India's approach to eliminating *Plasmodium falciparum* malaria: A modeling perspective

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Abstract

Approximately one-third of the world's population that is at risk to malaria lives in India. *Plasmodium falciparum*, a deadly form of malaria, accounts for about 50% percent of the cases there. Since 1940s India has used a number of programmes to combat the disease with variable success. Since 1998 the total numbers of malaria cases, and in particular *P. falciparum* cases, have been steadily declining, making India one of the success stories among the countries supported by the Roll Back Malaria Partnership (RBM). This article considers India's *P. falciparum* control methods from the perspective of a Ross-MacDonald type model. The model is fitted to the *P. falciparum* cases in India over the period 1983-2009. We focus on the disease reproduction number as being a measure of success of programs. Before the start of RBM measures the disease reproduction number was $\mathcal{R}_0 = 1.00732$, meaning that the incidence of disease was increasing among the population. With the new control measures $\mathcal{R}_c = 0.999457$, suggesting that *P. falciparum* cases may be declining to zero but extremely slowly. The model here projects 0.734 million cases of *P. falciparum* malaria for 2010, down from 1.14 million cases in 2000. This impressive 36% decrease falls somewhat short of the RBM's goal of 50% reduction. However, a sensitivity analysis of the disease reproduction number done here suggests that India's control programs do apply controls at the most critical points in the disease cycle; namely, mosquito biting rates, mosquito mortality, and treatment of infected humans. This suggests that as more resources become available, they should be applied to strengthening these controls. The novelty here is in fitting recent data on malaria from India to derive current values of the disease reproduction number.

Keywords: malaria, India, mathematical models, differential equations, reproduction number, control measures, mathematical epidemiology

AMS Subject Classification: 92D30, 92D40

1 Introduction

Malaria is among the most serious tropical infectious diseases, with *Plasmodium falciparum* malaria being the leading cause of death from a single pathogen [1]. According to the World Health Organization (WHO), approximately 3.3 billion people are at risk, resulting in about 250 million cases every year [2]. Following the industrialization and economic progress in the United States and Europe, the disease was nearly eradicated there by the late 19th century. But, malaria is endemic in many tropical regions with devastating impact in Africa where *P. falciparum* dominates and the majority of the malarial deaths occur [3].

The largest population at risk of malaria, 1,320 million people, now lives in the South-Eastern WHO Region. India is one of 11 countries in that region with nearly 980 million people at risk. According to WHO's estimated number of cases, India also has the largest number of malaria cases occurring outside of Africa [2]. India's official statistics suggest that *P. falciparum* accounts for about 50% of the clinical cases in India.

India has a long history of attacking malaria. Organized control programmes started in the 1940s used DDT to control mosquitoes. The programmes were originally very successful and brought malaria in India near elimination by 1961 [4]. Since that time, malaria has become re-established in India. As hopes for eradication dim, India has redirected resources to keeping the disease under control. The re-emergence of malaria has been accompanied by a steady rise in the percentage of *P. falciparum* among all malaria cases [5].

The resurgence of malaria throughout the world and the rising death toll have drawn the attention of the international community. WHO, the World Bank and several charitable organizations launched in 1998 the Roll Back Malaria Partnership (RBM), a global initiative that coordinates actions against malaria. The mission of the RBM Partnership has more recently been outlined in its Global Malaria Action Plan [6]. Some of the major goals of the Partnership are (1) Reduce global malaria cases from 2000 levels by 50% in 2010 and by 75% in 2015; (2) Reduce global malaria deaths from 2000 levels by 50% in 2010, and to near zero by 2015; (3) Eliminate malaria in 8-10 countries by 2015; and eventually (4) Achieve eradication of malaria world-wide.

The RBM Partnership provides financial and logistical support to many countries, including India. As the country with the largest population at risk from malaria, India's success in control and elimination of malaria is a key component of the RBM plans. India has recently experienced significant economic growth, becoming the second fastest growing major economy in 2008. The economic achievements of India have lead to significant reduction in poverty, thereby positioning India well for reducing the burden of malaria. In the period 1999-2009, India administered a number of control programs [7, 8, 9, 3] and made significant progress in managing malaria.

Malaria is a complex disease, and mathematical modeling has been instrumental in understanding and combating the disease [10, 11]. Early models of Ross and MacDonald [12] informed public health policy. In the 1970s those models were expanded and brought closer to data [13]. Nowadays, mathematical modeling is a powerful tool that plays an important role in investigations of alternative control strategies that can support malaria eradication [14, 15].

India's organized malaria programs accumulate statistics of the number of clinical

cases of malaria. The availability of such data creates fruitful conditions for development of useful mathematical models that may assist India's malaria control programs. Surprisingly, few models specific to India have been developed, and even fewer have been used in public health policy [16].

This article introduces a model of malaria that builds on work of Ross and MacDonald. India's progress towards elimination of *P. falciparum* malaria is studied here from the perspective of the model. Section 2 of the article describes the model, and discusses the various forms of the basic disease reproduction number. In Section 2, the model is also fitted to India's number of clinical cases for the period 1983-1997. Section 3 discusses India's malaria control programs over the period 1998-2009 and reformulates the model from Section 2 to account for those measures. In particular, the section introduces an improved model, in which the enhanced treatment, reduction in transmission, and vector death rate are explicitly incorporated. The new model is fitted to the data over the period 1983-2009. Section 3 also contains computation of the disease reproduction number and the control reproduction number, which are used to estimate the trend of *P. falciparum* malaria in India. Section 4 investigates two types of sensitivities of the reproduction number – sensitivity to parameters in the model, and sensitivity to the form of the model itself. A second model is introduced, fitted and compared to the first. Section 5 contains the summary of the results.

2 A model of *P. falciparum* malaria in India

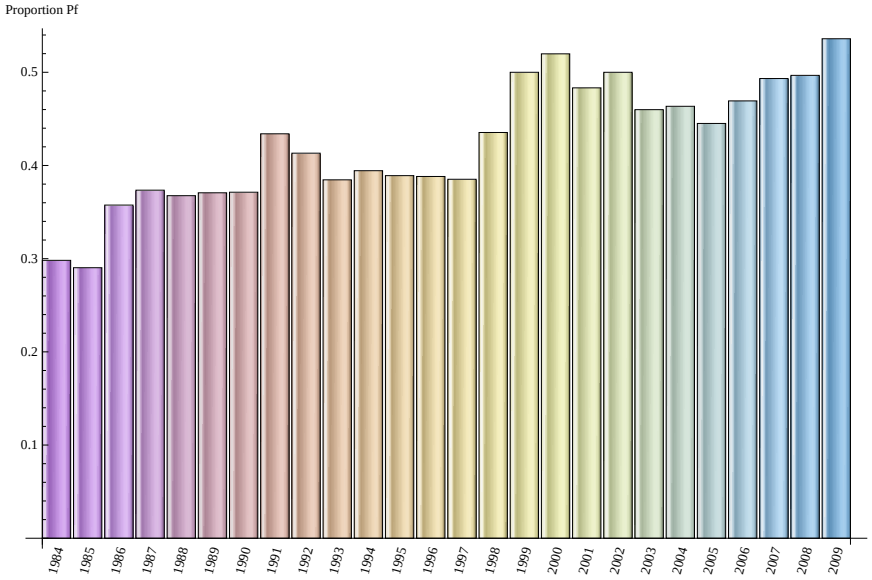

Figure 1: A chart of the proportion of *P. falciparum* cases in the total number of cases of malaria in India for the years 1984-2009.

Four species of the Plasmodium parasite cause malaria in humans: *P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Roughly half of the cases in India are caused by

P. falciparum and half by *P. vivax*. The other two kinds contribute little to the cases of malaria in India. *P. falciparum* causes fewer of the cases in India, but it has a shorter average incubation period in the mosquito vector, which accelerates the transmission, and it causes the highest morbidity and mortality. A trend of concern (Figure 1) shows that the proportion of the incidence (number of clinical cases) due to *P. falciparum* has been rising from about 30-35 % in 1984 to about 50% in 2008. Presumably, this trend is due to the ability of *P. falciparum* to evolve into strains, resistant to the classical single-drug therapies [17, 18].

In 2009 alone India had 1.53 million cases of malaria, 0.82 million of them were caused by *P. falciparum* [19, 20]. Official statistics reports that malaria cases in 2009 resulted in 1068 deaths [19, 20]. Since *P. falciparum* is responsible for most deaths from malaria in India, the above data give a crude case-fatality proportion (CFP) of *P. falciparum* cases of 0.0013. However, the official governmental malaria statistics appear to under-report both the incidence of malaria in India, as well as the number of deaths caused by it ([21, 5], Figure 7).

2.1 An augmented Ross-MacDonald model of malaria

A model of *P. falciparum* malaria in India was derived and studied by Ross (see [12], p.98). However, now Indian statistics track the number of infected individuals having clinical symptoms, so we augment Ross's model with an additional variable $C(t)$ that represents the number of clinical cases at time t. Time units in this model are measured in years, which averages over the seasonality in the dynamics of the disease.

The model involves humans and mosquitoes. The total population size of the mosquitoes, as in Ross's model, is assumed constant and is denoted by P_M. India's total population size, however, has grown significantly in the period 1984-2009. To account for population growth, we model the total human population size, say $P(t)$, using the logistic equation

$$\frac{dP}{dt} = aP(t)\left(1 - \frac{P(t)}{K}\right) \tag{2.1}$$

were a is the maximum growth rate and K is the carrying capacity. We note that since the total death rate of *P. falciparum* malaria is very small relative to number of cases and to the total population size, we assume it may be neglected.

Let $Y(t)$ denote the number of infected mosquitoes at time t. Once infected, mosquitoes do not become parasite-free until they die. This suggests that the simplest model of disease dynamics in the mosquito population is given by an $S \to I$ epidemic model. We may express the susceptible mosquito population at time t as a difference of a constant total mosquito population size P_M and the number of infected mosquitoes. This reduces the $S \to I$ system for the mosquito population to one equation for the infected mosquito population size $Y(t)$, as shown in equation (2.2)

$$\frac{dY}{dt} = r(P_M - Y(t))I(t) - dY(t), \tag{2.2}$$

where $I(t)$ is the number of infectious humans at time t. The death rate of mosquitoes is denoted by d, and it may include the impact of insecticides. The parameter r is the transmission coefficient of malaria from an infected human to a parasite free mosquito

through a blood meal. The transmission coefficient r depends on biting rates, as well as on the probability of transmission, given a bite. Table 1 defines the notations used in the model here.

Parameter or variable	**Interpretation**
μ	human natural death rate
β	transmission coefficient vector $\rightarrow$ human
$\lambda P(t)$	treatment-recovery rate
ν	symptomatic stage recovery rate
r	transmission coefficient human $\rightarrow$ mosquito
d	mosquito death rate
P_M	total mosquito population size
a	growth rate of the human population
K	carrying capacity of the human population
$P(t)$	total human population size at time t
$C(t)$	population size with clinical symptoms at time t
$Y(t)$	infected mosquito population size at time t
$I(t)$	infected human population size at time t
$y(t)$	proportion of infected mosquitoes at time t

Table 1: List of parameters and dependent variables with meanings.

As re-infection of recovered humans is common in malaria, the dynamics of the human population is described here by the graph

$$S \rightarrow C \rightarrow I \rightarrow R \rightarrow S,$$

in which both the susceptible and the recovered individuals may be infected. Newly infected humans develop symptoms and move to the symptomatic class $C(t)$. Symptomatic individuals develop mature gametocytes, become infectious and enter the infectious class $I(t)$. The total number of susceptible and recovered individuals who may be infected by malaria are then described together as being the difference between the total population size and the number of symptomatic and infected individuals. Since we do not distinguish between S and R in our model, they are lumped together in this way. With this, the human population model becomes one for C and I as shown in (2.3).

$$\begin{aligned} \frac{dC}{dt} &= \beta(P(t) - C(t) - I(t))Y(t) - (\nu + \mu)C(t) \\ \frac{dI}{dt} &= \nu C(t) - (\lambda P(t) + \mu)I(t). \end{aligned} \tag{2.3}$$

We make the following assumptions:

- Natural human mortality of infectives is given by μ. The *P. falciparum* malaria disease-induced death rate can be neglected.

- The transmission rate of the parasite from infected mosquitoes to humans is given by β, which depends on the biting rates as well as the probability of transmission of the parasite from an infected mosquito to a healthy human through a blood meal.

- The rate of transition from clinical symptoms to infectious is ν.

- The per capita treatment-recovery rate for infectious individuals is assumed to be an increasing function of time. For example, treatment may increase due to the development of new drugs, and wider accessibility to those already available, the proportion of treated individuals increases with time, compensating in part for the growth potential of the infection stemming from the population growth. Thus, we assume that the treatment-recovery rate is increasing, even in the presence of resistance, which might itself act to decrease the effect of treatment.

- We assume that the time-dependent per capita treatment-recovery rate is proportional to the population size. More specifically, we assume that the time-dependent per capita treatment-recovery rate is proportional to the total expenditures for control of malaria. Per capita expenditures for control of malaria in India have remained nearly constant until 2006 (see Figure 2), suggesting the modeling of the total expenditures as proportional to the total population size. We denote by λ the treatment-recovery proportionality constant.

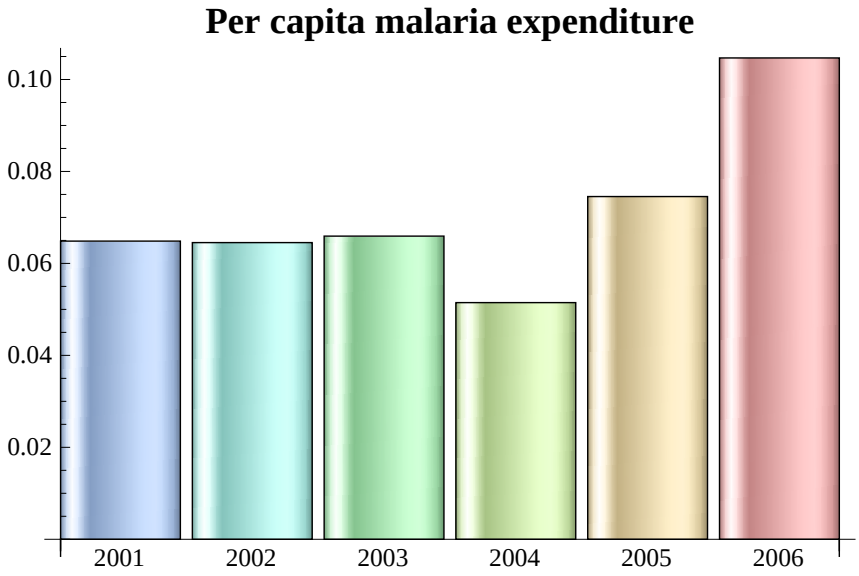

Figure 2: Per capita expenditures for malaria control in US dollars. Population size is taken as projected by model (2.1). Data on expenditures taken from [2].

- The model does not take into account super-infections. As 73% of India's population lives in non-endemic or low endemic areas, the model also neglects the build-up of immunity.

Parameters and variables with their meanings are summarized in Table 1.

System (2.2)-(2.3) has two epidemiologically relevant equilibria: a disease-free equilibrium, and an endemic equilibrium. The disease-free equilibrium $\mathcal{E}_0 = (K, 0, 0, 0)$ has no symptomatic humans, and no infectious humans or mosquitoes, and the total population size is its carrying capacity K. The local stability/instability of the disease-free equilibrium is reflected in the disease basic reproduction number $\mathcal{R}_0$, which identifies the threshold for the local stability of the disease-free equilibrium; that is, the disease-free equilibrium is locally asymptotically stable (the disease dies out) if $\mathcal{R}_0 < 1$ and unstable otherwise. This is a critical parameter for control of the disease, since if $\mathcal{R}_0 > 1$, introduction of a small amount of disease into the population may cause it to evolve into an endemic prevalence.

Various methods may be used to define the disease reproduction number [22]. For the model (2.2)-(2.3) the classical methods of Kermack and McKendrick [23] and Ross and MacDonald [24] may be used, as well as the more recent next-generation approach [25, 26]. The Kermack-McKendrick-MacDonald approach places one infected human in a population of susceptible mosquitoes; there will result $\mathcal{R}_H$ secondary infected mosquitoes. Similarly, placing one infected mosquito in a population of susceptible humans, will produce $\mathcal{R}_M$ infected humans, where

$$\mathcal{R}_H = \frac{rP_M\nu}{(\nu+\mu)(\lambda K+\mu)}, \qquad \mathcal{R}_M = \frac{\beta K}{d}.$$

To account for the secondary **human** infections that one infected human will produce, we notice that one infected human will produce $\mathcal{R}_H$ infected mosquitoes, each of which will produce $\mathcal{R}_M$ infected humans, giving $\mathcal{R}_H\mathcal{R}_M$ secondary human infections. This expression gives the classical malaria reproduction number.

More recently, an approach based on the next-generation operator derives a disease reproduction number as being the principal eigenvalue of the next-generation matrix [25, 26] giving the following reproduction number:

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_H\mathcal{R}_M} = \sqrt{\frac{\beta r K P_M \nu}{d(\nu+\mu)(\lambda K+\mu)}}$$

when the next-generation approach applied to the model (2.2)-(2.3). The fraction $\nu/(\nu+\mu)$ is the fraction of humans who survive the clinical stage and become infectious.

In the case $\mathcal{R}_0 > 1$, there is an endemic equilibrium, and the disease is persistent. In that case, the model (2.2)-(2.3) has a unique endemic equilibrium $\mathcal{E} = (K, C^*, I^*, Y^*)$ given by

$$C^* = \frac{(\lambda K+\mu)}{\nu} I^* \qquad I^* = K\frac{\mathcal{R}_0^2 - 1}{\hat{\mathcal{R}}_M(\zeta\hat{\mathcal{R}}_H + 1)} \qquad Y^* = P_M\frac{\mathcal{R}_0^2 - 1}{\hat{\mathcal{R}}_H(\hat{\mathcal{R}}_M + \zeta)}$$

where $\zeta = (\lambda K + \mu + \nu)/\nu$ and $\hat{\mathcal{R}}_M = r\mathcal{R}_M/\beta$, $\hat{\mathcal{R}}_H = \beta\mathcal{R}_H/r$. We show in the Appendix that the endemic equilibrium is locally asymptotically stable.

2.2 Fitting the model to India's malaria incidence 1984-2009

India collects regular statistics of malaria incidence. Most of the data provides the total number of clinical cases per year, the number of clinical cases of *P. falciparum* per year,

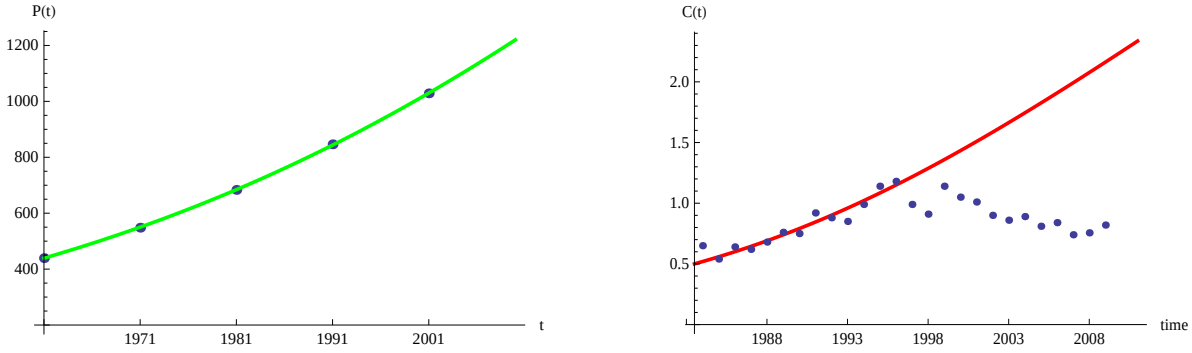

Figure 3: The left figure illustrates the fit of the India's population size as projected by model (2.1) plotted alongside census data. Time is measured in years since 1961. The right figure shows the number of clinical cases of malaria in India in 1984-2008 given as points. Data taken from [19]. The continuous red curve is the number of clinical cases among humans given by model (2.4). The curve shows remarkable agreement with data for the period 1984-1997. After 1997 the model projects significantly larger numbers of clinical cases than those actually observed.

and the number of deaths per year. For example, for the years 1984-2000 we use the data given in [7]. For the years 2002-2009 we use the official *Malaria Situation* statistics [19, 20]. The number of clinical cases for 2001 was obtained from [27].

Although differential equation modeling of malaria now has a long history and to date many models have been developed to account for the various simplifying assumptions in the Ross-MacDonald models, relatively little work seems to have been done in comparing these models to actual incidence data from endemic areas (but see [14]). Here, we fit model (2.2)-(2.3) to India's incidence of *P. falciparum* and use that fit to make projection.

Equation (2.1) for the human population does not depend on variables in the main disease model (2.2)-(2.3), and it may be fitted to data separately. India collects census statistics of the population every 10 years, and we use census data for 1961-2001 to estimate parameters in (2.1). The fit of the solution of equation (2.1) to the data is described in Figure 3, and the estimates of the parameters are shown in Table 2. The sum of squares error (SSE) of the fit is 13.4.

Parameter	**Estimated value**	**Conf. Int.**
a	0.02555203	0.02374-0.0273
K	4235.46	2674.17-5796.75
b	16.9923	13.739-20.246
r	0.017989	0.0145-0.0215
ξ	0.00626284	0.002828-0.009698
η	0.0391625	0.0-0.14042

Table 2: List of fitted parameters with values and confidence intervals

Since the total mosquito population is not known, even approximately, we re-scale the mosquito population to the proportion of infected mosquitoes. With $y(t) = Y(t)/P_M$

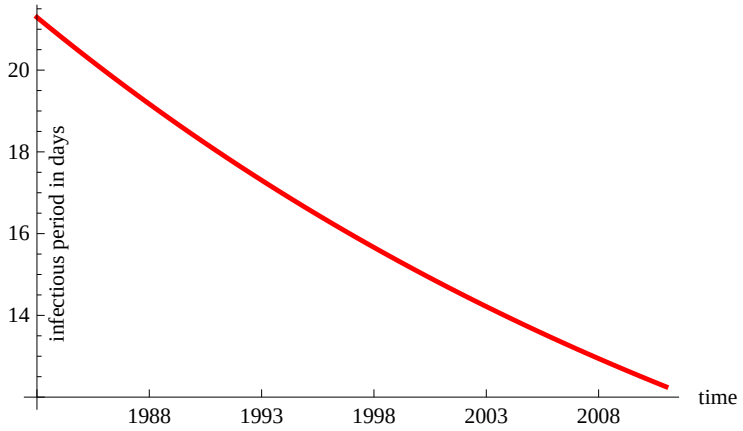

Figure 4: The infectious period as a function of time 1983-2008.

the model (2.2)-(2.3) may be rewritten as shown in (2.4).

$$\begin{aligned} \frac{dC}{dt} &= b(P(t) - C(t) - I(t))y(t) - (\nu + \mu)C(t) \\ \frac{dI}{dt} &= \nu C(t) - (\lambda P(t) + \mu)I(t) \\ \frac{dy}{dt} &= r(1 - y(t))I(t) - dy(t) \end{aligned} \tag{2.4}$$

where the new parameter $b = \beta P_M$. This reduces the number of parameters by one. The human classes are not re-scaled, since they must be compared to data.

We used Mathematica to fit the above model to India's incidence of malaria for the years 1984-2009, and we used NDSolve to solve the differential equation model (2.4) numerically, and NonlinearModelFit to perform the fitting and estimate parameters.

To begin, we estimate and fix certain parameters: The mosquito lifespan is taken to be about 29 days (0.07945 years). A human lifespan for India is estimated to be 65 years [28]. Our model (2.1) estimates India's population in 1983 to be 714.277 million people. We use that value to initialize $P(t)$ in 1983. The initial value of $C(t)$ is taken to be the number of cases in 1983, that is, 0.53 mil. as given by [19]. The initial value of $I(t)$ is taken to be the same. Reference [29] gives percentages of falciparum-infected mosquitoes in the range $0.7\% - 2\%$. We tried values from 0.1% to 3% and estimated a good initial guess to be 0.3%. Several references give the length of a clinical episode to be 7 days [14, 5].

The most challenging parameter to estimate is the constant of proportionality λ in the treatment-recovery rate. The parameter suggests that the infectious period declines from about 21 days in 1983 to about 13 days in 2008 (see Figure 4). The infectious period lasts on average six months for *P. falciparum* malaria when left untreated [14], but with treatment infectiousness may disappear within several days. Little seems to be known about the duration of the infectious period while infected individuals are treated. Duration depends on when treatment is applied, and how effective the assigned treatment is. Model (2.4) with constant infectious period does not appear to fit the data

at all, even in the period 1983-1996, so some decrease in the duration of infectiousness over this period appears to be necessary. The decline in the infectious period may be a mechanism that compensates for the relatively slower rise in the infectious individuals compared to the total population size over the period 1983-1996.

The model parameters in (2.4) were fit to India's incidence data for the period 1984-1996 with assumed values of parameters and initial conditions given in Table 3. In this first step we only fit the model to the time series data before the initiation of the Roll Back Malaria so that the model is calibrated to the background conditions at the start of the program. In the subsequent section we augment model (2.4) and fit again to time series data for the period 1997-2009 to evaluate the effect of the additional control measures brought by RBM. The parameters obtained from the fitting process together with their confidence intervals are given in Table 2. The sum of square error (SSE) of the fit over the 13 points is 0.0395113. The result of the initial fitting of the model plotted against the incidence data for 1984-2009 is shown in Figure 3.

Parameter	**Assumed value**	**Pre-estimated range**	**Refs**
μ	1/65 years^{-1}	1/70- 1/55	[28]
ν	365/7 years^{-1}	–	[14, 5]
λ	0.024 person-years^{-1}	–	see text
d	12.55 ($\approx$ 365/29)	365/100-365/14	[19]
y_0	0.003	0.0001-0.05	[29]
C_0	0.53 mil.	–	[19]
I_0	0.53 mil.	–	assumed
P_0	714.277 mil.	–	est. from (2.1)

Table 3: List of assumed parameter values and initial conditions.

The value of the disease reproduction number with the parameters in the Table 3 is $\mathcal{R}_0 = 1.00732$. Since the model parameters are estimated from the nearly endemic phase of malaria, rather than from the moment it invaded, we caution against inferring that this value is the disease reproduction number of malaria in India. We discuss this issue later.

3 Impact of malaria control in India

The number of malaria cases caused by *P. falciparum* experienced steady rise in India in the period 1961-1996. Sharma [17] fit a linear function of positive slope through the data to demonstrate the rise. In Figure 3 the model (2.4) also projects a rise for the period 1984-1997 suggesting that the increase was even faster than linear. The re-emergence of malaria in India has complex ecological and financial bases including resistance of the mosquitoes to insecticides, resistance of the parasite, particularly *P. falciparum*, to conventional single-drug treatment regimes, and wide-spread irrigation. Figure 3 shows that model (2.4) significantly overestimates the number of cases for the period 1997-2009, suggested that India implemented stricter and better control programs in that period.

3.1 Malaria control programs in India 1997-2009

In 1998 the United Nations and the World Bank joined the WHO to launch *Roll Back Malaria Partnership (RBM)*, which is an ambitious campaign to reduce the malaria burden by 50% by year 2010. RBM provided logistical support and financial assistance to multiple malaria-affected countries, including India [30]. With partial funding from the World Bank, India launched the Enhanced Malaria Control Project (EMCP) in October 1997. The project selectively targeted 100 districts within 8 states, deemed most high risk to malaria and accounting for about 70% of the *P. falciparum* incidence in the country in 1997. The EMCP reduced the *P. falciparum* cases in the targeted areas from about 0.72 million in 1997 to about 0.41 million in 2004, while the national incidence of *P. falciparum* malaria was reduced from 0.99 million cases in 1997 to 0.89 million cases in 2004 [31], largely due to efforts in the EMCP districts.

In response to rising incidence in malaria, and particularly malaria caused by *P. falciparum*, India adopted new approaches to malaria control, renaming the National Malaria Eradication Program (NMEP) into National Anti Malaria Programme (NAMP) in 1999. The basic components of the program are:

1. *Early detection and prompt treatment of malaria.* Due to growing wide-spread resistance of *P. falciparum* to conventional single-drug treatments, such as chloroquine, the country implemented combination therapies in 2006.

2. *Selective mosquito control.* As part of novel mosquito-control strategies, India began to move away from conventional insecticides (such as DDT) to more environmentally-friendly ones. Furthermore the wide-spread spraying was replaced by more targeted spraying of high risk areas. More recently satellite remote sensing technologies are beginning to be used for locating habitats of the vector. Mosquito larval control is implemented through larvivorous fish and biolarvicides.

3. *Medicated mosquito net program.* The program incorporated increase use of insecticide treated bed nets (ITNs) through local production, marketing and distribution.

4. *Strengthening institutions.* New approaches were taken toward social development by training of staff, disseminating malaria information, and improving management and information systems.

After the funding for the EMCP expired, the World Bank provided new funding in assistance of the Enhanced Vector Borne Disease Control Project (EVBDCP) in 2005. More recently, in 2008, the World Bank allocated to India additional funding to help reduce malaria to 50% from its 1996 peak by 2010, and eliminate the parasitic disease Kala-azar. In 2006, India also received financial assistance from the Global Fund which funded the Intensified Malaria Control Project (IMCP) [2, 9]. All these programs have helped India to intensify the malaria control measures and to stay on a steady path of malaria reduction in the period 1999-2009.

3.2 Accounting for improved control measures

Improved control measures in India over the period 1997-2009 clearly succeeded in stopping and reversing the upward trend of falciparum-caused malaria cases. Adding three

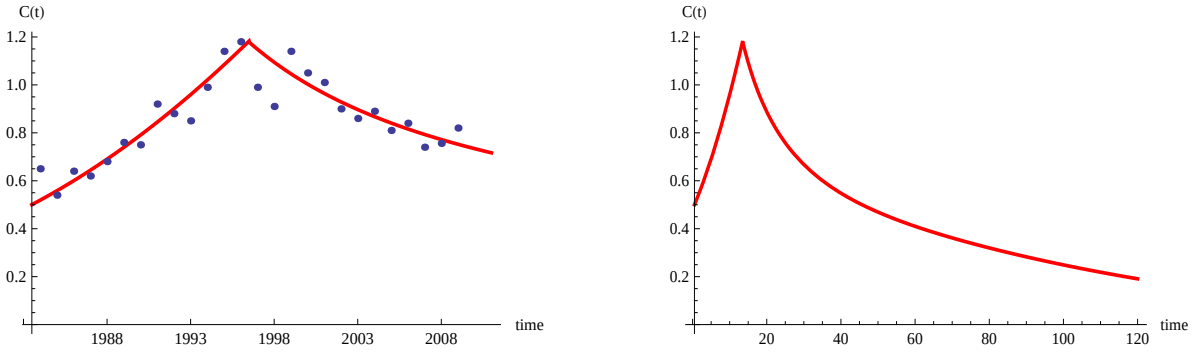

Figure 5: The left figure shows the number of clinical cases of malaria in India in 1984-2008 given as points. The continuous red curve is the incidence among humans given by model (3.1). The curve shows good qualitative agreement with data for the period 1984-2009. The right panel shows the long-term trend of the number of clinical cases with current control reproduction number $\mathcal{R}_c$.

separate terms to the model (2.4) reflects improved treatment through continuously decreasing infectious period, and improved speed and accuracy of diagnosis and treatment. Increasing the coefficient of treatment λ at the start of the EMCP accounts for enhanced treatment. This is done adding a step function of the form $cP(t)H(t-13.5)$ to the equation for the infected humans. (Here $H(t) = 0$ for $t \leq 0$ and $H(t) = 1$ for $t > 0$, and time $t = 0$ in 1983.) The choice of the jump being at $t = 13.5$ gives mid-year 1997, when EMCP was started. Here c is the added treatment coefficient. Furthermore, a variety of mosquito control measures were incorporated, all of which effectively reduce the mean mosquito life-span. While wide-spread Indoor Residual Spraying (IRS), particularly with DDT, declined significantly, better targeting was used as well as environmentally friendly interventions such as lavrivorous fish which may have been effective against developing mosquito resistance. These control measures are included by adding a term of the form $\eta H(t - 13.5)$ to the equation for the infected mosquitoes. The coefficient η denotes the additional mosquito death rate due to intervention. Finally, the EMCP succeeded in increasing the use of ITN [31]. Bed nets partly increase mosquito's death rate but primarily decrease the biting rates. The ITN-induced decrease in biting rates is included in the model by multiplying the transmission coefficients b and r by the fraction of biting rates that still remains when ITN are successfully used; that is, b is replaced by $b(1 - \xi H(t - 13.5)$ and r is replaced by $r(1 - \xi H(t - 13.5))$, where ξ indicates the strength of ITN. The modified model (2.4) takes the form in equation (3.1).

$$\begin{aligned}
\frac{dC}{dt} &= b(1-\xi H(t-13.5))(P(t)-C(t)-I(t))y(t) - (\nu+\mu)C(t) \\
\frac{dI}{dt} &= \nu C(t) - (\lambda P(t) + cP(t)H(t-13.5) + \mu)I(t) \qquad (3.1) \\
\frac{dy}{dt} &= r(1-\xi H(t-13.5))(1-y(t))I(t) - (d+\eta H(t-13.5))y(t)
\end{aligned}$$

Fitting the new parameters ξ, c and η to the second part of the data for the period 1997-2009, shows that the model describes the decline in the infectious period (see Figure 4). The best fit of c is ≈ 0. The model was rewritten with $c = 0$, and the resulting

values of ξ and η are listed in Table 2. The SSE over all points is 0.129. With both enhanced control terms the model reflects well the number of clinical cases of falciparum malaria in India for the period 1984-2009 (Figure 5).

3.3 Is India on the road to eliminating *P. falciparum* malaria?

Our model suggests that the ambitious goal set forth by Roll Back Malaria of decreasing the number of cases by half will require another paradigm shift. Model (3.1), when extended past 2009, suggests that if India continues the current trend in *P. falciparum* malaria cases, in year 2010 there will be 0.734 million cases. If that is the case, the RBM program and world effort would have reduced number of clinical cases in India by 0.446 million cases from its peak of 1.18 million in 1997, or with 37.8%. This is impressive, although somewhat short of the goal. The number of malaria cases as projected by model (3.1) are given in Table 4. The provisional number of cases for 2009 was already available while this article was being revised. The number of cases for 2009 was given to be 0.82 mil.[20] which suggests that our model potentially will underestimate the number of cases in 2010.

Year	**2009**	**2010**	**2011**
number of cases	0.75 mil.	0.734 mil.	0.72 mil.
total population	1196.8 mil.	1218.8 mil.	1241.1 mil.
infectious period	12.7 days	12.5 days	12.25 days

Table 4: Projected numbers of cases of *P. falciparum* malaria and total population size. Infectious period for model (3.1).

The number of clinical cases of *P. falciparum* malaria in India has been decreasing steadily since 1999. Will the long-term trend, if kept, lead to stabilization of the incidence at a new, lower equilibrium? Is it declining to zero? The answers to these questions are given by the reproduction number of model (3.1), called *control reproduction number* $\mathcal{R}_c$. If $\mathcal{R}_c > 1$, malaria will stabilize at a new lower equilibrium; if $\mathcal{R}_c < 1$, if trend continues, *P. falciparum* malaria will eventually be eliminated. The control reproduction number is given by

$$\mathcal{R}_c = \sqrt{\frac{brK\nu(1-\xi)^2}{(d+\eta)(\nu+\mu)(\lambda K + cK + \mu)}}$$

and for the parameters presented in Table 2 and Table 3, $\mathcal{R}_c = 0.999457$, using the estimated optimal values for ξ and η.

Being lower but almost equal to one, the control reproduction number suggests that the current trend of *P. falciparum* malaria is towards eradication (see Figure 5); however, this evolution is very slow, it is heavily dependent on causing and maintaining short infectious period (see Table 4). Certainly, more effective control efforts are necessary to keep this trend. Although India would likely not succeed in decreasing *P. falciparum* malaria incidence by half, the fact that $\mathcal{R}_c$ appears to be less than 1.0 suggests that with present strategies, all things being equal, India's efforts in the fight against malaria have been successful this far.

3.4 Critical threshold values for control

P. falciparum malaria incidence in India has steadily declined in the period 1999-2008. The critical values of the additional control measures, compared to the baseline year 1997, necessary to sustain decline in the number of clinical cases can be computed from the equation

$$\mathcal{R}_c = 1.$$

In terms of treatment, the model suggests that it is sufficient to sustain the projected decline in the infectious period (see Figure 4 and Table 4). The joint critical values of enhanced mosquito mortality η and the fraction decrease in biting ξ that make the reproduction number equal to one define a level curve in the (η, ξ) plane, illustrated in Figure 6. Critical values for individual control strategies may be computed explicitly. In the absence of additional treatment ($c = 0$) and added mosquito mortality ($\eta = 0$), the reduction in the biting rates, necessary to maintain $\mathcal{R}_c$ below one is given by:

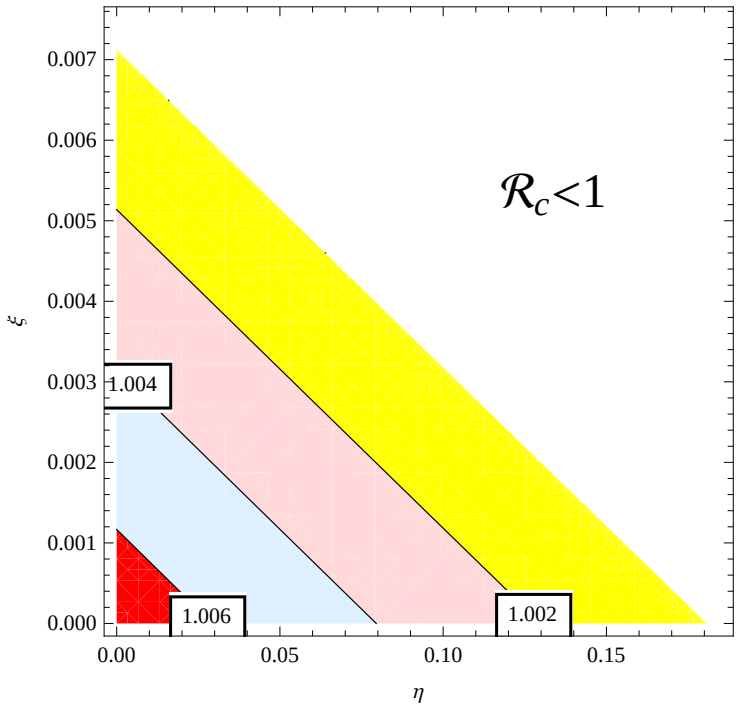

Figure 6: Contour plot of the control reproduction number $\mathcal{R}_c$ in the (η, ξ) plane where the control reproduction number is above one. Level curves are labeled at levels $\mathcal{R}_c \approx 1.002, 1.004, 1.006$. For example, if point (η, ξ) lies in the region where $\eta + \xi < 0.15$, then the control parameter will be < 1.002, etc.

$$\xi_{crit} = 1 - \frac{1}{\mathcal{R}_0}.$$

Recall that $\mathcal{R}_0$ is the reproduction number computed using the next generation approach. The reproduction number that gives the number of secondary cases that one

infected human individual will produce in an otherwise entirely susceptible human population is given by $\mathcal{R}_0^2$. Figure 6 suggests that $\xi_{crit} \approx 0.0072$. That is, one needs 0.72% decrease in biting rates for elimination of malaria in the absence of enhanced mosquito mortality. Reducing bites was one of the critical mechanisms during the EMCP, when India increased the use of bed nets nearly 100 fold in the period 1998-2005 [31]. The critical value of the enhanced mosquito control through added mosquito mortality in the absence of reduction in biting rates ($\xi = 0$, $c = 0$) for which the reproduction number equal to one is given by

$$\eta_{crit} = d(\mathcal{R}_0^2 - 1).$$

Figure 6 suggests that $\eta_{crit} \approx 0.18$. If $\eta_{crit} = \hat{\eta}_{crit} d$, then $\hat{\eta}_{crit}$ depends only on the reproduction number:

$$\hat{\eta}_{crit} = \frac{\eta_{crit}}{d} = \mathcal{R}_0^2 - 1.$$

Similarly, one can compute a critical threshold value for the added treatment-recovery coefficient c. Setting $\xi = 0$ and $\eta = 0$, from the equation $\mathcal{R}_c = 1$ we obtain c_{crit}

$$c_{crit} = \frac{\lambda K + \mu}{K}(\mathcal{R}_0^2 - 1).$$

Using the estimated and fitted values of the parameters, we may estimate that $c_{crit} \approx 0.000352897$. It is interesting to note that the fitted values of ξ, η and c are all bellow their critical values, suggesting that the reduction of the reproduction number below one is a result of the symbiotic action of several control mechanisms.

4 Sensitivity of the reproduction number

The reproduction number $\mathcal{R}_0$ and the control reproduction number $\mathcal{R}_c$, as used in the endemic phase, measure the strength of a disease and produce values close to the threshold value one. To understand how the values of the reproduction numbers depend on the variability of the estimated parameters we investigate two types of sensitivities of the reproduction number.

4.1 Sensitivity to the parameters of the model

Malaria is a complex disease whose control or elimination can only be achieved through diverse control measures; still, knowing the relative impact of various control measures on the reproduction number may help prioritize control measures. Prior work on the sensitivities of the reproduction number has determined that the reproduction number is most sensitive to the biting rates [32], suggesting that the use of bed nets may be strategy with the greatest impact. Parameters of model (3.1) are estimated based on fitting, and fitting does not allow for separate estimation of the biting rate, since the biting rate always appears in a product of parameters. As a result, the reproduction number $\mathcal{R}_0$ depends on the biting rate only through b and r. Following [32], we define *normalized forward sensitivity index*, also called elasticity, of the reproduction number $\mathcal{R}_0$ with respect to a parameter p by

$$\mathcal{S}_p = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}.$$

Sensitivities	**Expression**	**Value**	**Comment**
$\mathcal{S}_b$	$\frac{1}{2}$	0.5	$\mathcal{S}_b + \mathcal{S}_r = 1$
$\mathcal{S}_r$	$\frac{1}{2}$	0.5	$\mathcal{S}_r + \mathcal{S}_d = 0$
$\mathcal{S}_d$	$-\frac{1}{2}$	-0.5	$\mathcal{S}_b + \mathcal{S}_d = 0$
$\mathcal{S}_\nu$	$\frac{1}{2}\frac{\mu}{\nu+\mu}$	$0.14748 \cdot 10^{-3}$	*local*
$\mathcal{S}_K$	$\frac{1}{2}\frac{\mu}{\lambda K+\mu}$	$0.7566 \cdot 10^{-4}$	*local*
$\mathcal{S}_\lambda$	$-\frac{1}{2}\frac{\lambda K}{\lambda K+\mu}$	-0.499924	$\mathcal{S}_K + \lvert\mathcal{S}_\lambda\rvert = \frac{1}{2}$
$\mathcal{S}_\mu$	$-\frac{1}{2}\left[\frac{\mu}{\nu+\mu} + \frac{\mu}{\lambda K+\mu}\right]$	$-0.22314 \cdot 10^{-3}$	$\mathcal{S}_\nu + \mathcal{S}_K + \mathcal{S}_\mu = 0$

Table 5: Sensitivities of the reproduction number $\mathcal{R}_0$ with respect of the parameters of model (3.1). The **Value** is computed with the parameters in Table 2 and Table 3.

Table 5 summarizes the sensitivities of $\mathcal{R}_0$ with respect to the parameters in (3.1). The sensitivities of $\mathcal{R}_0$ with respect to r, b, and d are constants and do not depend on the parameters of model (3.1). The sensitivities with respect to the remaining parameters are *local*, since they depend on the parameters of the model and the best computed values for those parameters (see the expressions in Table 5). If a sensitivity is positive, that means that $\mathcal{R}_0$ increases as a parameter increases; if a sensitivity is negative, that means that $\mathcal{R}_0$ decreases as a parameter increases. More specifically, $\mathcal{S}_d = -0.5$ means that increasing mosquito mortality rate d by 10% will decrease the reproduction number by 5%. Some sensitivities add to zero:

$$\mathcal{S}_r + \mathcal{S}_d = 0 \qquad \mathcal{S}_\nu + \mathcal{S}_K + \mathcal{S}_\mu = 0.$$

This means that the same percentage increase in, say d and r, would produce no impact on the reproduction number, and

$$\mathcal{S}_b + \mathcal{S}_r = 1$$

means that a given percentage increase/decrease in both b and r will produce the same percentage increase/decrease in $\mathcal{R}_0$. For instance, a 10% decrease in both b and r will decrease $\mathcal{R}_0$ by 10%. Joint decrease in b and r can be achieved if the control measures act on the biting rate, which is a component in both b and r. In that sense our results agree with those in [32]; namely, that the reproduction number is most sensitive to the biting rate. Table 5 suggests that the reproduction number $\mathcal{R}_0$ is most sensitive to the transmission rates b and r, as well as the mosquito death rate d. Sensitivity to the treatment rate is slightly lower but still approximately equal to the sensitivity of the transmission and mosquito death rates. It is important to note that the biting rates, mosquito death rate and treatment are the three major control parameters in India's malaria control programs.

4.2 Sensitivity to the choice of model

Modeling is a powerful tool that assists understanding malaria and possibilities for control [10], even in the case when different models result in essentially different predictions [11].

Here we test the predictions made in the previous sections using another simple malaria model that has recently been used to investigate the impact of optimally timing primaquine treatment of *P. falciparum* malaria [14]. The epidemiological model in [14] is similar to model (3.1) but differs in one significant aspect, since it involves a class of asymptomatic individuals. Asymptomatic individuals are not treated, and they may remain infectious for a period of time of six months or more. The proportion of asymptomatic individuals may be as high as 30%, particularly in high transmission areas. Since 27% of India's population lives in high transmission areas [2], the contribution of the asymptomatic individuals to malaria transmission in India may be significant.

We keep most assumptions of the model in [14], including the assumption that the total population size is constant. Here, as in (3.1), it is assumed that the total mosquito population is constant, and re-scaled to the value 1.0. Further, in contrast to [14], the across-border migration is ignored. After some adaptation, our version of the model in [14] is given in equations (4.1).

$$\begin{aligned}
\frac{dL}{dt} &= b(1-\xi H(t-13.5))(P_H - L(t) - C(t) - I(t) - A(t))z(t) - (\sigma+\mu)C(t) \\
\frac{dC}{dt} &= p\sigma L(t) - (\nu+\mu)C(t) \\
\frac{dI}{dt} &= \nu C(t) - (\lambda + cH(t-13.5) + \mu)I(t) \\
\frac{dA}{dt} &= (1-p)\sigma L(t) - (q+\mu)I(t) \\
\frac{dy}{dt} &= r(1-\xi H(t-13.5))(1-y(t)-z(t))(I(t)+A(t)) - (d+v+\eta H(t-13.5))y(t) \\
\frac{dz}{dt} &= vy(t) - (d+\eta H(t-13.5))z(t)
\end{aligned} \tag{4.1}$$

where $L(t)$ is the number of individuals with liver-stage only malaria, $A(t)$ is the number of asymptomatic individuals, $y(t)$ is the proportion of latent mosquitoes and $z(t)$ is the proportion of infectious mosquitoes. Parameter meanings are listed in Table 6. Refer to [14] for details on the model and its interpretation.

In estimating the parameters in (4.1) we use values for v, σ, ν from [14]. Furthermore, we use the values for d from the value used in (3.1). Little information seems to be available in the literature regarding the proportion of asymptomatic individuals in India.[1] Lawpoolsri [14] takes $p = 0.99$ for the low endemicity area being studied. However, India has areas of high endemicity, where 27% of the population lives, areas of low endemicity, where 58% of the population lives, and areas with no malaria with 15% of the population [2]. We assume $p = 0.9$ but some extended simulations suggest that varying that value

[1] A study in pregnant women in Jharkhand State suggests that 45-55% of the pregnant women are asymptomatic [33].

Parameter	Interpretation	Value	Source
σ	rate of progression to symptomatic stage	365/18	[14]
p	proportion of progression to symptomatic stage	0.9	est.
b	transmission coefficient vector $\rightarrow$ human	8.08171	fitted
λ	treatment-recovery rate	22.5	est.
ν	rate of becoming infectious	365/7	[14]
r	transmission coefficient human -> mosquito	0.0282399	fitted
d	mosquito death rate	365/29	est.
v	rate of progression of vectors to infectious stage	365/12	[14]
ξ	fraction reduction in biting rates	0.00122	fitted
η	control-added vector mortality	0.04473	fitted
c	added treatment-recovery rate	1.99947	fitted
P_H	total human population	895 mil.	est.

Table 6: List of parameters with meanings and values for model (4.1)

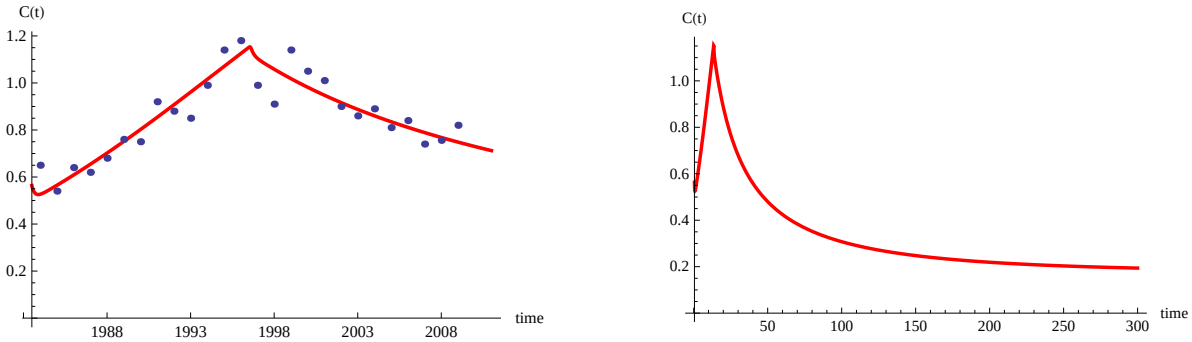

Figure 7: The left figure shows the number of clinical cases of malaria in India in 1984-2009 given as points (year 1984 is year 1). The continuous red curve is the incidence among humans given by model (4.1). Curve shows good agreement with data for the period 1984-2009. The right figure shows the long-term trend of the number of clinical cases as projected by model (4.1).

in the range $0.9 - 0.99$ reflects little on the outcome. Model (2.1) suggests that India's population in 1983 was 714 mil. people. Estimates for India's total population in 2008 give 1150 mil. people. We pre-estimate a constant population of 895 mil. Initial values of the model variables are assigned as follows: $L(0) = Q(0) = I(0) = 0.53$ mil., $A(0) = 0.05$ mil., $y(0) = 0.01$, and $z(0) = 0.13$.

We first fit the data in the period 1983-1996 to estimate b and r as earlier. Those values are listed in Table 6. In the second stage, we assign these values for b and r, and then fit the parameters ξ, η, and c to the data in the period 1998-2009. The SSE of the fit of all data is 0.111469 which is slightly lower than the total SSE obtained from the fitting of model (3.1) to the data. Figure 7 illustrates the fit.

The next-generation approach allows the computation of the reproduction number of model (4.1) [25, 26]. The control reproduction number is given in this case by the

formula:

$$\mathcal{R}_c = \sqrt{\frac{brP_H v(1-\xi)^2}{(v+d+\eta)(d+\eta)}\left[\frac{p\sigma\nu}{(\sigma+\mu)(\nu+\mu)(\lambda+c+\mu)} + \frac{(1-p)\sigma}{(\sigma+\mu)(q+\mu)}\right]}.$$

The basic disease reproduction number $\mathcal{R}_0$ is obtained from the control reproduction by setting the additional control variables to zero, that is with $c = 0$, $\eta = 0$, $\xi = 0$. The reproduction number of a mosquito is given by

$$\mathcal{R}_M = \frac{bP_H v}{d(v+d)}$$

where the fraction $v/(v+d)$ gives the probability of the mosquito to survive the incubation period and become infectious. The reproduction number of a human is given by

$$\mathcal{R}_H = \frac{rp\sigma\nu}{(\sigma+\mu)(\nu+\mu)(\lambda+\mu)} + \frac{r(1-p)\sigma}{(\sigma+\mu)(q+\mu)}.$$

The first term in the humans gives the proportion of secondary mosquito infections generated by one symptomatic individual, and the second term gives the proportion of infections generated by one asymptomatic individual. A newly infected human individual has a probability $\sigma/(\sigma+\mu)$ of surviving the liver-stage only disease and becoming symptomatic with probability p or asymptomatic with probability $1-p$. A symptomatic human has probability $\nu/(\nu+\mu)$ of surviving a clinical episode and becoming infectious when he will infect r mosquitoes per unit of time for $1/(\lambda+\mu)$ time units. At the same time a symptomatic individual will infect r mosquitoes per unit of time for $1/(q+\mu)$ time units. The number of secondary infections that one infected human will produce in the human population is given, as before, by $\mathcal{R}_0^2 = \mathcal{R}_M\mathcal{R}_H$.

Evaluating the basic reproduction number $\mathcal{R}_0$ with the parameters in Table 6 we get $\mathcal{R}_0 = 1.02392$. The additional control measures give a control reproduction number with value $\mathcal{R}_c = 1.0019$. As the control number is slightly greatly than one, it suggests that, if these control strategies persist, long-term, malaria will stabilize at a new, lower, endemic equilibrium – see Figure 7. The proportion decrease in the reproduction number, brought by additional control measures is

$$\text{proportion decrease} = 1 - \frac{\mathcal{R}_c}{\mathcal{R}_0} = 0.0215.$$

That is, the additional control measures have reduced the reproduction number by 2.15%.

The percent changes in the parameters $\mathcal{R}_0$, d, λ and b or r (denoted respectively by $\hat{\mathcal{R}}_0$, $\hat{\eta}$, $\hat{c}$, $\hat{\xi}$), brought about by the RBM added control measures, are estimated in Table 7. Estimates of the parameters in Table 2 and Table 3 are used for the estimation of the percentage change.

Comparing the control reproduction numbers from model (3.1) and model (4.1), leads to the important observation that the values of $\mathcal{R}_c$ often fall in the range

$$0.99 < \mathcal{R}_c < 1.01.$$

Continued and increased investment seems necessary to intensify and optimize malaria control, to ensure that the control reproduction number is steady and less than one.

Model	$\hat{\mathcal{R}}_0$	$\hat{\eta}$	$\hat{c}$	$\hat{\xi}$
model (3.1)	0.8%	0.312%	0	0.63%
model (4.1)	2.15%	0.356%	8.89%	0.12%

Table 7: Percentage change in control parameters for model (3.1) and model (4.1).

5 Discussion

With its large and heterogenous population, diverse landscape, remarkable bio-diversity and warm weather, India faces significant challenges for the elimination of malaria [34]. Roll Back Malaria Partnership's goal to eradicate malaria globally provides excellent opportunities for India to benefit from international knowledge and funding. Malaria is a complex disease whose epidemiology and control may be greatly advanced through mathematical modeling. Yet, surprisingly few applications of mathematical models seem to have been used to analyze malaria in India.

Here, we introduce a simple generalization of the Ross and MacDonald model, and we use it to study *P. falciparum* malaria, which in India has been showing a disturbing trend to increase in its proportions. Our model accounts for the population growth in India in the last 20-30 years. We fit the total population size and the number of clinical cases of *P. falciparum* malaria in India from 1983 through 2009. We observed that the model would not fit the data unless treatment improves in time, suggesting that India's strengthening health system has partly compensated for the growth in the population size, even while malaria incidence has grown during 1983-1997. Therefore, we assume in the model that the infectious period has declined from about 21 days in 1983 to about 13 days in 2008. The model projects 0.734 million cases of *P. falciparum* malaria in 2010 – the target year given by RBM programme when malaria burden has to be decreased by 50% from its level in 2000. According to our model by 2010, India would have achieved a 36% decrease from its 1.14 million *P. falciparum* malaria cases in 2000. Though slightly short of the goal, the reduction is significant. One possible explanation is that funding in the period 1997-2009 was insufficient to cause greater decline in the number of cases. Another possible explanation is that funding was not optimally distributed. India traditionally allocates the largest proportion of the funding to diagnosis and treatment [2]. At the same time chloroquine remains the first line of treatment for most of India, and has been used extensively even for *P. falciparum* cases. In fact, India's consumption of anti-malarials increased since 1970's ten times despite a significant reduction in the number of cases [35]. Incidentally, this coincides with the rise in the proportion *P. falciparum* cases. Spreading resistance necessitated the partial introduction of artimisine-based combination therapy (ACT) for *P. falciparum* cases in 2005. In 2008, as part of India's new approach to combating malaria, ACT was adopted as a first line treatment for all confirmed *P. falciparum* cases.

Our model gives a disease reproduction number that is slightly larger than one for *P. falciparum* malaria in India before 1997. After 1998, with the institution of the new control measures, we estimate that the new *control* reproduction number is $\mathcal{R}_c = 0.999457$, suggesting an extremely slow decline of *P. falciparum* cases to zero. Because the control reproduction number is so close to one, and it is sensitive to variations in parameters,

it would be premature to proclaim *P. falciparum* malaria in India conquered. In fact, we tested the sensitivity of the control reproduction number on the model by fitting a variant of the *P. falciparum* malaria model studied in [14] to India's data. The second model gave control reproduction number $\mathcal{R}_c = 1.0019$ which also predicts extremely slow decline but not to zero. The sensitivity of the control reproduction number to the model is certainly worth exploring with other models that encompass various different structures. For instance, there is significant evidence that prior malaria infections progressively build up immunity that decreases the risk of new infection and the risk of clinical infection if nevertheless infected. This type of model may be relevant for the high endemicity areas of India. Models that account for the build-up of immunity, just as the model with asymptomatic infection, may lead to somewhat higher estimates of the reproduction number. Other models we investigated also produced control reproduction numbers $\mathcal{R}_c \approx 1$ suggesting that *P. falciparum* in India has been brought to the critical elimination threshold. The introduction of ACT as a first line of treatment in 2008, in this respect, may hold significant promise to finally subdue this deadly pathogen.

One significant distinction between our main model and the model in [14] is that the model in [14] is more complex and involves a class of asymptomatic individuals. Asymptomatic individuals do not show clinical symptoms and do not get treated in India. Therefore, they remain infected for much longer periods, as long as a year or more. Asymptomatics may represent a significant source of infection, capable of carrying malaria from one wet season to the next, even if the treatment of the symptomatic individuals is timely and comprehensive. The presence of asymptomatic individuals in the Lawpoolsri *et al.* model [14] is the most likely reason that keeps the control reproduction number for that model above one. Our results, as the ones in [14], suggest that when asymptomatic individuals are accounted for, the current control measures may not eliminate malaria. There seem to be few studies of the presence of asymptomatic individuals and their fraction among the infected individuals. Such a study may greatly enhance ones ability to correctly assess India's prognosis for reducing and eliminating malaria.

Sensitivity with respect to the parameters of the disease reproduction number of the main model shows that it is most sensitive to the transmission rates for the mosquito $\rightarrow$ human and human $\rightarrow$ mosquito transmission pathways, as well as mosquito death rates. Following closely behind is the treatment rate. This suggests that the three focal points of India's control programs, namely interruption of contact, vector mortality, and treatment, are indeed applied at the most critical (sensitive) points where the disease reproduction number is the most sensitive. Preventive measures, such as the use of ITN, which decrease the biting rates, act on both transmission pathways simultaneously and have highest influence on the disease reproduction number.

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Appendix

In this appendix we show the local stability of the endemic equilibrium of the model without control (2.4). Theorem 1 gives this result.

Theorem 1 *Let $\mathcal{R}_0 > 1$. Then the unique endemic equilibrium $\mathcal{E}^* = (K, C^*, I^*, y^*)$ is locally asymptotically stable.*

Proof. The local stability is given by the Jacobian $\mathcal{J}$, obtained after the linearization around the endemic equilibrium.

$$\det(\mathcal{J} - \rho I) = \begin{vmatrix} -by^* - (\nu + \mu) - \rho & -by^* & b(K - C^* - I^*) \\ \nu & -(\lambda K + \mu) - \rho & 0 \\ 0 & r(1 - y^*) & -rI^* - d - \rho \end{vmatrix}$$

Expanding the determinant, we obtain the following third order characteristic polynomial

$$\det(\mathcal{J} - \rho I) = \rho^3 + \alpha_2 \rho^2 + \alpha_1 \rho + \alpha_0 = 0$$

where the coefficients α_2, α_1, α_0 are given in terms of the entries of the Jacobian as follows:

$$\begin{aligned} \alpha_2 &= rI^* + d + \lambda K + \mu + \nu + \mu + by^* \\ \alpha_1 &= (\lambda K + \mu + \nu + \mu + by^*)(rI^* + d) + (by^* + \nu + \mu)(\lambda K + \mu) + by^* \nu \\ \alpha_0 &= (by^* + \nu + \mu)(\lambda K + \mu)(rI^* + d) + by^* \nu (rI^* + d) - (\nu + \mu)(\lambda K + \mu) d \end{aligned} \tag{5.1}$$

In obtaining the above coefficients, the following relationship has been used which follows from the equations for the equilibrium:

$$br(K - C^* - I^*)(1 - y^*)\nu = (\nu + \mu)(\lambda K + \mu) d.$$

Routh-Hurwitz criterion ([36], p. 150) can be applied to give the local stability. We have $\alpha_2 > 0$, $\alpha_1 > 0$, and $\alpha_0 > 0$. It remains to be established that

$$\alpha_2 \alpha_1 > \alpha_0.$$

This inequality is easily seen as the first factor in α_0 is compensated by from the multiplication of the first factor in α_1 with the $(\lambda k + \mu)$ factor in α_2. Similarly, the second term in α_0 is compensated by the product of the last term in α_1 with the $(rI^* + d)$ term in α_2. This concludes the proof.

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