I_C(a)/I_{C0})^{\kappa_C}}, \qquad \text{[S7]}$$

where $I_C(a,t) = I_{CA}(a,t) + I_{CM}(a,t)$ and κ_C and I_{C0} are estimated parameters.

The revised immunity parameters were estimated by fitting to the age-stratified parasite prevalence and clinical incidence data from 56 settings in Africa using prior estimates for the EIR in each location as previously described [42].

Reduced parasite density. Blood-stage immunity that reduces parasite density and hence the duration of patent infection was assumed to develop as a function of age and decay at a constant rate $1/d_A$. Thus the rate of progression from patent to sub-patent infection is given by:

$$r_A(a) = r_{A0}\left(1 + (w_A - 1)\frac{(I_A/I_{A0})^{\kappa_A}}{1 + (I_A/I_{A0})^{\kappa_A}}\right), \qquad \text{[S8]}$$

where I_A is the level of parasite immunity and values for r_{A0}, κ_A, I_{A0} and w_A were obtained from previous model fitting to data from the Garki project [42,70].

Mosquito model The dynamics of infection within the mosquito vectors was modelled using three stages, susceptible S_M, latently infected E_M and infectious I_M with vectors transferring through these stages according to the following equations:

$$\frac{dS_M}{dt} = -\Lambda_M S_M + B - \mu S_M \quad [S9]$$

$$\frac{dE_M}{dt} = \Lambda_M S_M - \Lambda_M(t-\tau_M)\mathrm{S}_M(t-\tau_M)\mathrm{P}_M - \mu E_M \quad [S10]$$

$$\frac{dI_M}{dt} = \Lambda_M(t-\tau_M)\mathrm{S}_M(t-\tau_M)P_M - \mu I_M \quad [S11]$$

Here τ_M is the extrinsic incubation period and $P_M = \exp(-\mu\tau_M)$, the probability of a newly infected mosquito surviving during this time. As the model assumes constant EIR the birth rate of susceptible mosquitoes remains constant $B = \mu N_M$, with $N_M = S_M + E_M + I_M$. The force of infection acting upon mosquitoes, Λ_M is obtained by summing the contribution of each human age, infection and biting rate heterogeneity category. The infection probabilities in each stage used in this calculation were obtained previously by fitting the transmission cycle to biting rate and parasite prevalence data [42].

The prior and posterior distributions of the parameters of the general population model fitted for this analysis, are listed in Supplementary Table S1.

Supplementary Note 2

Linking and fitting the general malaria model and the model of placental infection

Parameters for the general population model were fitted using the parasite prevalence data detailed in Griffin et al [42], along with additional parasite prevalence data from the Garki project [70] and clinical disease data from a further 20 settings (Supplementary Table S2), using the same fitting procedure described in [42]. Supplementary Table S1 lists those parameters which have been updated as a result of these extra data. The parameters of this model were then all fixed to their posterior median and only the EIR in each location was allowed to vary when fitting the model of placental infection to the placental infection data.

To fit the placental infection model, each individual woman was allocated a heterogeneity in biting frequency category drawn with probability equal to the proportion of individuals within this category and was assumed to remain within this category for all subsequent pregnancies. The course of external infection experienced during any pregnancy was simulated according to the prevalence and incidence of infection for the age-category she was within when she first became pregnant, drawn from the age- and parity-specific model of fertility. Any infection, ongoing or incidental, which was in either an untreated clinical disease (D), patent (A) or sub-patent (U) stage, had not previously caused placental infection, was not blocked by infection-blocking immunity and had not been cleared prior to sufficient placental development, was assumed to lead to parasite sequestration within the placenta (we assumed a rate of non-pregnancy-specific treated clinical disease (T) in

pregnant woman as in non-pregnant women of the same age. Although in both settings, the proportion of women with clinical disease predicted by the model is low, we assume treatment then prevents the incidental infection sequestering within the placenta and results in a period of prophylaxis (P). For simplicity, and because this would only happen in a small minority of cases, we also make the assumption that non-IPTp treatment has no effect on ongoing placental infection.).

We allocated an informative prior to the EIR in each setting based upon entomological surveys carried out in the each region around the time each study took place. We also allocated reasonably uninformative priors to our rates of progression, allowing these rates to represent mean durations of between less than a day and much longer than the duration of pregnancy. To take into account the fact that, due to the nature of rate parameters, a uniform prior would allocate a larger degree of prior probability to rates indicative of shorter durations (e.g. it allocates less prior probability for a duration in the interval of 1-2 days than it does a duration in interval 0.2-0.25 days), we also chose priors which allocated increasing weight to smaller rates (distributed Gamma(0.4,0.6) with 95% CrI (4.4E-5-1.33)). The functions used to determine the extent of each form of parity-dependent immunity include an offset parameter which determines the number of exposures necessary for the level of exposure (either duration of chronic of infection or probability of sequestration following infection in our final models) by 50%. As a result we gave these parameters reasonably uninformative priors allowing for them to take a value of less than one or more than 70 exposures (distributed Gamma(1,20) with 95% CrI (0.5-73.7)). The second parameters of these functions are power parameters determining how the function reaches this 50% reduction. Roughly speaking a value greater than 1 indicates a function which increases slowly then speeds up rapidly as it approaches the value of the offset parameter 50%, whereas a value of less than 1 indicates a function which increases rapidly initially but slows to reach the specified value of the offset parameter (see Supplementary Figure S2). As a result these parameters were given a prior which allows a wide range of values but allocates approximately equal weight as to whether this value is above 1 (distributed Gamma(0.5,4) with 95% CrI (0.002-10.04)). In tandem, these parameters, and the priors allocated to them, provide the model fitting procedure with a very flexible function, allowing for a wide variety of different shaped immunity profiles to match to the data. The posterior distributions of the two final models are presented in Supplementary Figure S3)

The different models were fitted to the data using a random-walk Metropolis-Hastings sampler run for 90,000 iterations, with every tenth iteration treated as a sample from the joint posterior, following a 10,000 iteration burn-in period. ρ, the parameter determining the proportion of infections which leave behind “substantial pigment”, had a Normal proposal distribution. The new values for all other parameters were drawn on the log-scale from a Normal distribution centred on the logarithm of the existing parameter, in order to take into account the fact we required the algorithm to explore values over multiple orders of magnitude. The variances of these normal distributions were calibrated to ensure adequate mixing (defined as an acceptance rate of 10-20% and confirmed visually) and convergence was ensured by running multiple chains from various different starting points.

The values of DIC of each modelled mechanism of immunity, as well as the posterior deviance and model complexity (or effective number of model parameters), are presented in Supplementary Table S2

Supplementary Note 3

Sensitivity analysis of the assumption that all infections have the ability to sequester within the placenta

At delivery, the large majority of women with detectable peripheral infection have histological signs of infection [22]. As a result, we made the assumption in our baseline analysis that all ongoing or incidental infections can sequester within the placenta, infection is not cleared before the parasite is able to switch to antigens capable of adhering to placental receptors. To look at the sensitivity of our model to this assumption we did a further analysis where we refitted the model making the assumption that only a proportion (90%, 75% or 50%) of infections can ever sequester within the placenta. We found that when we reduced the proportion of infections able to sequester the model fit became progressively worse, with even a 10% reduction in the proportion of infection able to sequester producing a substantially worse fit as measured by DIC (Supplementary Table S4). Moreover, in order to achieve the observed high cumulative levels of exposure to placental infection in the data (e.g. 85% of all primigravidae had evidence of placental infection at delivery in Ifakara), the model has to fit a progressively higher EIR for each setting, to the extent that, if we assume the proportion of infection which sequester is 75% or less, we estimate a level of transmission in excess of that observed in contemporary entomological studies [39,40].

Supplementary Note 4

Sensitivity analysis of the duration of infection necessary to lead to sequestration

The forms of immunity included in the final model (sequestration blocking and faster progression from chronic to past infection stage) were not affected by the choice of duration of infection necessary to cause placental sequestration and the fitted parameters were largely insensitive, although, in order to ensure a sufficient level of transition to the past infection stage, the rate of progression through acute and chronic infection increased with increasing time to sequestration (Supplementary Table S5).

Assuming that IPTp is effective at clearing all post-liver-stage parasites (placental or non-placental), the effectiveness of this intervention increases with a longer assumed time to sequestration. This is because IPTp is able to clear an increased number of ongoing infections which have yet to sequester the placenta whilst being able prevent the same number of infections during the subsequent duration of prophylaxis (Supplementary Figure S4).

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