

Identifying key factors of the transmission dynamics of drug-resistant malaria

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Abstract

Development of resistance to malaria treatments remains a great threat to continued malaria burden reduction and elimination. Quantifying the impact of key factors which increase the emergence and spread of drug resistance can guide intervention strategies. Whilst modelling provides a framework to understand these factors, we show that a simple model with a sensitive–resistant dichotomy leads to incorrectly focusing on reducing the treatment rate as a means to prevent resistance. Instead we present a model that considers the development of resistance within hosts as a scale, and we then quantify the number of resistant infections that would arise from a single sensitive infection. By including just one step before full resistance, the model highlights that disrupting this development is more effective than reducing treatment rate. This result is compounded when the model includes the more realistic scenario of several intermediary steps. An additional comparison to transmission probabilities, where resistant infections are less likely to be transmitted (cost of resistance), confirms that preventing the establishment of resistance is more effective than controlling the spread. Our work strongly advocates for further studies into within-host models of resistance, including the potential of combination therapies to disrupt emergence.

Keywords: Ross-MacDonald model, malaria treatment, resistance emergence, resistance spread, resistance establishment, mutation

1. Introduction

Resistance threatens not just control of malaria but also our potential to eliminate malaria in low prevalence settings. Several historical examples of

4 development of the spread of resistance to malaria treatment exist, such as
5 widespread chloroquine resistance and less geographically spread sulfadox-
6 ine/pyrimethamine resistance, and more recently, resistance to artemisinin
7 (Yeung, 2004, WHO, 2018). Even once a drug is no longer in use, the resis-
8 tant genotypes may decline slowly, or even persist indefinitely (Liechti et al.
9 2017).

10 In the early 2000s combination therapy, where an infected individual is
11 treated with two or more drugs, became accepted as an approach to prevent
12 resistance to a given particular drug given as monotherapy (World Health
13 Organization 2001). Artemisinin combination therapies were introduced with
14 short-acting artemisinin derivatives formulated with different longer-acting
15 partner drugs, such as lumefantrine or Mefloquine (Nosten and White 2007).
16 Nonetheless, resistance continues to occur, with artemisinin resistance devel-
17 oping in South East Asia (Ménard et al. 2016) with fear of further spread-
18 ing and thus threatening both morbidity control and elimination of malaria.
19 More recently triple combination therapies with the view to delay emergence
20 and spread are being tested (Shanks et al. 2014). The community state
21 that to eliminate malaria policy decisions need to be preemptive, not reac-
22 tive (Boni et al. 2016). This requires a deeper understanding of resistance
23 which cannot be gained from generalisations of specific case studies. To test
24 and understand key drivers of resistance, mathematical models provide an
25 invaluable framework.

26 zur Wiesch et al. (2011) consider the overall dynamics, and discuss which
27 factors could influence the growth of resistance, including mutation, recom-
28 bination and *de novo* versus transmitted resistance. Typically reducing the
29 probability that *de novo* resistance mutations occur is often the focus, mean-
30 ing that pathogens are rapidly eliminated and patients continue treatment
31 after they feel better. However, Read et al. (2011) argue that the more ag-
32 gressive the regime, the greater the selection pressure in favour of resistance.
33 Essentially, reducing resistance is a balance between reducing the probability
34 of *de novo* resistance whilst not creating opportunity for mutated genotypes
35 to grow rapidly (Day and Read 2016). Kouyos et al. (2014) relate this bal-
36 ance to high and low transmission areas, advising moderate treatment where
37 malaria has high-transmission since co-infection is more frequent, and thus
38 resistant and sensitive strains compete more often within an individual host.
39 Aggressive treatment would be more likely to cause the removal of a sensi-
40 tive competitor. In a summary of population genetics and epidemiological
41 models for drug resistance, Mackinnon (2005) states that the two overriding

42 factors are the proportion of humans treated with drugs, and the efficacy of
43 the drug in clearing parasites.

44 When drug concentration is low enough to kill the sensitive genotype,
45 it may not necessarily be high enough to kill partially-resistant mutations.
46 With more uninfected blood cells, partially-resistant and resistant genotypes
47 can multiply rapidly. This selection process is often summarised by the
48 selection coefficient, which is simply the difference between the growth rate
49 of the mutant type and the sensitive type for a given drug concentration - the
50 relative fitness (Huijben et al. 2011). So a large selection coefficient implies
51 that the mutant type is growing rapidly. Day et al. (2015) contend that
52 instead of the relative fitness, the absolute fitness is a better measure. That
53 is, the growth rate of the mutant type is compared to itself at a baseline rate
54 defined by both the drug concentration and a within patient state variable,
55 such as the density of resources, or immune cells.

56 Having established that a resistant infection develops within a host, the
57 transmission of this infection throughout the homogeneous population can
58 be modelled via a compartment model. The most well-known example of a
59 compartmental model for malaria transmission is the Ross-MacDonald model
60 (Ross 1911, Macdonald 1957, Dietz 1974). This model puts the main burden
61 of transmission on mosquito-specific features, and thus motivated mosquito-
62 based malaria control programmes (Mandal et al. 2011). The simplicity
63 and relevance of the Ross-MacDonald has ensured that it continues to be a
64 strong basis for a broader theory of mosquito-borne disease transmission
65 and control (Smith et al. 2012).

66 There are several compartmental models that include a treated popula-
67 tion, and a population resistant to treatment. We compare our model to
68 six models which we are aware of, see Table 1. Two of the models, Koella
69 and Antia (2003) and Chiyaka et al. (2009), include an immune population.
70 As expected, the three models which explicitly include a treated population
71 (Koella and Antia (2003), Esteva et al. (2009) and Chiyaka et al. (2009))
72 find that the proportion treated has an effect on the spread of drug resis-
73 tance. The models of Koella and Antia (2003) and Esteva et al. (2009)
74 also find that the spread of resistant infections depends on the effectiveness
75 of the treatment (defined in terms of the period of infection), and the cost
76 of resistance (defined in terms of the reduction of intensity of transmission
77 due to mutation). Their models do not indicate transmission as a significant
78 factor. Chiyaka et al. (2009) also show that the spread of drug resistance
79 depends on the infectious periods, defined here as the ratio of the infectious

80 periods of treated and untreated humans. Unlike Koella and Antia (2003)
81 and Esteva et al. (2009), Chiyaka et al. (2009) find the transmission rates
82 from infectious humans with resistant and sensitive infections to influence
83 the spread of resistant infections. Tumwiine et al. (2014) and Tchuente et
84 al (2014) show that as the evolution of drug resistance grows, so does the
85 number of infections in the population. However, these models do not con-
86 sider the transmission of resistant infections - mosquitoes are either infected
87 or susceptible only such that resistance only occurs from evolution within a
88 treated host. More recently, Legros and Bonhoeffer (2016) modelled the resis-
89 tance within-host, and used this model to determine the transmission rates
90 in a simple compartmental (susceptible-infected) model. Unlike the other
91 models in Table 1, there is not a separation of hosts infected with sensitive
92 or resistant infections, since resistance is incorporated in the transmission
93 rates, which depend on the within-host model of the density of gametocytes.

94 Generally, compartmental models which explicitly include a resistant
95 class, do not include a partially-resistant class, although field evidence sug-
96 gests that assuming only sensitive and fully-resistant gene classes is often
97 invalid (Hastings et al. 2002). Resistance is a process, and thus better repre-
98 sented as a scale than a dichotomy. Tchuente et al (2014), who do include
99 partial resistance, do not include this class within the mosquito population,
100 and thus ignoring the transmission of partially resistant infections. This is
101 particularly relevant when considering the spread of resistance.

102 To summarise the overall findings of the compartmental models in Ta-
103 ble 1, drug resistance increases in the population as treatment increases, and
104 decreases as the period of infection decreases (drug efficacy increases). This
105 is agreement with Mackinnon’s (2005) summary on population genetics and
106 epidemiological models. When the evolution of drug resistance is included,
107 it is found to be a driving factor, but a comparison of this factor to the
108 transmission probabilities of sensitive and resistant infections is currently
109 missing. This omission has become more important as recent work interfaces
110 within-host models with population models via these probabilities (Legros
111 and Bonhoeffer, 2016 and Bushman *et al.*, 2018).

112 This paper presents a novel compartmental model that includes the evo-
113 lution of an infection within a treated host, such that a sensitive infection
114 becomes a partially resistant infection, which becomes a fully resistant in-
115 fection. This transference is defined by the ‘replacement rate’. The replace-
116 ment rate is a summary statistic that could be interpreted as an evolution
117 rate which leads to the emergence of resistance. There has been a variety of

118 approaches to model the emergence of resistance (Day *et al.*, 2015, Day *et al.*,
 119 2016, Hastings, 2003, Hastings and Hodel, 2014, Hastings *et al.*, 2002, Hast-
 120 ings and Watkins, 2005, MacKinnon, 2005, Read *et al.* 2011, Stepniewska
 121 and White, 2008, zur Weisch *et al.*, 2011). In Section 4 we demonstrate
 122 how three different approaches can be combined with our model to interface
 123 within host models with population models.

124 Since ‘replacement rate’ is a summary statistic, it’s definition is flexible
 125 to the question at hand, and thus the definition of partial resistance. For
 126 example, when treatment is a combination of two drugs - partial resistance
 127 may represent that the host has developed resistance to one drug, but not
 128 the second. Alternatively, resistance may require several mutations, as is
 129 the case with sulphadoxine pyrimethamine which has five important point
 130 mutations that have been found to be associated with resistance (Sarmah
 131 *et al.*, 2017). These mutations occur incrementally, and thus less than five
 132 mutations can be considered as partial resistance. In fact, instead of one
 133 level of partial resistance, the model could be adapted to have four levels
 134 of partial resistance, one for each mutation. See Subsection 3.4 for further
 135 discussion about increasing the number of partially resistant classes.

136 In this model, the three different classes of infections are passed to mosquitoes
 137 such that mosquitoes can transmit partially resistant and fully resistant in-
 138 fections, where different classes of infections have different probabilities of
 139 being transmitted due to a cost of resistance. The key contribution of this
 140 paper is that we quantify the great importance of understanding the evolu-
 141 tion of drug resistance - the replacement rate. Comparing this replacement
 142 rate to transmission properties, we show that controlling the emergence of
 143 drug resistance within a host is more effective than controlling the spread.

144 Our model compliments current research on resistance since it is this
 145 precise replacement rate that other research attempts to quantify, either
 146 by pharmacokinetic/pharmacodynamic modeling analysis (Hastings *et al.*
 147 2002), theoretical modelling (Day and Read 2016), or within-host models
 148 (Bushman *et al.* 2016). The interface between this research and our model is
 149 discussed more in Section 4. Our model suggests that in areas of high trans-
 150 mission, the effect of the replacement rate is greater, so it is more important
 151 to minimise it by, for example, using drugs with a short half life (Hastings
 152 *et al.* 2002).

153 We do not include factors such as age structure, socio-economic factors,
 154 and migration since a malaria model that incorporates all factors and vari-
 155 ables becomes an overwhelmingly complex system (Mandal *et al.* 2011).

Moreover, our aim is to quantify the effect of treatment, and highlight what treatment and resistance variables are of most importance, so we include the minimum factors required. This is an introductory model that can act as the foundation for further studies which include multiple infections, and immunity.

Table 1: The human and mosquito compartments used by previous malaria transmission models which include a resistant population: Koella and Antia (2003), K, Esteva et al. (2009), E, Chiyaka et al. (2009), C; Legros and Bonhoeffer (2011) (where immunity is modelled within host - denoted by *); Tchuente et al. (2011); Tumwiine et al. (2014); and this paper, LP. All models include a susceptible population of humans and mosquitoes, omitted from the table for clarity.

	Human										Mosquito					
	Exposed	Infected	Infected partially-resistant	Infected resistant	Treated	Treated partially-resistant	Treated resistant	Immune	Partially immune	Partially immune resistant	Exposed	Exposed partially-resistant	Exposed resistant	Infected	Infected partially-resistant	Infected resistant
K		✓			✓		✓	✓			✓		✓			✓
E		✓			✓		✓							✓		✓
C	✓	✓		✓	✓				✓	✓	✓			✓		✓
L		✓						✓*						✓		
Tc		✓	✓	✓	✓	✓					✓		✓	✓		✓
Tu		✓		✓				✓						✓		
LP		✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓

2. The model

The model is based on the Ross-McDonald delay differential equation model (Ross 1911, Macdonald 1957) where populations of humans and mosquitoes

are either susceptible or infected. Infected mosquitoes bite susceptible humans who then become infected. Mosquitoes which bite infected humans become exposed (infected but not infectious), and after $\hat{\tau}$ time, become infectious if they have not already recovered. It is assumed that mosquito and human populations are constant. To model drug resistance, a treated human population is required, so we allow infections be to treated at a rate r_x , see Figure 1.

A novel aspect of this model is to follow three distinct infection classes: sensitive $j = \mathcal{S}$, partially-resistant $j = \mathcal{P}$, and fully-resistant $j = \mathcal{R}$ in both the human and mosquito population. Transference between the three classes, of the form $\mathcal{S} \rightarrow \mathcal{P} \rightarrow \mathcal{R}$, occurs in the treated population only, via a process we call ‘replacement’. Replacement depends on factors such as the drug pressure, the mutation rate, and the *de novo* hazard. At a practical level these factors depend on inadequate dosage levels, poor compliance, combination therapy, and other implementation factors. Three different methods to quantify the replacement rate, ϕ , are discussed in Section 4.

Resistance also occurs in the human population via mosquito transmission, which we consider separately since the resistance evolution is not directly affected by the transmission intensity (Hastings et al. 2005). Resistant infections may not be transmitted as easily, which is included in our model via the transmission probabilities b_j and c_j . The probabilities that a bite leads to an infection in a human are related such that $b_{\mathcal{S}} \geq b_{\mathcal{P}} \geq b_{\mathcal{R}}$, and the probabilities that a bite leads to an infection in a mosquito are related such that $c_{\mathcal{S}} \geq c_{\mathcal{P}} \geq c_{\mathcal{R}}$. This allows the possibility that even when the cost of resistance is infinite, and so transmission of fully-resistant infections is zero, $b_{\mathcal{R}} = c_{\mathcal{P}} = 0$, fully-resistant infections can persist due to the replacement of partially-resistant infections within treated hosts. Additionally, even when within-host resistance evolution has been removed, $\phi = 0$, resistant infections may persist via transmission.

2.1. Human population

The total number of humans, which remains constant, is N , and is thus the sum of susceptible hosts S , infected hosts I_j and treated hosts T_j ($j = \mathcal{S}, \mathcal{P}, \mathcal{R}$),

$$N = S(t) + I(t) + T(t),$$

where $I = I_{\mathcal{S}} + I_{\mathcal{P}} + I_{\mathcal{R}}$ and $T = T_{\mathcal{S}} + T_{\mathcal{P}} + T_{\mathcal{R}}$. The recovery and death rates for all untreated infections, and treated fully-resistant infections, are assumed

to be the same, (r_I and α respectively). Perfect treatment is assumed so that the death rate for individuals with sensitive and partially-resistant treated infections is the same as the background death rate μ . The recovery rates for sensitive and partially-resistant infections are r_{T_S} and r_{T_P} . Comparing the recovery and death rates for the different classes: $r_I < r_{T_P} < r_{T_S}$ and $\mu < \alpha$.

2.1.1. Infected human population, $I_j(t)$

There are three classes of infected humans. For a given infection, the population is increased by the susceptible population which are bitten by a mosquito in class j , and decreased according to a recovery rate and background death rate,

$$\frac{dI_j}{dt} = ab_j m \frac{S}{N} \hat{I}_j - (r_I + r_x + \alpha) I_j, \quad (1)$$

where a is the biting rate of mosquitoes, m is the density of female mosquitoes, and \hat{I}_j is the number of mosquitoes with a class j infection. All variables and parameters are defined in Tables 2 and 3.

2.1.2. Treated human population, $T_j(t)$

Infected humans are treated at a rate r_x . Within the treated population, there is replacement ($\mathcal{S} \rightarrow \mathcal{P} \rightarrow \mathcal{R}$) due to growing resistance, via the replacement rate ϕ ,

$$\frac{dT_S}{dt} = r_x I_S - (\phi + \mu + r_{T_S}) T_S, \quad (2)$$

$$\frac{dT_P}{dt} = r_x I_P - (\phi + \mu + r_{T_P}) T_P + \phi T_S, \quad (3)$$

$$\frac{dT_R}{dt} = r_x I_R - (\alpha + r_I) T_R + \phi T_P. \quad (4)$$

The replacement $\mathcal{S} \rightarrow \mathcal{P}$ is assumed to occur at the same rate as $\mathcal{P} \rightarrow \mathcal{R}$ for ease of analysis, but they could be different rates. Note that I_R and T_R are the same: fully-resistant infections are unaffected by treatment, either because treatment was not administered I_R or it is ineffective T_R . However, using separate compartments allows us to monitor for infections that were initially partially-resistant T_R (establishment), and those that arise from mosquito transmission I_R (development).

223 *2.2. Mosquito population*

224 The total number of mosquitoes \hat{N} remains constant in time,

$$\hat{N} = \hat{S}(t) + \hat{E}(t) + \hat{I}(t), \quad (5)$$

225 and we assume recovery rates and death rates do not vary due to infec-
226 tion. There are three classes of mosquitoes to correspond with the sensitive,
227 partially-resistant, and fully-resistant infections.

228 *2.2.1. Exposed mosquito population, $E_j(t)$*

229 For a given infection, $j = \mathcal{S}, \mathcal{P}, \mathcal{R}$, the population is increased by the
230 susceptible population which bite an infectious human in class j . At each
231 time interval, a proportion leave the exposed population because the latency
232 period $\hat{\tau}$ has expired, as well as the background death rate $\hat{\mu}$,

$$\frac{d\hat{E}_j}{dt} = ac_j \frac{I_j + T_j}{N} \hat{S} - ac_j \frac{I'_j + T'_j}{N'} \hat{S}' e^{-\hat{\mu}\hat{\tau}} - \hat{\mu} \hat{E}_j, \quad (6)$$

233 where $(\cdot)'$ is (\cdot) at time $t - \hat{\tau}$.

234 *2.2.2. Infected mosquito population, $\hat{I}_j(t)$*

235 The population is increased from the exposed population whose latency
236 period has expired, and decreased according to the background death rate,

$$\frac{d\hat{I}_j}{dt} = ac_j \frac{I'_j + T'_j}{N'} \hat{S}' e^{-\hat{\mu}\hat{\tau}} - \hat{\mu} \hat{I}_j. \quad (7)$$

237 *2.3. Example simulations*

238 The model is run for three years using the values in Table 3, and initially
239 no infected humans nor mosquitoes with partially-resistant nor fully resistant
240 infections,

$$I_{\mathcal{P}} = I_{\mathcal{R}} = \hat{E}_{\mathcal{P}} = \hat{E}_{\mathcal{R}} = \hat{I}_{\mathcal{P}} = \hat{I}_{\mathcal{R}} = 0.$$

241 However, there are initially a small proportion of treated humans with the
242 more resistant classes. The non-zero compartments at $t = 0$ are

$$S = 99.4, I_S = 0.5, T_S = T_{\mathcal{P}} = T_{\mathcal{R}} = 0.099, \text{ and } \hat{S} = 80, \hat{E}_S = \hat{I}_S = 10. \quad (8)$$

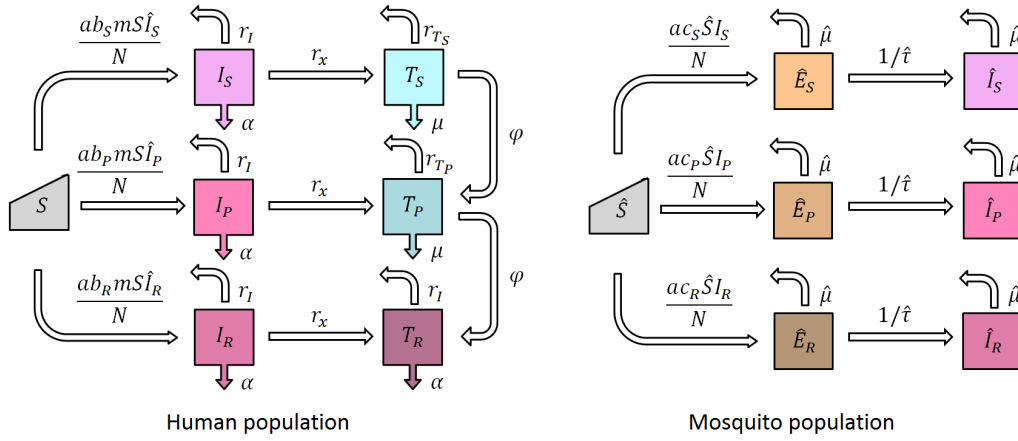


Figure 1: Schematic diagram of our malaria model. Infections are either sensitive $j = \mathcal{S}$, a partially-resistant $j = \mathcal{P}$ or a fully-resistant $j = \mathcal{R}$. Susceptible mosquitoes become infected in relation to the proportion of infected humans. After a latency period of $\hat{\tau}$, mosquitoes become infectious and may infect susceptible humans. Infections in humans are treated at rate r_x . In the human population, each compartment has a down arrow to represent death, at either the background rate μ , or the rate due to infection α ($\mu < \alpha$). The up arrows represent recovery ($r_{T_S} < r_{T_P} < r_I$), where all recovered persons become susceptible again. For clarity, this return to susceptible is not explicitly shown. In the mosquito population, the up arrow represent death at rate $\hat{\mu}$, where death is replaced by new susceptible mosquitoes.

Table 2: Model variables

Epidemiological compartments	Symbol
Total number of humans	N
Susceptible humans	S
Humans with sensitive infection	I_S
Humans with partially-sensitive infection	I_P
Humans with fully-resistant infection	I_R
Total infected humans	I
Treated humans with sensitive infection	T_S
Treated humans partially-sensitive infection	T_P
Treated humans fully-resistant infection	T_R
Total number of mosquitoes	\hat{N}
Susceptible mosquitoes	\hat{S}
Mosquitoes exposed to sensitive infection	\hat{E}_S
Mosquitoes exposed to partially-resistant infection	\hat{E}_P
Mosquitoes exposed to fully-resistant infection	\hat{E}_R
Total exposed mosquitoes	\hat{E}
Mosquitoes infected with sensitive infection	\hat{I}_S
Mosquitoes infected with partially-resistant infection	\hat{I}_P
Mosquitoes infected with fully-resistant infection	\hat{I}_R
Total infected mosquitoes	\hat{I}

Table 3: Parameter description and their default values. Unless indicated by a *, values are from Mandal et al. 2011. The values indicated by a * are guesstimates.

	Parameter	Symbol	Value
	Natural death rate of humans	μ	0.017/365 day ⁻¹
	Death rate of treated humans (assume perfect treatment)	μ	0.017/365 day ⁻¹
	Death rate of not treated humans	α	*0.17/365 day ⁻¹
	Natural death rate of mosquitoes	$\hat{\mu}$	0.2 day ⁻¹
	Latent period of mosquito	$\hat{\tau}$	11 days
	Biting rate	a	0.25 day ⁻¹
	Prob. that a bite transmits a sensitive infection to a human	b_S	0.3
	Prob. that a bite transmits a partially-resistant infection to a human	b_P	0.28
	Prob. that a bite transmits a fully-resistant infection to a human	b_R	0.2
	Prob. that a bite transmits a sensitive infection to a mosquito	c_S	0.5
	Prob. that a bite transmits a partially-resistant infection to a mosquito	c_P	0.4
	Prob. that a bite transmits a fully-resistant infection to a mosquito	c_R	0.3
	Ratio of female mosquitoes to humans	m	28
	Rate that infected humans receive treatment	r_x	0.03 day ⁻¹
	Average recovery rate of untreated infections	r_I	0.02 day ⁻¹
	Average recovery rate of treated, sensitive infections	r_{TS}	*0.06 day ⁻¹
	Average recovery rate of treated, partially-resistant infections	r_{TP}	*0.04 day ⁻¹
	Replacement rate	ϕ	*1/110 day ⁻¹

243 Despite a very low initial presence of resistance, the proportion of resistant
244 infections grows rapidly, but then it appears that an endemic equilibrium is
245 reached, see Figure 2a. Whereas when there is no cost of resistance, such that
246 $b_S = b_P = b_R$ and $c_S = c_P = c_R$ (Figure 2b), the infected proportion contin-
247 ues to increase. The specific requirements for an endemic equilibrium, and
248 the effect of the transmission probabilities, is discussed further in Section 3.2.

249 As previously mentioned, even when $b_R = c_R = 0$, fully-resistant infec-
250 tions persist due to the replacement of partially-resistant infections within
251 treated hosts, see Figure 2c. This figure also has the rate of replacement set
252 to zero after one year. Together with Figure 2d, this shows that resistance
253 persists in a population once once the possibility of resistance developing
254 within a host is removed.

255 3. Results

256 Having established the model, and discussed some examples, we present
257 some analyses to track the emergence and spread of resistance. In Section 3.1,
258 the number of secondary infections arising from a single infection is calcu-

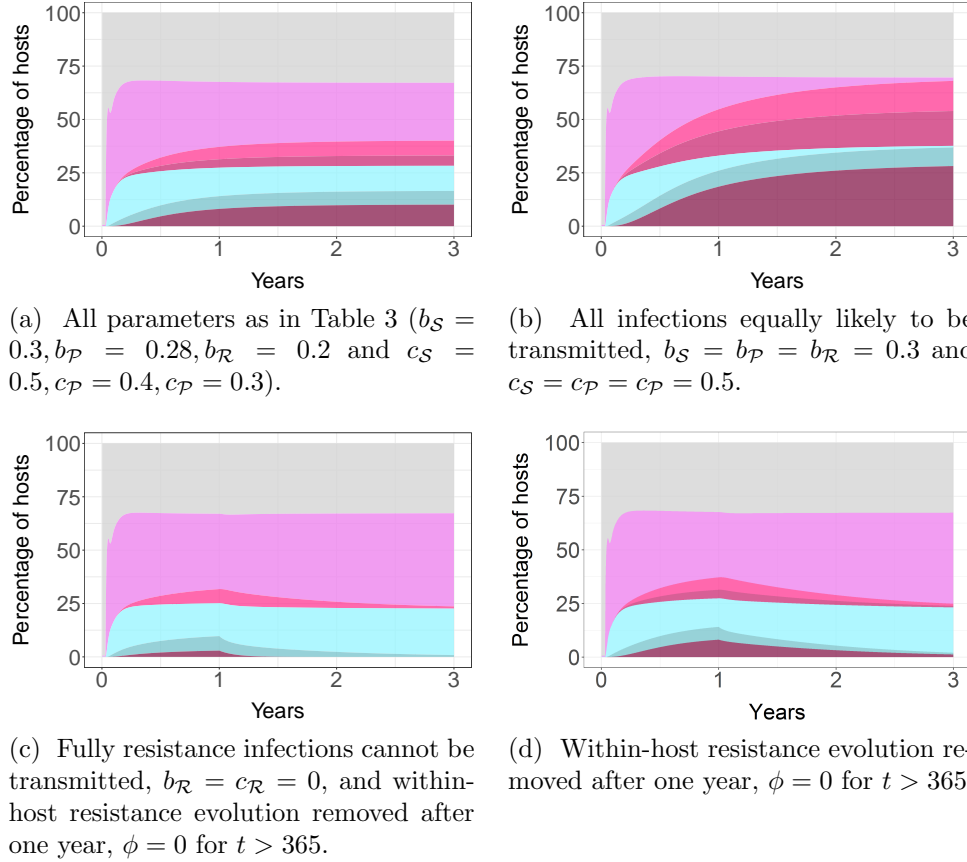


Figure 2

Example simulations to show the effect of varying transmission probabilities and within-host evolution. All parameters are as in Table 3, unless otherwise stated. The colours correspond to the compartment colours in

Figure 1: Pink compartments are the infected populations, without treatment, and the blue compartments are the treated population. Except the darkest pink, which is the treated population with the fully resistant infection (this compartment is equivalent to the fully-resistant infected population without treatment, second darkest pink). The darker tone correspond to more resistant infections.

259 lated. By keeping the three classes of infections separate, we focus on the
 260 number of resistant infections that arise from a sensitive infection. The affect
 261 of the different treatment variables is discussed, and the importance of the

262 replacement rate ϕ is quantified. Then we discuss the requirements for an
 263 endemic equilibrium.

264 The importance of ϕ is verified for two model adaptations, which would
 265 make the model more realistic. Firstly, in Subsection 3.3, we show that
 266 the results remain the same when an asymptomatic human population is
 267 included. Secondly, in Subsection 3.4, we show that as more levels of resis-
 268 tance evolution are included, the replacement rate ϕ actually becomes more
 269 important.

270 3.1. Reproductive numbers

271 As resistance grows, so does the total number of infected individuals. The
 272 reproductive number is a measure of the number of secondary, infectious,
 273 infections expected after one new infection. The number of infections of any
 274 class, arising from a single infection of any class, is denoted by $R_{S \mathcal{P} \mathcal{R} \rightarrow S \mathcal{P} \mathcal{R}}$
 275 and is the sum of

$$\left. \begin{array}{l} R_{I_S \rightarrow \hat{I}_S} R_{\hat{I}_S \rightarrow I_S} \\ R_{I_S \rightarrow T_S \rightarrow \hat{I}_S} R_{\hat{I}_S \rightarrow I_S} \end{array} \right\} R_{S \rightarrow S}, \quad (9)$$

$$\left. \begin{array}{l} R_{I_P \rightarrow \hat{I}_P} R_{\hat{I}_P \rightarrow I_P} \\ R_{I_P \rightarrow T_P \rightarrow \hat{I}_P} R_{\hat{I}_P \rightarrow I_P} \end{array} \right\} R_{P \rightarrow P}, \quad (10)$$

$$\left. \begin{array}{l} R_{I_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R} \\ R_{I_R \rightarrow T_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R} \end{array} \right\} R_{R \rightarrow R}, \quad (11)$$

$$R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow \hat{I}_P} R_{\hat{I}_P \rightarrow I_P} \left\} R_{S \rightarrow P}, \quad (12)$$

$$R_{I_P \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R} \left\} R_{P \rightarrow R}, \quad (13)$$

$$R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R} \left\} R_{S \rightarrow R}, \quad (14)$$

276 where the subscripts indicate the movement of the initial infection through
 277 the different compartments. For example, infection of class j in a mosquito
 278 passed to a human is $R_{\hat{I}_j \rightarrow I_j}$. The reproductive numbers (12)–(14) relate to
 279 resistance emerging, with (14) being of particular interest as it relates to the
 280 number of fully resistant infections arising from a single sensitive infection.
 281 Once fully resistant infections are established, the reproductive number (11)
 282 relates to the fully resistant infection spreading. From the model, (9)–(14)
 283 are defined as,

$$R_{S \rightarrow S} = \frac{a^2 b_{SCSm}}{\hat{\mu}} \left[\frac{r_{T_S} + r_x + \phi + \mu}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}, \quad (15)$$

$$R_{\mathcal{P} \rightarrow \mathcal{P}} = \frac{a^2 b_{\mathcal{P}} c_{\mathcal{P}} m}{\hat{\mu}} \left[\frac{r_{T_{\mathcal{P}}} + r_x + \phi + \mu}{(r_I + r_x + \alpha)(r_{T_{\mathcal{P}}} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}, \quad (16)$$

$$R_{\mathcal{R} \rightarrow \mathcal{R}} = \frac{a^2 b_{\mathcal{R}} c_{\mathcal{P}} m}{\hat{\mu}} \left[\frac{1}{r_I + \alpha} \right] e^{-\hat{\mu}\hat{\tau}}, \quad (17)$$

$$R_{\mathcal{S} \rightarrow \mathcal{P}} = \frac{a^2 b_{\mathcal{P}} c_{\mathcal{P}} m}{\hat{\mu}} \left[\frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}, \quad (18)$$

$$R_{\mathcal{P} \rightarrow \mathcal{R}} = \frac{a^2 b_{\mathcal{R}} c_{\mathcal{P}} m}{\hat{\mu}} \left[\frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_{\mathcal{P}}} + \phi + \mu)(r_I + \alpha)} \right] e^{-\hat{\mu}\hat{\tau}}, \quad (19)$$

$$R_{\mathcal{S} \rightarrow \mathcal{R}} = \frac{a^2 b_{\mathcal{R}} c_{\mathcal{P}} m}{\hat{\mu}} \left[\frac{r_x \phi^2}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu)(r_I + \alpha)} \right] e^{-\hat{\mu}\hat{\tau}}. \quad (20)$$

284 The derivation of (15)–(20) is provided in Appendix A. The terms outside
 285 the square brackets relate to the reproductive number of the delay Ross-
 286 McDonald model,

$$R_{\mathcal{S}} = \frac{a^2 b c m e^{-\hat{\mu}\hat{\tau}}}{\hat{\mu}}, \quad (21)$$

287 (Ruan et al. 2009). That is, reduction in transmission is most strongly af-
 288 fected by the exponent terms: the death rate of mosquitoes $\hat{\mu}$, and the latency
 289 time period $\hat{\tau}$; the biting rate a has a stronger affect than the transmission
 290 probabilities b, c (here b_j, c_j) and the mosquito density m . These known af-
 291 fects have more impact for the reproductive numbers (15)–(20) which have a
 292 larger term inside the square brackets. This is especially true for the variables
 293 to the left of the square brackets, which relate to transmission rates, because
 294 the terms in the square brackets are of the same order as the transmission
 295 terms, whereas the latency period and mosquito death rate are exponents.

296 We now investigate when the reproductive numbers relating to resistance
 297 emerging (18)–(20) are large for varying parameters, and thus informing when
 298 the transmission rates and latency period have a stronger effect on the spread
 299 of resistance.

300 Let us assume that the recovery rate from infection r_I , the death rate
 301 from infection α and background death rate μ are fixed. Therefore, the
 302 reproductive numbers (15)–(20) only vary by the treatment variables:

- 303 • the recovery rates for sensitive and partially-resistant infections which
 304 are being treated, $r_{T_{\mathcal{S}}}, r_{T_{\mathcal{P}}}$. It is assumed that these rates range between
 305 2 and 10 times larger than the recovery rate of non-treated individu-
 306 als r_I ,

- 307 • the rate of infections being replaced by more resistant infections $\phi \in$
308 $[0, 1]$,
- 309 • the treatment rate $r_x \in (0, 1]$;

310 and the cost of resistance, represented by the transmission probabilities b_j
311 and c_j . Overall, the number of infections can be reduced by increasing the
312 treatment rate r_x and increasing the recovery rates, r_{T_S} and r_{T_P} . However,
313 as the replacement rate ϕ increases, so does the total number of infections,
314 see Figure 4a.

315 Previous studies confirm that increasing the rate of treatment increases
316 the rate of resistance spread (Koella and Antia 2003, Esteva et al. 2009,
317 Chiyaka et al. 2009); and increasing the cost of resistance reduces the spread
318 of resistance (Koella and Antia 2003, Esteva et al. 2009). However, like
319 Tchuenche et al (2011) and Tumwiine et al. (2014) who include resistance
320 growth, we show that the replacement rate has a much stronger affect, see
321 Figure 3. Moreover, by including partial resistance in the mosquito popula-
322 tion, we can separate resistant infections that are transmitted and those that
323 develop within the host.

324 When the replacement rate is high, there are a lot of secondary fully-
325 resistant infections arising from a single sensitive infection, $R_{S \rightarrow R}$. This is
326 because the development of fully-resistant infections from sensitive infections,
327 $R_{S \rightarrow R}$, is affected by the replacement rate twice, hence equation (20) is $O(\phi^2)$,
328 which is the same order as the biting rate a . Therefore, in this model, the
329 replacement rate has an equal affect as the biting rate. Since the replacement
330 rate ϕ and the transmission variables a , b_j , c_j and m are of similar order,
331 in areas of high transmission, reducing the replacement rate has a strong
332 effect. Moreover, this is actually more effective than reducing the treatment
333 rate r_x , or increasing the cost of resistance b_j , c_j , at mitigating resistance
334 spread. The limited effect of transmission rates b_j and c_j is in agreement
335 with Gandon et al. (2001, 2003), where they showed that vaccines limiting
336 transmission have little effect on evolution.

337 Nonetheless, one must be careful when interpreting the specifics of this
338 model. For example, treatment rate per day is likely to be considerably
339 larger than the replacement rate per day. Under this model, there is reason
340 to believe that under certain conditions, the treatment rate may actually
341 create more resistance emergence than the replacement rate (for example, the
342 treatment rate is $r_x = 0.9$ and the replacement rate is $\phi = 0.01$, see Figure
343 4b). However, as we discuss later in Section 3.4, only including one step to

344 resistance is perhaps still too coarse a lens, which would make this example
 345 meaningless. Instead, when interpreting the resistance emerging reproductive
 346 number $R_{\mathcal{S} \rightarrow \mathcal{R}}$, consider the overall result that whilst the influence of the
 347 replacement rate is compounded, the treatment rate and transmission rates
 348 remain unchanged.

349 All resistance emerging reproductive numbers, $R_{\mathcal{S} \rightarrow \mathcal{P}}$, $R_{\mathcal{P} \rightarrow \mathcal{R}}$, $R_{\mathcal{S} \rightarrow \mathcal{R}}$, (15)–
 350 (20) are inversely related to the treatment rates $r_{T_{\mathcal{S}}}$ and $r_{T_{\mathcal{P}}}$. Therefore,
 351 improved recovery rates not only reduce the overall number of infections,
 352 but it is especially beneficial for reducing the emergence of drug resistance.
 353 Note that $R_{\mathcal{S} \rightarrow \mathcal{P}}$, $R_{\mathcal{P} \rightarrow \mathcal{R}}$, $R_{\mathcal{S} \rightarrow \mathcal{R}}$, (15)–(20) depend on the treatment rate of
 354 partially-resistant infections $r_{T_{\mathcal{P}}}$, whereas the treatment rate of sensitive in-
 355 fections $r_{T_{\mathcal{S}}}$ affects $R_{\mathcal{S} \rightarrow \mathcal{P}}$ and $R_{\mathcal{P} \rightarrow \mathcal{R}}$ only. Therefore the recovery rate of
 356 partially-resistant infections is of more importance at mitigating the spread
 357 of resistance. In fact, the recovery rate of partially-resistant infections $r_{T_{\mathcal{P}}}$
 358 has a stronger affect than the treatment rate r_x , see Figure 4a.

359 3.2. Equilibrium

360 When considering the disease free equilibrium, we consider the case of a
 361 constant human population. Without treatment, the system reduces to the
 362 delay Ross-McDonald model, and thus the disease free equilibrium is trivial.
 363 The endemic equilibrium is

$$\frac{I^*}{N} = \frac{R_{\mathcal{S}} - 1}{R_{\mathcal{S}} + ace^{-\hat{\mu}\hat{\tau}}/\hat{u}},$$

364 where $R_{\mathcal{S}}$ is as in (21), from Ruan et al. 2009. For the full model presented
 365 here, with treatment and resistance, the disease free equilibrium is when

$$\begin{aligned} I_j^* &= \frac{\beta_j}{r_I + r_x + \alpha}, \\ T_{\mathcal{S}}^* &= \frac{r_x \beta_{\mathcal{S}}}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)}, \\ T_{\mathcal{P}}^* &= \frac{r_x [\phi \beta_{\mathcal{S}} + (r_{T_{\mathcal{S}}} + \phi + \mu) \beta_{\mathcal{P}}]}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu)}, \\ T_{\mathcal{R}}^* &= \frac{r_x [\phi^2 \beta_{\mathcal{S}} + \phi(r_{T_{\mathcal{S}}} + \phi + \mu) \beta_{\mathcal{P}} + (r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu) \beta_{\mathcal{R}}]}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu)(r_I + \alpha)}, \end{aligned}$$

366 where $\beta_j = ab_j m(S^*/N) \hat{I}_j^*$. As expected, when $\beta_{\mathcal{S}} = \beta_{\mathcal{P}} = \beta_{\mathcal{R}} = 0$, the
 367 equilibrium is the disease free equilibrium. These conditions are not met in
 368 the examples in Figure 2, but it is clear that the difference is negligible.

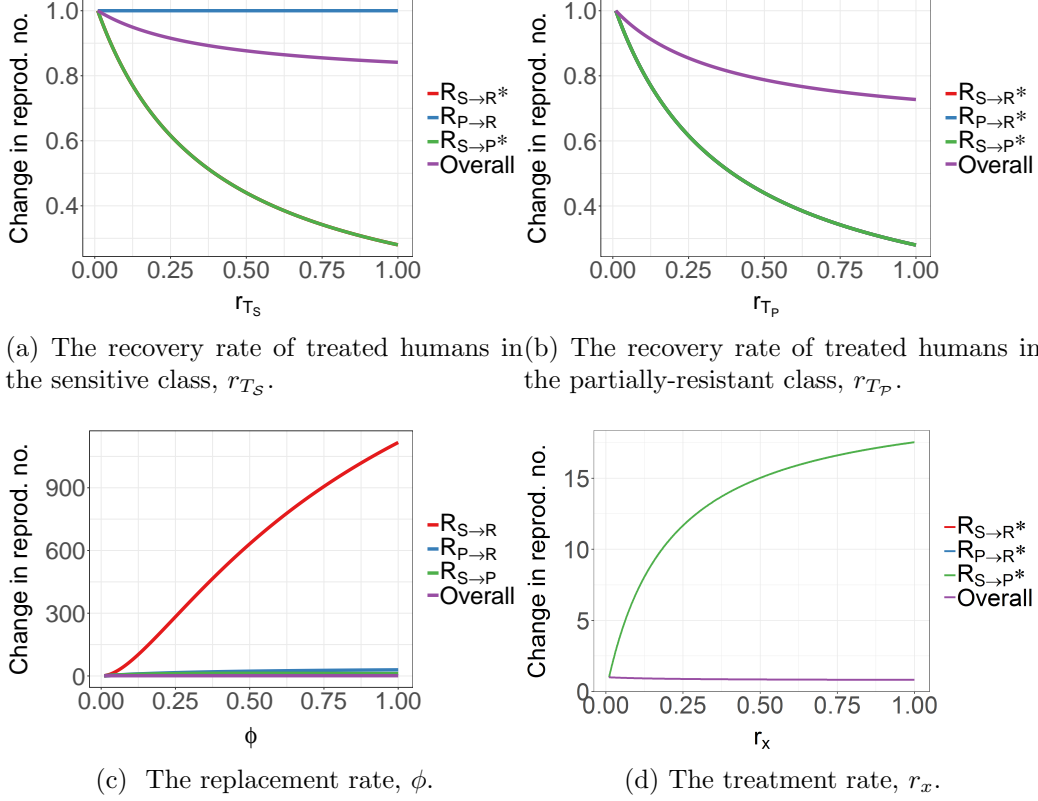


Figure 3

The change in the resistance emerging reproductive numbers $R_{S \rightarrow P}$, $R_{P \rightarrow R}$ and $R_{S \rightarrow R}$, and the overall reproductive number $R_{S \rightarrow P \rightarrow R}$, relative to the recovery rate of the treated population r_T , the treatment rate r_x , and the replacement rate ϕ . The * in the legend indicates the lines are the same.

369 We now discuss the conditions required for an equilibrium where only the
 370 sensitive, and partially-resistant infections are present,

$$I_{\mathcal{R}} = T_{\mathcal{R}} = \hat{I}_{\mathcal{R}} = 0. \quad (22)$$

371 If fully-resistant infections are absent from $I_{\mathcal{R}}$ and $\hat{I}_{\mathcal{R}}$, they can only enter
 372 the population via $T_{\mathcal{P}}$. Therefore the equilibrium (22) will only remain stable
 373 if there is no movement from $T_{\mathcal{P}}$ to $T_{\mathcal{R}}$. From (19), and assuming that the
 374 death and recovery rates are non-zero, $\alpha, r_I > 0$, it is clear that movement

375 from $T_{\mathcal{P}}$ to $T_{\mathcal{R}}$ is only prevented if the treatment or replacement rate is zero,
 376 $r_x = 0$ or $\phi = 0$. Similarly, the conditions for sensitive only infections is only
 377 stable under the same conditions. Moreover, even when the cost of resistance
 378 prevents transmission of the fully-resistant infection, this class of infection
 379 persists unless $r_x = 0$ or $\phi = 0$ due to resistance developing within a treated
 380 host.

381 3.3. Including an asymptomatic population

382 An infection in a human may be asymptomatic A_j , such that infections
 383 in humans could transfer $S \leftrightarrow A_j \leftrightarrow I_j \rightarrow T_j$ (as well as $S \leftrightarrow I_j \rightarrow T_j$ as
 384 before), where A_j represents asymptomatic infections. We now discuss how
 385 the reproductive numbers (15)–(20) change with this added feature.

386 With these new compartments, the recovery rate of infections (untreated
 387 or fully-resistant) r_I , is the sum of the recovery rates from infected to sus-
 388 ceptible r_{IS} and from infected to asymptomatic r_{IA} . Similarly, the recovery
 389 rates from treated infections r_{T_j} , $j = \mathcal{S}, \mathcal{P}$, is the sum of the recovery rates
 390 from treated to susceptible $r_{T_j S}$ and from treated to asymptomatic $r_{T_j A}$. This
 391 change does not alter the reproductive numbers (15)–(20). However, more
 392 significantly, an asymptotic population adds an exponential term $e^{-(r_A + \mu)\tau}$,
 393 where r_A is the recovery rate of asymptotic infections, and τ is the asymptotic
 394 period. This highlights results consistent with previous models - the period
 395 of time that humans are infectious is key factor of transmission dynamics
 396 (Chiyaka et al. 2009).

397 3.4. Resistance as a scale

398 Consider a model for a single infection without partial-resistance, such
 399 that fully-resistant infections replace sensitive infections directly. In this cir-
 400 cumstance the number of secondary fully-resistant infections arising from a
 401 single sensitive infection, $R_{\mathcal{S} \rightarrow \mathcal{R}}$, would be $O(b_{\mathcal{R}})$, $O(c_{\mathcal{P}})$, $O(r_x)$, and $O(\phi)$,
 402 not $O(\phi^2)$ as in this model. This would have led to the conclusion that
 403 transmission probabilities, treatment rate, and replacement rate are equally
 404 important. Alternatively, consider a single infection with n steps towards full
 405 resistance, where each step is equally likely. Then the number of secondary
 406 fully-resistant infections arising from one sensitive infection $R_{\mathcal{S} \rightarrow \mathcal{R}}$, would
 407 be $O(b_{\mathcal{R}})$, $O(c_{\mathcal{P}})$, $O(r_x)$, as before, but now $O(\phi^n)$. Therefore, because in-
 408 fections evolve through different stages before becoming fully-resistant, con-
 409 trolling this evolution is incredibly important, and much more important
 410 than transmission probabilities and treatment rate. By modelling resistance

411 emergence as a scale, and not a sensitive-resistant dichotomy, the potential
 412 of combination therapies to disrupt emergence comes into focus.

413 To demonstrate, suppose that a sensitive infection evolves resistance to a
 414 drug at rate ϕ_A , and develops resistance to a partner drug at rate ϕ_B . From
 415 our analysis we observe that the number of fully resistant infections to result
 416 from a single sensitive infection, $R_{S \rightarrow R}$, would be $O(\phi_A \phi_B)$. (Both rates
 417 relate to within-host evolution, so the conclusion that within-host dynamics
 418 is the driver of resistance still holds.) In this form it is clear that eliminating
 419 one step ($\phi_A = 0$ or $\phi_B = 0$) prevents full resistance developing.

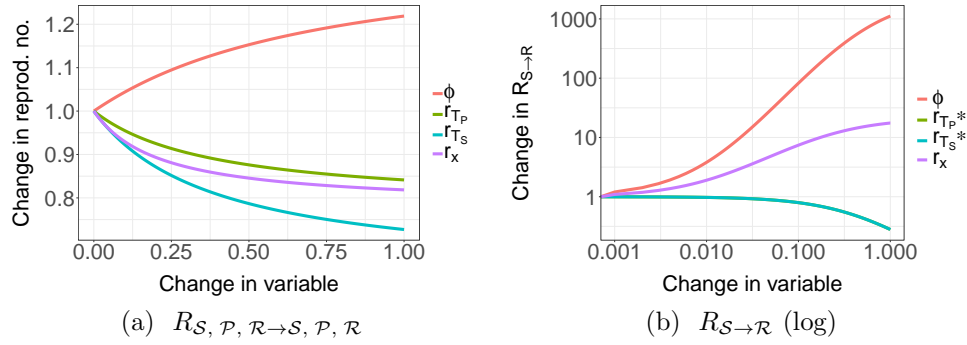


Figure 4

The change in the overall reproductive number and the resistance emerging
 reproductive number, relative to changes in the treatment variables. The *
 in the legend indicates the lines are the same. Note that as the model
 becomes more realistic so as to incorporate additional levels of resistance,
 the effect of the recovery rates, r_{T_S} , r_{T_P} , and treatment rate, r_x , remain the
 same, but the effect of the replacement rate ϕ (the red line) increases
 dramatically.

420 4. Parameterising the replacement rate ϕ

421 Having established that the replacement ϕ is the most important treat-
 422 ment variable, we discuss three different methods to determine an approx-
 423 imate value. This value is bounded by 0, meaning no resistance evolution,
 424 and 1, meaning instant transference from sensitive to resistant.

425 4.1. The selection window

426 When a treatment is first administered a patient is protected from partially-
 427 resistant and sensitive infections. Once the drug concentration is below a

certain value, the resistant genotypes are no longer inhibited by the drug and spreads to replace the original, sensitive infection. This time period is referred to as the selection window (Kay and Hastings 2015, Hastings, Watkins and White 2002). Let us assume that during this selection window, sensitive parasites are ‘replaced’ by partially-resistant parasites, and thus ϕ is connected to the selection window.

Kay and Hastings (2015) use the selection window to calculate the probability, as a function of time, of parasites successfully surviving residual drug levels. They show that artemether-lumefantrine and artesunate-mefloquine kept the probability of successful emergence (our ‘replacement’) below 10% for 10 to 20 days post-treatment. This corresponds to $0.0055 \leq \phi \leq 0.011$. Whereas resistance is more likely to occur with DHA piperaquine, which kept the probability of successful emergence (‘replacement’) below 40% for 10 days post-treatment, $\phi = 0.05$. We use a default value of $\phi = 1/110 = 0.0091$ (see Table 3), which lies in the range of a combined artesunate treatment.

4.2. The probability of resistance

Day and Read (2016) calculate the probability of resistance, dependent on the drug concentration c . This corresponds to ϕ in our model such that

$$\phi = 1 - e^{-H(c)}, \quad (23)$$

where $H(c)$ is the sum of the *de novo* hazard and the standing hazard. The *de novo* hazard depends on the rate which resistant mutations appear after the start of the treatment, and the probability of escape of any such mutant. The standing hazard is the hazard due to a standing population of resistant microbes that are already present at the start of treatment. The full equation for $H(c)$ is provided in Appendix B. Unlike Hastings, Watkins and White (2002), which focuses on the effect of drug pressure only, Day and Read (2016) find that sometimes moderate treatment is preferred. Equation (23) provides useful insight, but parameterising it remains an open challenge.

4.3. Within-host modelling

Lastly, one could model the dynamics within-host (Bushman et al. 2016), and interface the two models, as in Legros and Bonhoeffer (2016). In Legros and Bonhoeffer (2016), the transmission probability b , depends on the number of gametocytes, which is determined by a within-host model. The results

460 from this paper indicate that it would be more important to include the re-
 461 placement rate. This could be done by considering the erythrocytes infected
 462 with the sensitive clone, $Y_{\mathcal{R}}$, such that

$$\phi = \epsilon(1 - \mu_y)\mu_m Y_{\mathcal{R}}, \quad (24)$$

463 where $\epsilon \in [0, 1]$ is the treatment efficacy, and μ_y is the death rate of infected
 464 erythrocytes, which are both included in the original Legros and Bonhoeffer
 465 (2016) model. The new variable $\mu_m \in [0, 1]$ relates to the proportion of
 466 erythrocytes infected with the sensitive clone which evolve to become infected
 467 with the resistant clone. Replacement rate (24) allows a transference from
 468 sensitive to resistant erythrocytes that increases as the treatment efficacy
 469 increases, whilst still allowing for reduction in erythrocytes due to death.
 470 Of note, as the number of erythrocytes infected with the sensitive clone $Y_{\mathcal{R}}$
 471 changes over time, so does the replacement rate ϕ .

472 5. Discussion

473 Generally, previous models which monitor the spread of resistance have
 474 found that reducing the proportion of people treated is one of the most reli-
 475 able ways to reduce resistance, which is clearly an undesirable strategy both
 476 for control and elimination. Our model agrees with this finding, but more
 477 encouragingly and realistically, reducing the replacement rate has a stronger
 478 effect at reducing resistance spread. Models which include the evolution of
 479 drug resistance show that it is important, but omit mosquitoes transmit-
 480 ting varying infections, so a comparison to the transmission probabilities is
 481 missing.

482 In fact, for a model that considers one partially-resistant class only, the
 483 effectiveness of this control strategy is directly comparable to the conclusions
 484 from the original Ross-MacDonald model which found that reducing the bit-
 485 ting rate of mosquitoes is more effective than reducing density of mosquitoes.
 486 However, when one considers that resistance is a continuous scale, the evolu-
 487 tion within-host is the most important factor, which emphasises the potential
 488 of combination therapies to disrupt emergence.

489 The replacement rate ϕ is not specific to a given drug, but instead it is
 490 a measure which can be influenced by implementation procedures, such as
 491 pharmacokinetics, pharmacodynamics, poor adherence or combination ther-
 492 apy. The parameterisation examples provided in Section 4 could be consid-

493 ered as a single factor of a much more complex system. Whilst reasonably pa-
 494 rameterising this more complex system may be overreaching, understanding
 495 the various factors should still be the focus of policy decisions. For example,
 496 when administering combination therapy, it may be challenging to under-
 497 standing the different rates of resistance to individual drugs, but because it
 498 is understood that combination therapy lowers the overall replacement rate,
 499 it should be the preferred treatment strategy. This focus on keeping evolu-
 500 tion low by treatment administration protocol is also discussed by Bell and
 501 MacLean (2016), who present an evo-epidemiological model of antibiotic re-
 502 sistance. Their work predicts that it should be possible for any antibiotic to
 503 be effectively evolution-proof, as long as the antibiotic is administered in a
 504 way that prevents the epidemic spread of resistant lineages.

505 6. Conclusion

506 As resistance spreads, treatment becomes ineffective. To understand
 507 drivers of resistance we developed a compartmental model that includes
 508 partial resistance and full resistance, and we then quantified the number
 509 of resistant infections that arise from a single sensitive infection. Previous
 510 models for single infections, where resistance is a dichotomy, find that treat-
 511 ment rate and the cost of infection to be key factors that contribute to the
 512 spread of resistance. By including just one intermediary step before full re-
 513 sistance, in both the human and mosquito population, we demonstrate that
 514 although these factors are important, the transmission of resistance is actu-
 515 ally best mitigated by controlling the evolution within a host. This result is
 516 compounded when one considers that the development to full resistance is
 517 actually a continuous process. This model can be used in combination with
 518 other models that are investigating this replacement process, and thus one
 519 can track how certain factors (such as reducing the selection window) affect
 520 the transmission dynamics.

521 Secondly, provided there is a replacement of sensitive infections with more
 522 resistant variants, a disease free equilibrium does not exist. Moreover, a
 523 population with only sensitive or partially-resistant infections is not possi-
 524 ble. This again highlights the importance of understanding what treatment
 525 strategies are the most effective at reducing this replacement rate.

526 Our work strongly advocates for policies which reduce resistance emerg-
 527 ing (or to at least act quickly once it has emerged). However, resistance to
 528 malaria treatment has been observed in Africa, yet it has not been estab-

529 lished. This may be because the model presented here only considers single
 530 infections, and ignores the dynamics within a mosquito. Notwithstanding
 531 these additions, the model supports further research into resistance develop-
 532 ing within hosts.

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657 Appendix A. The reproductive numbers

658 The disease free equilibrium point is when the human population is

$$I_S = I_P = I_R = T_S = T_P = T_R = 0 \text{ and } S = N,$$

659 and the mosquito population is

$$\hat{E}_S = \hat{E}_P = \hat{E}_R = I_S = I_P = I_R = 0 \text{ and } \hat{S} = \hat{N} = 1.$$

660 Consider a single newly infectious mosquito with any class of infection. At
 661 time t this mosquito has a probability $e^{-\hat{u}t}$ of surviving its infectious period,
 662 and infects humans at a rate $ab_j m S/N$. Hence the total number of humans
 663 who become infectious, from each class, due to this mosquito during its entire
 664 infectious period is

$$\begin{aligned} R_{\hat{I}_j \rightarrow I_j} &= ab_j m \frac{S}{N} \int_0^\infty e^{-\hat{u}t} dt \\ &= \frac{ab_j m}{\hat{\mu}} \end{aligned} \quad (\text{A.1})$$

665 A similar process is used to derive the total number of mosquitoes who be-
 666 come infectious from a human during his/her entire infectious period. How-
 667 ever, there are several different routes the infection can take, see (9)–(11).
 668 These different routes are detailed below.

669 *Appendix A.1. Equation (9):* $R_{S \rightarrow S} = (R_{I_S \rightarrow \hat{I}_S} + R_{I_S \rightarrow T_S \rightarrow \hat{I}_S}) R_{\hat{I}_S \rightarrow I_S}$

670 The expected number of mosquitoes who become infectious with a sensi-
 671 tive infection, from one human with this infection who is not treated, is

$$\begin{aligned} R_{I_S \rightarrow \hat{I}_S} &= ac_S e^{-\hat{\mu}\hat{\tau}} \int_0^\infty e^{-(r_I + r_x + \alpha)t} dt \\ &= ac_S \frac{1}{r_I + r_x + \alpha} e^{-\hat{\mu}\hat{\tau}}. \end{aligned} \quad (\text{A.2})$$

672 And if the human is treated, which occurs at a rate r_x , the expected number
 673 of infectious mosquitoes is,

$$\begin{aligned} R_{I_S \rightarrow T_S \rightarrow \hat{I}_S} &= ac_S e^{-\hat{\mu}\hat{\tau}} r_x \int_0^\infty \int_0^\infty e^{-(r_I + r_x + \alpha)u} e^{-(r_{T_S} + \phi + \mu)t} du dt \\ &= ac_S \frac{r_x}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)} e^{-\hat{\mu}\hat{\tau}}. \end{aligned} \quad (\text{A.3})$$

674 Combining with (A.1) gives the total number of secondary sensitive infections
 675 from one human infected with a sensitive infection,

$$R_{S \rightarrow S} = \frac{a^2 b_S c_S m}{\hat{\mu}} \left[\frac{r_{T_S} + r_x + \phi + \mu}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}.$$

676 *Appendix A.2. Equation (10):* $R_{P \rightarrow P} = (R_{I_P \rightarrow \hat{I}_P} + R_{I_P \rightarrow T_P \rightarrow \hat{I}_P}) R_{\hat{I}_P \rightarrow I_P}$

677 The expected number of mosquitoes who become infectious with the
 678 partially-resistant infection, from one human with this infection who is not
 679 treated, is the parallel to (A.2). Similarly, if the human is treated, which
 680 occurs at a rate r_x , the expected number of infectious mosquitoes is the
 681 parallel to (A.3). Therefore, the total number of secondary infected humans,
 682 with a partially-resistant infection, from one human infected with a partially-
 683 resistant infection, is

$$R_{P \rightarrow P} = \frac{a^2 b_P c_P m}{\hat{\mu}} \left[\frac{r_{T_P} + r_x + \phi + \mu}{(r_I + r_x + \alpha)(r_{T_P} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}.$$

684 *Appendix A.3. Equation (11):* $R_{R \rightarrow R} = (R_{I_R \rightarrow \hat{I}_R} + R_{I_R \rightarrow T_R \rightarrow \hat{I}_R}) R_{\hat{I}_R \rightarrow I_R}$

685 The expected number of mosquitoes who become infectious with the fully-
 686 resistant infection, from one human with this infection who is not treated, is
 687 the same as (A.2). However, if the human is treated, which occurs at a rate
 688 r_x , the expected number of infectious mosquitoes is

$$\begin{aligned} R_{I_R \rightarrow T_R \rightarrow \hat{I}_R} &= ac_P e^{-\hat{\mu}\hat{\tau}} r_x \int_S^\infty \int_S^\infty e^{-(r_I + r_x + \alpha)u} e^{-(r_I + \alpha)t} du dt \\ &= ac_P \frac{r_x}{(r_I + r_x + \alpha)(r_I + \alpha)} e^{-\hat{\mu}\hat{\tau}}. \end{aligned}$$

689 Combining with (A.1) gives the total number of secondary infected humans,
 690 with a fully-resistant infection, from one human infected with a fully-resistant
 691 infection,

$$R_{R \rightarrow R} = \frac{a^2 b_R c_P m}{\hat{\mu}} \frac{1}{r_I + \alpha} e^{-(r_A + \mu)\tau} e^{-\hat{\mu}\hat{\tau}}. \quad (\text{A.4})$$

692 *Appendix A.4. Equation (12):* $R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow \hat{I}_P} R_{\hat{I}_P \rightarrow I_P}$

693 A human infected with a sensitive infection may infect a mosquito with
 694 partially-resistant infection. This human would be treated at a rate r_x , and

695 become partially-resistant at rate ϕ , giving,

$$\begin{aligned} R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow \hat{I}_P} &= ac_S e^{-\hat{\mu}\hat{\tau}} r_x \phi \int_S^\infty \int_S^\infty \int_S^\infty e^{-(r_I+r_x+\alpha)v} e^{-(r_T+\phi+\mu)u} \\ &\quad e^{-(r_T+\phi+\mu)t} du dv dt \\ &= \frac{ac_S \mu}{\lambda} \frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)(r_{T_P} + \phi + \mu)} e^{-\hat{\mu}\hat{\tau}}. \end{aligned}$$

696 Combining with (A.1) gives the total number of secondary infected humans,
697 with a partially-resistant infection, from one human infected with a sensitive
698 infection,

$$R_{S \rightarrow P} = \frac{a^2 b_P c_S m}{\hat{\mu}} \left[\frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)(r_{T_P} + \phi + \mu)} \right] e^{-\hat{\mu}\hat{\tau}}.$$

699 *Appendix A.5. Equation (13): $R_{I_P \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R}$*

700 A human infected with a sensitive infection may infect a mosquito with a
701 partially-resistant infections. This human would be treated at a rate r_x , and
702 become partially-resistant at rate ϕ , giving,

$$\begin{aligned} R_{I_P \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} &= ac_P e^{-\hat{\mu}\hat{\tau}} r_x \phi \int_S^\infty \int_S^\infty \int_S^\infty e^{-(r_I+r_x+\alpha)v} e^{-(r_T+\phi+\mu)u} \\ &\quad e^{-(r_I+\alpha)t} du dv dt \\ &= ac_P \frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_P} + \phi + \mu)(r_I + \alpha)} e^{-\hat{\mu}\hat{\tau}}. \end{aligned}$$

703 Combining with (A.1) gives the total number of secondary infected humans,
704 with a fully-resistant infection, from one human infected with a partially-
705 resistant infection,

$$R_{P \rightarrow R} = \frac{a^2 b_R c_P m}{\hat{\mu}} \left[\frac{r_x \phi}{(r_I + r_x + \alpha)(r_{T_P} + \phi + \mu)(r_I + \alpha)} \right] e^{-\hat{\mu}\hat{\tau}}.$$

706 *Appendix A.6. Equation (14): $R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} R_{\hat{I}_R \rightarrow I_R}$*

707 A human infected with a sensitive infection may infect a mosquito with
708 partially-resistant infection. This human would be treated at a rate r_x , be-
709 come partially-resistant at rate ϕ , and then fully-resistant at rate ϕ , giving,

$$\begin{aligned} R_{I_S \rightarrow T_S \rightarrow T_P \rightarrow T_R \rightarrow \hat{I}_R} &= ac_S e^{-\hat{\mu}\hat{\tau}} r_x \phi^2 \int_S^\infty \int_S^\infty \int_S^\infty \int_S^\infty e^{-(r_I+r_x+\alpha)w} e^{-(r_T+\phi+\mu)v} \\ &\quad e^{-(r_T+\phi+\mu)u} e^{-(r_I+\alpha)t} dw du dv dt \\ &= ac_S \frac{r_x \phi^2}{(r_I + r_x + \alpha)(r_{T_S} + \phi + \mu)(r_{T_P} + \phi + \mu)(r_I + \alpha)} e^{-\hat{\mu}\hat{\tau}}. \end{aligned}$$

710 Combining with (A.1) gives the total number of secondary infected humans,
 711 with a fully-resistant infection, from one human infected with a sensitive
 712 infection,

$$R_{\mathcal{S} \rightarrow \mathcal{R}} = \frac{a^2 b_{\mathcal{R}} c_{\mathcal{S}} m}{\hat{\mu}} \left[\frac{r_x \phi^2}{(r_I + r_x + \alpha)(r_{T_{\mathcal{S}}} + \phi + \mu)(r_{T_{\mathcal{P}}} + \phi + \mu)(r_I + \alpha)} \right] e^{-\hat{\mu} \hat{\tau}}.$$

713 **Appendix B. Day and Read 2016**

714 The probability of resistance emerging is approximately equal to

$$\phi = 1 - e^{-H(c)},$$

715 where $H(c)$ is the resistant hazard,

$$H(c) = D(c) + S(c).$$

716 The quantity $D(c)$ is the *de novo* hazard,

$$D(c) = \int_S^a \lambda[p(s; c), c] \pi[x(s; c), c] \, ds.$$

717 Is is comprised of the integral of the product of $\lambda[p(s; c), c]$, the rate at
 718 which resistant mutants appear at time s after the start of treatment, and
 719 $\pi[x(s; c), c]$, the probability of escape of any such mutant.

720 The quantity $S(c)$ is the standing hazard - the hazard due to a standing
 721 population of n resistant microbes that are already present at the beginning
 722 of treatment,

$$S(c) = -n \ln(1 - \pi[x(0; c), c]).$$