Early transmission of *Plasmodium vivax* sensitive strain slows down emergence of drug resistance

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Abstract

Malaria remains endemic in multiple countries, in which interventions based on antimalarial drugs have had limited effect due to the spread of drug resistance. Majority of malaria cases are caused by the parasites *Plasmodium falciparum* and *Plasmodium vivax* and the evolution of drug resistance has a different temporal and geographic pattern between these *Plasmodium* species. In order to compare the different pattern, we develop here a compartmental model to estimate the effect of the monotherapies, combination therapies, the asymptomatic cases, the gametocytocidal use, the window of selection, the prophylactic period, and the resistance cost. The evaluation of the reproductive numbers and simulations showed the emergence of drug resistance in *P. falciparum* faster than *P. vivax* due to the highest effectiveness of the treatment against sensitive parasites but the delay to the emergence depends on the therapy. By contrast, the slower spread of drug resistance in *P. vivax* was produced by the transmission of sensitive parasites before the treatment and their transmission through the asymptomatic cases. These results suggest that improvements in the rapid attention can increase the risk of drug resistance and development of new therapies is necessary.

Introduction

alaria mortality and morbidity rates produced about 435.000 deaths and 219 million human cases in 2017 [35]. Most cases are caused by *Plasmodium vivax* and *Plasmodium falciparum* parasites whose life cycles differ markedly. The development of antimalarial drugs has been the main strategy in malaria control allowing the decrease in the disease prevalence during the last decade. However, the emergence of drug resistance has decreased the antimalarial effectiveness, remaining as a challenge in the malaria control [36].

Currently, the evidence shows an evolution in drug resistance with different temporal and geographical patterns between *P. vivax* and *P. falciparum* parasites. For instance, the current first-line treatment suggested to treat the infection by *P. vivax* parasite in most endemic regions is the administration of chloroquine (CQ) [20]. In contrast, the suggested treatment for malaria infection by *falciparum* parasite is the artemisininbased combination therapy (ACT) because monotherapies as chloroquine (CQ) are ineffective due to reports of cloroquine resistance dating from 1950 in South America, Southeast Asia and subsequently spread to all endemic regions between 1960 to 1970 [37, 38].

In the *P. falciparum* case, ACTs had their efficacy decreased in the Greater Mekong sub-region since the first report of treatment failure in 2008 [39, 40]. On the other hand, CQ resistance by *P. vivax* has been confirmed in Indonesia and New Guinea but cases can be underestimated due to the recurrences in *P. vivax* infection are also caused by the hypnozoites relapse [41]. As a consequence of reports of CQ resistance in *P. vivax*, WHO has issued the use of ACTs to treat *P. vivax* cases as an alternative but CQ remains as the first-line option [20].

In order to explain how *P. vivax* and *P. falciparum* evolved towards drug resistance with different patterns, previous researches have evaluated a few biological factors associated with the parasite life cycle. An initial hypothesis involved different selection pressure by immune response against merozoites in *P. falciparum* and *P. vivax* caused by difficult recognition of *P. vivax* antigens [42]. Moreover, the early gametocyte relapse in *P. vivax*, i.e. before treatment, and longer life span in *P. falciparum* gametocytes were analyzed in an evolutionary model where a high frequency of

resistant *P. falciparum* parasites was achieved in less time than *P. vivax* due to the long selection period after treatment in *P. falciparum* [12].

Despite previous studies testing different evolution of drug resistance between *Plasmodium* species, most of the previous studies have been focusing in *P. falciparum* drug resistance [40]. This is the case of the evaluation of the selection force in *P. falciparum* parasites through the window of selection, WoS, that represents the period post-treatment where the resistant parasites can emerge by the drug selection [13]. Additionally, previous studies evaluated the selection force in *P. falciparum* through the potential transmission showing that resistant strains have a reduction in the relapse of gametocytes between 0% to 60% in comparison to the wild type strains [18, 19].

Another important property in the spread of drug resistance is the geographical pattern that is accelerated in zones of low transmission conditions as South America and Southeast Asia, in contrast with endemic zones in Africa [40]. Hamza *et al.* suggest that asymptomatic cases in high transmission conditions help to carry the population of wild-type parasites avoiding the spread of resistant strains [43]. Moreover, the existence of co-infection between sensitive and resistant strains in high transmission conditions make a competitive advantage to the wild-type due to the fitness cost associated with the resistance [26].

In order to estimate the effect of determinants in the spread of drug resistance and the malaria transmission, mathematical models have been a useful tool to evaluate this dynamic [44]. This kind of models have evaluated the emergence and the spread of drug resistance according to the selection force of some treatment regimens [12, 13, 25, 32, 44, 52–55]. Besides, models of transmission dynamics in human populations have allowed to estimate the effect of campaigns with drug administration to achieve malaria control and elimination [4–7, 15, 16, 22]. However, these models have been developed to *P. falciparum* transmission only. We compare the effect of the drug campaigns on populations affected by *P. falciparum* and *P. vivax* parasites to find determinants in their different pattern of drug resistance. Moreover, the results can be extended to make suggestions in the control programs using antimalarials.

1 Models of drug resistance dynamics

In the current section, we present two models to represent the dynamics of malaria drug resistance to the cases of *P. falciparum* and *P. vivax* separately to compare the effect of the drug administration in the emergence and spread of drug resistance involving the differences between life cycles of these *Plasmodium* species. Both approximations were based in the compartmental Ross-Macdonald models with states in a human and mosquito populations [48]. Model parameters are described in the Table 1.

1.1 Model features

In order to explain some model features, we listed a set of important key points involved in the modeling scope.

- Resistance cost: the modifications in a resistant genotype can imply a fitness cost in the parasite development. This cost is measured as a reduction in the growth rate, parasite density and parasite persistence that produce a decline in the infectiousness and the infectious period [19].

- Prophylaxis period: after applications of an antimalarial, the patient takes a period of time to eliminate the drug. This period is denominated prophylaxis period because the drug continues acting and it confers a temporally protection against new infection. This period varies with the applied treatment [57].

- Window of selection (WoS): a period during the prophylaxis when the drug concentration eliminates sensitive parasites while partial resistant parasites can emerge [32]. During this period, the resistant parasites can be transmitted.

- Asymptomatic contribution: these individuals are considered as parasite reservoirs because they are be able to transmit the parasite without the control of antimalarials [8]. This condition is associated with the immunological evolution of the host by the frequent exposition to the pathogen. Nevertheless, the infectious capacity of an asymptomatic host can be considered lower than a symptomatic [58].

1.2 Model of drug treatment targeting transmission of *P. falciparum*

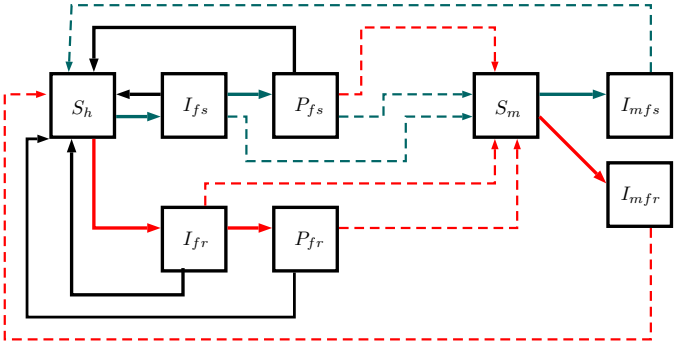

Figure 1. *P. Falciparum* compartmental model of the interaction between susceptible humans S_h, infected humans by sensitive strain I_{fs}, humans in prophylaxis after the infection by sensitive parasite P_{fs}, infected humans by resistant strain I_{fr}, humans in prophylaxis after the infection by resistant parasite P_{fr}, susceptible mosquitoes S_m, infected mosquitoes by sensitive strain I_{mfs}, and infected mosquitoes by resistant strain I_{mfr}. The dotted lines represent the interactions between humans and mosquitoes where P_{fs} state can transmit the sensitive and resistant strains by the drug selection pressure.

In the case of *P. falciparum* transmission, we build a compartmental model comprised of number S_h of susceptible human individuals, I_{fs} humans infected by sensitive strain, P_{fs} human individuals in prophylaxis after the infection by sensitive parasite, I_{fr} humans infected by resistant strain and P_{fr} human individuals in prophylaxis after infection by resistant parasite, S_m susceptible mosquitoes, I_{mfs} infected mosquitoes by sensitive strain and I_{mfr} infected mosquitoes by resistant strain states, as shown in Figure 1. This model represents a wild type strain (sensitive) and a resistant strain that can be originated by the parasite selection during the window of selection in the prophylaxis state P_{fs}.

$$\frac{dI_{fs}}{dt} = mab\frac{I_{mfs}}{N_m}S_h - (1-\eta\sigma_f)r_{fs}I_{fs} - \eta\sigma_f\gamma_{fs}I_{fs} - \mu_h I_{fs}, \tag{1}$$

$$\frac{dP_{fs}}{dt} = \eta\sigma_f\gamma_{fs}I_{fs} - \frac{P_{fs}}{\kappa} - \mu_h P_{fs}, \tag{2}$$

$$\frac{dI_{fr}}{dt} = (1-\varrho)mab\frac{I_{mfr}}{N_m}S_h - (1-\eta\sigma_f)r_{fr}I_{fr} - \eta\sigma_f\gamma_{fr}I_{fr} - \mu_h I_{fr}, \tag{3}$$

$$\frac{dP_{fr}}{dt} = \eta\sigma_f\gamma_{fr}I_{fr} - \frac{P_{fr}}{\kappa(n+1)} - \mu_h P_{fr}, \tag{4}$$

$$\frac{dS_h}{dt} = \Lambda_h N_h - mab\frac{I_{mfs}}{N_m}S_h - (1-\varrho)mab\frac{I_{mfr}}{N_m}S_h + \frac{P_{fs}}{\kappa} + \frac{P_{fr}}{\kappa(n+1)} \tag{5}$$

$$+(1-\eta\sigma_f)r_{fs}I_{fs}+(1-\eta\sigma_f)r_{fr}I_{fr}-\mu_h S_h$$

$$\frac{dI_{mfs}}{dt}=ac_s\sigma_f\frac{I_{fs}}{N_h}S_m+ac_a(1-\sigma_f)\frac{I_{fs}}{N_h}S_m+ac_s(1-\varphi)(1-\nu)\frac{P_{fs}}{N_h}S_m-\mu_m I_{mfs}, \quad (6)$$

$$\frac{dI_{mfr}}{dt}=ac_s\sigma_f(1-\varrho)\frac{I_{fr}}{N_h}S_m+ac_a(1-\sigma_f)(1-\varrho)\frac{I_{fr}}{N_h}S_m+ac_s(1-\varrho)(1-\varphi)\frac{P_{fr}}{N_h}S_m \quad (7)$$

$$+ac_s(1-\varrho)(1-\varphi)\nu\frac{P_{fs}}{N_h}S_m-\mu_m I_{mfr},$$

$$\frac{dS_m}{dt}=\Lambda_m N_m-[ac_s\sigma_f+ac_a(1-\sigma_f)]\frac{I_{fs}}{N_h}S_m-ac_s(1-\varphi)(1-\nu)\frac{P_{fs}}{N_h}S_m \quad (8)$$

$$-[ac_s\sigma_f+ac_a(1-\sigma_f)](1-\varrho)\frac{I_{fr}}{N_h}S_m-ac_s(1-\varrho)(1-\varphi)\frac{P_{fr}}{N_h}S_m$$

$$-ac_s(1-\varrho)(1-\varphi)\nu\frac{P_{fs}}{N_h}S_m-\mu_m S_m$$

Where the human population N_h and the mosquito population N_m are

$$N_h=S_h+I_{fs}+I_{fr}+P_f,$$
$$N_m=S_m+I_{mfs}+I_{mfr}$$

The equations of the model are presented from the equations 1 to 8, and the model parameters are described in Table 1.

To represent the spread of drug resistance, infections in the model can be either by sensitive parasite fs or by resistant parasite fr. The equations for number of infected individuals differ in the recovery and transmission rates. The average recovery rate in infected humans is (in sensitive strain are $(1-\eta\sigma_f)r_{fs}I_{fs}-\eta\sigma_f\gamma_{fs}I_{fs}$) given by two terms, the first one representing the recovery rate of untreated infected humans and the second term being the recovery rate of treated infected humans. We assume that $\gamma_{fs}>\gamma_{fr}$ due to the a more effective treatment against infected by sensitive strain in terms of infectious time and recurrences originated by the drug resistance.

The model also takes into account asymptomatic cases. A proportion σ_f of symptomatic humans is constant and it affects the real coverage of the drug in humans and the transmission to susceptible mosquitoes. The proportion of treated humans is $\eta\sigma_f$ where the expected drug coverage η is used in symptomatic cases only. On the other hand, the transmission contribution of asymptomatic infected humans is

different due to a lesser parasitaemia level in these individuals. To represent the parasite transmission from asymptomatic infected humans, we considered transmission probabilities in asymptomatic and symptomatic c_a and c_s, respectively, where $c_a < c_s$.

In the model, the resistant strain has transmission probability lower than the sensitive strain because the decrease in the gametocytes density as consequence of resistance cost [19]. To model this behavior, we define the term $(1 - \varrho)$ that reduces the transmission rates between infected humans by resistant strain and susceptible mosquitoes in a ϱ percentage.

Furthermore, our model includes a prophylaxis state in humans representing individuals treated for a prophylaxis period of time. This prophylaxis state takes into account the effect of the parasite selection within human host post-treatment. In this state, humans remain infectious because gametocytes remain in the blood while the drug is eliminating during the WoS at $1/\kappa$ rate [12]. In fact, the selection given from the drug allows the humans in prophylaxis state by sensitive parasite to develop a resistant parasite that can be transmitted to a susceptible mosquito with a ν probability that varies according to the drug therapy [21]. Nevertheless, a human in P_{fs} state is able to transmit a sensitive parasite with a likelihood of $1 - \nu$.

A human infected by resistant strain has the same recovery time from an infected by the sensitive strain but it has n recurrences due to resistance effect with rate $\gamma_{fr} = \gamma_{fs}/(n + 1)$. Hence, the average infectious period in I_{fr} is $(1/\gamma_{fs})(n + 1)$. Moreover, the average time of prophylaxis (or infectious period in prophylaxis) by the resistant strain depends on the number of recurrences $(k(n + 1))$.

Finally, we made the transmission blocking effect of the inclusion of a gametocytocidal as primaquine (PQ) [20]. Consider the parameter φ as the proportion of treated humans with gametocytocidal that do not have the potential to transmit the parasite. The treated humans correspond to the P_{fs} and P_{fr} states and we penalized the infectious potential to susceptible mosquitoes multiplying the transmission rates of them by $1 - \varphi$ to susceptible mosquitoes as you can see in the equations in mosquito population (see equations 6-8).

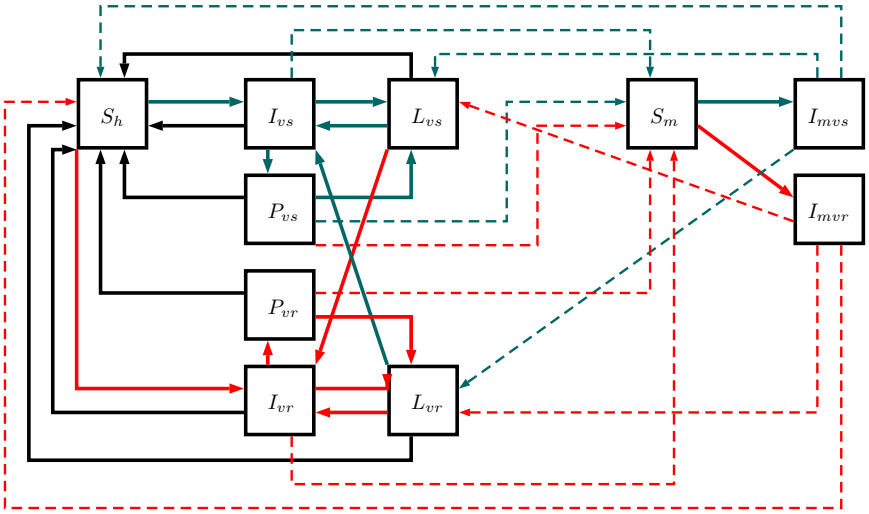

Figure 2. *Vivax* compartmental model of the interaction between susceptible humans S_h, infected humans by sensitive strain I_{vs}, human in latent state by sensitive strain L_{vs}, humans in prophylaxis after infection by sensitive parasite P_{vs}, infected humans by resistant strain I_{vr}, human in latent state by resistant strain L_{vr}, humans in prophylaxis after infection by resistant parasite P_{vr}, susceptible mosquitoes S_m, infected mosquitoes by sensitive strain I_{mvs}, and infected mosquitoes by resistant strain I_{mvr}. The dotted lines represent the interactions between humans and mosquitoes where P_{vs} state is able to transmit the sensitive and resistant strains by the drug selection. Additionally, this structure has the possibility of representing the superinfection of humans in latent state.

1.3 Model of drug treatment targeting transmission of *P. vivax*

The model for transmission of *P. vivax* differs mainly by the possibility of relapses due to latent state by hypnozoites and superinfection in latent state. Hence, the model now includes variables representing the latent states human in latent state by sensitive strain L_{vs}, human in latent state by resistant strain L_{vr} states. Similar to the *P. falciparum* case, the resistant strain can be originated by the parasite selection during the prophylaxis state P_{vs}.

$$\frac{dI_{vs}}{dt} = mab\frac{I_{mvs}}{N_m}S_h - (1-\eta\sigma_v)r_{vs}I_{vs} - \eta\sigma_v\gamma_{vs}I_{vs} + \psi L_{vs} + mab\rho_{sr}\frac{I_{mvs}}{N_m}L_{vr} \tag{9}$$

$$\frac{dL_{vs}}{dt} = (1-\eta\sigma_v)\phi_u r_{vs}I_{vs} + \frac{\phi_t(1-\varphi)}{\kappa}P_{vs} - \mu_{vl}L_{vs} - \psi L_{vs} - mab\frac{I_{mvs}}{N_m}L_{vs}] \tag{10}$$

$$\begin{aligned} &+mab\tfrac{I_{mvs}}{N_m}L_{vs} + mab(1-\rho_{rs})\tfrac{I_{mvr}}{N_m}L_{vs} - \mu_h I_{vs} \\ &-mab(1-\varrho)\tfrac{I_{mvr}}{N_m}L_{vs} - \mu_h L_{vs} \end{aligned}$$

$$\frac{dP_{vs}}{dt} = \eta\sigma_v\gamma_{vs}I_{vs} - \frac{P_{vs}}{\kappa} - \mu_h P_{vs} \tag{11}$$

$$\frac{dI_{vr}}{d_t} = mab(1-\varrho)\frac{I_{mvr}}{N_m}S_h - (1-\eta\sigma_v)r_{vr}I_{vr} - \eta\sigma_v\gamma_{vr}I_{vr} + \psi L_{vr} + mab(1-\varrho)\frac{I_{mvr}}{N_m}L_{vr} \tag{12}$$

$$+mab(1-\varrho)\rho_{rs}\tfrac{I_{mvr}}{N_m}L_{vs} + mab(1-\rho_{sr})\tfrac{I_{mvs}}{N_m}L_{vr} - \mu_h I_{vr}$$

$$\frac{dL_{vr}}{dt} = (1-\eta\sigma_v)\phi_u r_{vr}I_{vr} + \frac{\phi_t(1-\varphi)}{\kappa(n+1)}P_{vr} - \psi L_{vr} - \mu_{vl}L_{vr} - mab(1-\varrho)\frac{I_{mvr}}{N_m}L_{vr} \tag{13}$$

$$-mab\tfrac{I_{mvs}}{N_m}L_{vr} - \mu_h L_{vr}$$

$$\frac{dP_{vr}}{dt} = \eta\sigma_v\gamma_{vr}I_{vs} - \frac{P_{vr}}{\kappa(n+1)} - \mu_h P_{vs} \tag{14}$$

$$\frac{dS_h}{dt} = \Lambda_h N_h - mab\frac{I_{mvs}}{N_m}S_h - mab(1-\varrho)\frac{I_{mvr}}{N_m}S_h + (1-\eta\sigma_v)(1-\phi_u)(r_{vs}I_{vs}+r_{vr}I_{vr}) \tag{15}$$

$$+\mu_{vl}(L_{vs}+L_{vr}) + \tfrac{[1-\phi_t(1-\varphi)]}{\kappa}P_{vs} + \tfrac{[1-\phi_t(1-\varphi)]}{\kappa(n+1)}P_{vr} - \mu_h S_h$$

$$\frac{dI_{mvs}}{dt} = ac_s\sigma_v\frac{I_{vs}}{N_h}S_m + ac_a(1-\sigma_v)\frac{I_{vs}}{N_h}S_m + ac_s(1-\varphi)(1-\nu)\frac{P_{vs}}{N_h}S_m - \mu_m I_{mvs}, \tag{16}$$

$$\frac{dI_{mvr}}{dt} = ac_s\sigma_v(1-\varrho)\frac{I_{vr}}{N_h}S_m + ac_a(1-\varrho)(1-\sigma_v)\frac{I_{vr}}{N_h}S_m + ac_s(1-\varrho)(1-\varphi)\frac{P_{vr}}{N_h}S_m \tag{17}$$

$$+ac_s(1-\varrho)(1-\varphi)\nu\tfrac{P_{vs}}{N_h}S_m - \mu_m I_{mvr},$$

$$\frac{dS_m}{dt} = \Lambda_m N_m - [ac_s\sigma_v + ac_a(1-\sigma_v)]\frac{I_{vs}}{N_h}S_m - ac_s(1-\varphi)(1-\nu)\frac{P_{vs}}{N_h}S_m \tag{18}$$

$$-[ac_s\sigma_v + ac_a(1-\sigma_v)](1-\varrho)\tfrac{I_{vr}}{N_h}S_m - ac_s(1-\varrho)(1-\varphi)\tfrac{P_{vr}}{N_h}S_m$$

$$-ac_s(1-\varrho)(1-\varphi)\nu\tfrac{P_{vr}}{N_h}S_m - \mu_m S_m$$

Where the human population N_h and the mosquito population N_m are

$$N_h = S_h + I_{vs} + L_{vs} + I_{vr} + L_{vr} + P_v,$$
$$N_m = S_m + I_{mvs} + I_{mvr}$$

The model equations are presented from the equations 9 to 18.

Similar to the model of transmission of *P. falciparum*, the infected state is decreased by the recovery rate, the asymptomatic proportion of cases is constant, the transmission cost is in the resistant strain and the transmission is penalized by the effect of the proportion of treated with gametocytocidal. Additionally, the prophylaxis

state in sensitive strain makes the parasite selection, the infectious time in resistant strain and the prophylaxis time are dependent from the number of recurrences.

The latent state represents the humans that were infected by *P. vivax* but they remain with hypnozoites that are be able to produce new recurrences of the disease. An individual stays in latent state for hypnozoites development in either an untreated human or a treated human. The equations of L_{vs} and L_{vr} include that the untreated proportion of infected humans $((1-\eta\sigma_v)I_v)$ has a ϕ_u probability of passing to latent state after it recovers. On the other hand, when an infected human is treated and progress to prophylaxis state, there is a probability $\phi_t(1-\varphi)$ that the infection will turn to latent state. In the *P. vivax* case, we assume that gametocitocydal also attacks hypnozoites as the primaquine works and for this reason we join the $(1-\varphi)$ term [20].

Furthermore, the decrease into the population in latent state depends on natural clearance of hypnozoites $(\mu_{vl}L_v)$, the hypnozoites activation and the superinfection. The hypnozoites activation depends on the transmission conditions where we set as tropical and temperate modifying the ψ rate as proposed by White *et al.* [4]. Also, similar to previous *P. vivax* malaria models, we consider an expression to involve the superinfection as a contact between an infected mosquito and a human in latent state where the human can develop a sensitive strain or resistant strain [4,49]. To model the subsequent superinfection case, we explain the case of a contact between an infected mosquito by sensitive strain I_{mvs} and a human in latent state of resistant strain L_{vr} where the transmission rate mab/N_m is multiplied by the probability of developing a superinfection of a sensitive strain in a latent human by resistant strain ρ_{sr}. In fact, the complementary $(1-\rho_{sr})$ is the activation probability of infection by resistant strain when the same contact occurs. We designed the same relation with the contact between the I_{mvr} and L_{vs} where the parameter ρ_{rs} is multiplied by the transmission cost $(1-\varrho)$ as we can see in the equation of I_{vr}.

2 Basic reproduction number

Here we derive the basic reproduction number using the next generation matrix proposed in [3,50,51]. The first step is to assume a constant population in humans N_h and mosquitoes N_m where $\Lambda_h = 0$, $\mu_h = 0$ and $\Lambda_m = \mu_m$. In this way, we can use the

disease free disease-stable steady state where the human and mosquito populations are susceptible ($S_h = N_h$, $S_m = N_m$).

2.1 Analysis of basic reproduction number R_0 for *P. falciparum*

We obtained two reproduction numbers associated with the sensitive strain R_{0fs} and the resistant strain R_{0fr} (equations 19 and 20).

$$R_{0fs} = \sqrt{\frac{ma^2b}{\mu_m[(1-\eta\sigma_f)r_{fs}+\eta\sigma_f\gamma_{fs}]}\left[c_s\sigma_f + c_a(1-\sigma_f) + \kappa c_s(1-\nu)(1-\varphi)\eta\sigma_f\gamma_{fs}\right]} \tag{19}$$

$$R_{0fr} = (1-\varrho)\sqrt{\frac{ma^2b}{\mu_m[(1-\eta\sigma_f)r_{fr}+\eta\sigma_f\gamma_{fr}]}\left[c_s\sigma_f + c_a(1-\sigma_f) + \kappa(n+1)c_s(1-\varphi)\eta\sigma_f\gamma_{fr}\right]} \tag{20}$$

For both compartments of infection due to sensitive or resistant strains, the basic reproduction number is proportional to the the number of mosquitoes per human, the biting rate and the transmission probabilities b, c_a and c_s. On the other hand, R_0 decreases with recovery rate in human and the death rate in the mosquito population. In the R_{0fs} case, the expression 19 involves the $\kappa c_s(1-\nu)(1-\varphi)\eta\sigma_f\gamma_{fs}$ term that represents the transmission rate of a human in prophylaxis of a sensitive strain. Actually, this term increases R_{0fs} because the strain has an additionally way to survive when a treatment is used without a gametocytocidal.

On the other hand, R_{0fr} involved a reduction by the resistance cost transmission with the product with the expression $(1-\varrho)$. Similar to deriving R_{0fs}, R_{0fr} has a term that represents the contribution of humans in prophylactic state. In this manner, it is necessary increase the recovery rate using a treatment or implement programs to reduce the transmission rates to obtain malaria control.

The growth of the resistant strain depends on the reproduction number where the resistant strain increases its frequency above the sensitive strain when $R_{0fr} > R_{0fs}$. The balance between strains depends on the drug coverage η where the condition to avoid the increase of resistant cases is $R_{0fs} > R_{0fr}$. In order to compare the basic reproduction number along the coverage variation with the effect of the resistance cost

ϱ, the gametocytocidal coverage φ,the window of selection κ and the symptomatic proportion of cases σ_f, we calculated the basic reproduction numbers (see the Figure 3).

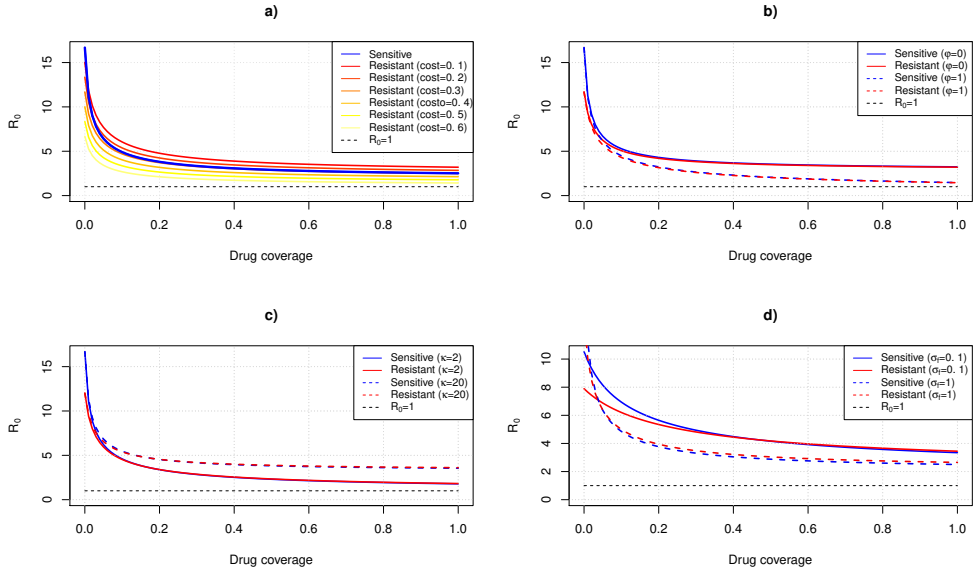

Figure 3. Basic reproduction number between *P. falciparum* strains along the variation of the drug coverage with other determinants. The Figure a) represents the variation with the resistance cost, b) represents the variation with the gametocytocidal coverage, c) represents the variation with the window of selection and d) represents the variation with symptomatic cases.The parameter values are in Table 2

The increase in the drug coverage from 0 to 1 decreases the basic reproduction number in all scenarios. In the case of the resistance cost, the increase in the cost over 0.3 allows the sensitive strain to has a greater reproduction number in some conditions of drug coverage. On the other hand, the figures b) and c) (see Figure 3) show that the increments in the use of gametocytocidal and the window of selection do not have a significant effect in the difference between R_{0fs} and R_{0fr} but both parameters help in the reduction of all reproduction numbers. Finally, we can see in the figure d) that the increase in the symptomatic cases decreases the R_0s and it benefits the resistant strain in low coverage such that it allows to increase the real drug coverage.

2.2 Analysis of basic reproduction number R_0 for *P. vivax*

As the *P. falciparum* case, we derive expressions for the basic reproduction number R_{0vs} in the case of sensitive strain and R_{0vr} in the case of resistant strain, as follows.

$$R_{0vs} = \sqrt{\frac{ma^2b(\psi+\mu_{vl})[c_s\sigma_v + c_a(1-\sigma_v) + \kappa c_s(1-\nu)(1-\varphi)\eta\sigma_v\gamma_{vs}]}{\mu_m\left[[(1-\eta\sigma_v)r_{vs} + \eta\sigma_v\gamma_{vs}](\psi+\mu_{vl}) - \psi[\phi_t(1-\varphi)\eta\sigma_v\gamma_{vs} + \phi_u(1-\eta\sigma_v)r_{vs}]\right]}} \tag{21}$$

$$R_{0vr} = (1-\varrho)\sqrt{\frac{ma^2b(\psi+\mu_{vl})[c_s\sigma_v + ca_a(1-\sigma_v) + \kappa(n+1)c_s(1-\varphi)\eta\sigma_v\gamma_{vr}]}{\mu_m\left[[(1-\eta\sigma_v)r_{vr} + \eta\sigma_v\gamma_{vr}](\psi+\mu_{vl}) - \psi[\phi_t(1-\varphi)\eta\sigma_v\gamma_{vr} + \phi_u(1-\eta\sigma_v)r_{vr}]\right]}} \tag{22}$$

The reproduction number in both cases is proportional to the number of mosquitoes per human, the biting rate and the transmission probabilities b, c_a and c_s. Likewise, R_{0vs} and R_{0vr} are inversely proportional to the recovery rates in human and the death rate in mosquitoes. The difference as the previous *P. falciparum* model is the inclusion of parameters from latent state where the denominator represents an average rate of recovery from *P. vivax* parasite infection (it involved infected and latent states) with $[(1-\eta\sigma_v)r_{vs} + \eta\sigma_v\gamma_{vs}](\psi+\mu_{vl})$ as the exit rate from infected state and $\psi[\phi_t(1-\varphi)\eta\sigma_v\gamma_{vs} + \phi_u(1-\eta\sigma_v)r_{vs}]$ as the progression rate to latent state where the *P. vivax* infection remains. Thus, the difference between the exit rate from infected state and the progression rate to latent state is the real recovery rate from *P. vivax* infection. In fact, a high progression rate to latent state decreases the denominators of R_{0vs} and R_{0vr} and it increases the basic reproduction number producing a greater difficulty to control the malaria caused by *P. vivax*. These statements are applied in both strains.

Similar to the *P. falciparum* case, the basic reproduction number of the resistant strain involved the transmission cost $(1-\varrho)$. Moreover, R_{0vs} and R_{0vr} has the transmission contribution from prophylactic state. We obtain the reproduction number along the variation of drug coverage involving variations in the resistance cost ϱ, gametocytocidal coverage φ, the window of selection κ and the symptomatic proportion of cases σ_v (Figure 4). It is important to remark that the increase in the drug coverage decreases the reproduction number at less rate than the reproduction numbers of *P. falciparum* and it suggests that the drug coverage is less effective against the *P. vivax* parasite.

In the case of the resistance cost, R_{0vs} always is greater than R_{0vr} with resistant

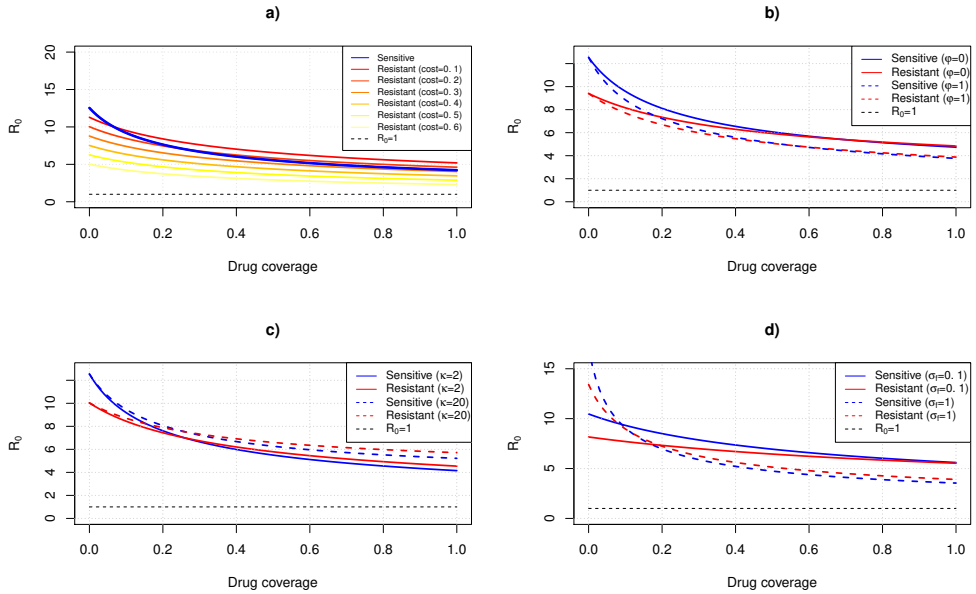

Figure 4. Basic reproduction number between *P. vivax* strains along the variation of the drug coverage with other determinants . The figure a) represents the variation with the resistance cost, b) represents the variation with the gametocytocidal coverage, c) represents the variation with the window of selection and d) represents the variation with symptomatic cases.The parameter values are in Table 2

cost greater or equal than 0.3 and additionally, there are exist a set of drug coverage where $R_{0vs} > R_{0vr}$ when the cost is above from 0.3. Actually, the effect of drug coverage and the transmission cost is less intense than *P. falciparum* case allowing to use greater drug coverage without $R_{0vr} > R_{0vs}$. On the other hand, the figure b) shows that a growth in gametocytocidal decreases all the reproduction numbers in the same proportion and it does not have an important effect in the emergence of a resistant strain. This behaviour is similar from the *P. falciparum* such that the $(1-\varphi)$ term affects in the same proportion the expressions 19, 20, 21 and 22.

In the figure c), we found that the window of selection does not have an important contribution in the difference between basic reproduction numbers while a less value of it achieves a low fall in the reproduction numbers because this parameter regulate the prophylactic period where the treated human is able to transmit the parasite without gametocytocidal. Finally, the symptomatic cases allows the decrease of the reproduction numbers but they promote the condition $R_{vr} > R_{vs}$ where the resistant strain has the advantage in most values of drug coverage. Thus, the real coverage is proportional to the risk of drug resistance.

3 Impact of drug campaigns in the emergence of drug resistant

In order to estimate the impact of the use of drug campaigns, we simulated the model with a total drug coverage ($\eta = 1$) according with the decisions of using a monotherapy or a combined therapy accompanied or not with gametocytocidal where the monotherapy implies a probability $\nu = 10^{-12}$ and the combination therapy $\nu = 10^{-24}$ [21]. At same time, we represent the gametocytocidal use with $\varphi = 0.95$ assumed a 5% of treatment failure and $\varphi = 0$ when the simulation is not use the gametocytocidal. It is important to remark that we simulated with a resistance cost of $\varphi = 0.1$ where the resistant strain emerges because we must estimate the appearance time between campaigns. The simulations were performed in R using deSolve library.

3.1 Campaigns against infected by *P. falciparum*

Initially, a monotherapy without primaquine strategy is simulated where the resistant strain replaced the sensitive strain in around seven years of administration (Figure a-5). Initially, the campaign maintained the infection prevalence around the 15% while the prevalence of humans in prophylactic state was around the 57% before the emergence of resistant strain. Then, the infection prevalence of the resistant strain arose to the 18% while the humans in P_{fr} state were 65%. Despite of the small increment in the infected humans when the resistant strain replaces the sensitive, it implies additional treatments and less effectiveness in the campaign.

With the addition of gametocytocidal, the emergence of the resistant strain started sooner as we can see in the b) part of Figure 5. However, the gametocytocidal inclusion reduced the proportion of infected at 10% before the emergence of the resistant strain because the humans in P_{fs} state decreases their contribution in the parasite transmission such that gametocytocidal use. This is the key point that allowed the premature emergence of the resistant strain because the humans in P_{fs} have the potential of transmitting and maintaining the sensitive parasite.

The inclusion of a combined therapy delayed the emergence of resistant strain as we can see in the figures c) and d) (see Figure 5) where Without the gametocytocidal,

the sensitive parasite remained during 13 years before the emergence of resistant strain. As same as monotherapy, the gametocytocidal acelerated the emergence of the resistant strain while it was reducing the disease prevalence. In summary, the combined therapy maintain the effectiveness for more time than the monotherapy, in despite of the imminent emergence of the resistant strain, and the gametocytocidal helps on the reduction of disease prevalence but it increases the risk of drug resistant.

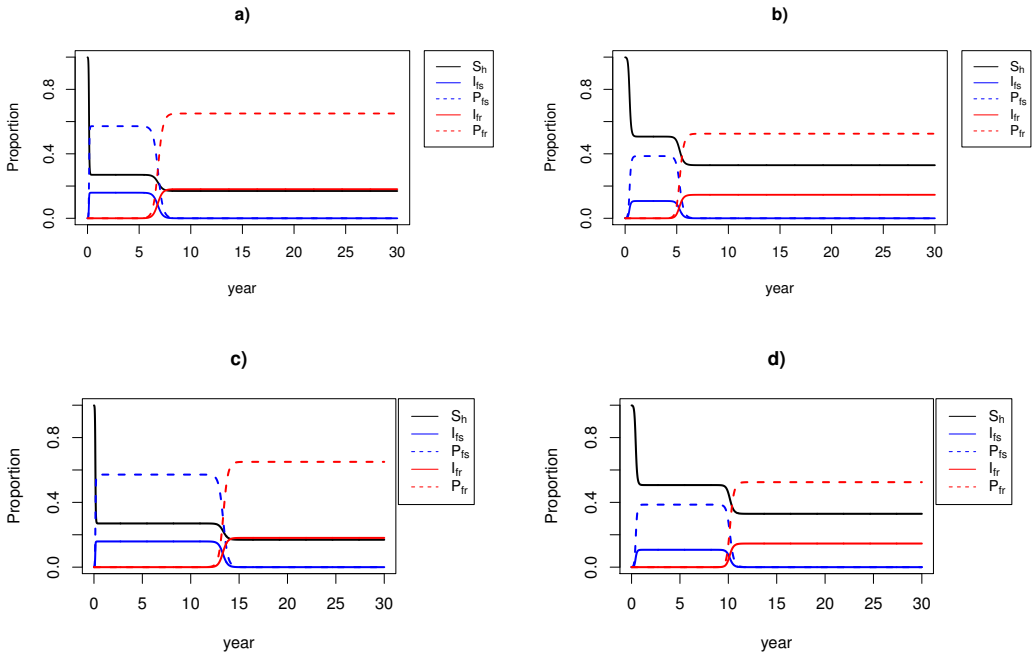

Figure 5. Simulating the inclusion of campaigns with monotherapy, combined therapy and gametocytocidal against the malaria caused by *P. falciparum*. The figure a) shows the monotherapy use ($\nu = 10^{-12}$ and $\varphi = 0$), b) represents the monotherapy plus gametocytocidal ($\nu = 10^{12}$ and $\varphi = 0,95$), c) develops the implementation of combined therapy ($\nu = 10^{-24}$ and $\varphi = 0$) and d) involves the combined therapy with gametocytocidal ($\nu = 10^{24}$ and $\varphi = 0,95$). The parameter values used in the simulation are in Table 2

3.2 Campaigns against infected by *P. vivax*

We evaluated the *P. vivax* model without effect of superinfection in latent state such that most of the recurrences are produced by the hypnozoites release as observed in some endemic regions [22]. The results are in the Figure 6 where we can see longer periods of time before the emergence of the resistant strain in contrast to the *P. falciparum* results. Nevertheless, the drug coverage against infected by *P. vivax* is less

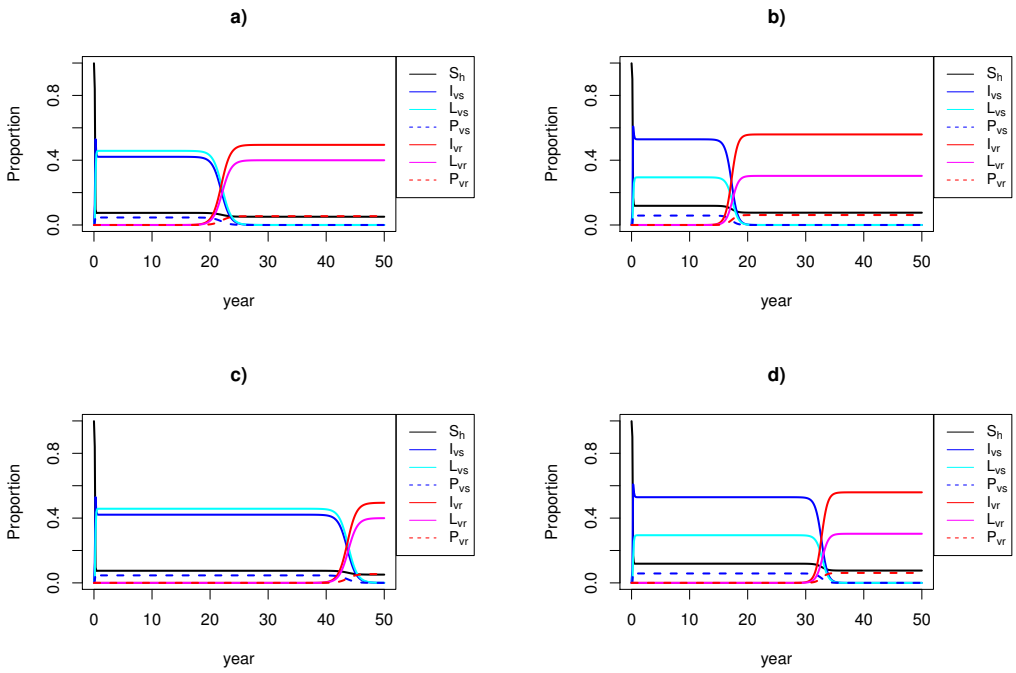

Figure 6. Simulating the inclusion of campaigns with monotherapy, combined therapy and gametocytocidal against the malaria caused by *Plasmodium vivax* without taking into the account the superinfection. The figure a) shows the monotherapy use ($\nu = 10^{-12}$ and $\varphi = 0$), b) represents the monotherapy use plus gametocytocidal ($\nu = 10^{12}$ and $\varphi = 0, 95$), c) develops the implementation of combined therapy ($\nu = 10^{-24}$ and $\varphi = 0$) and d) involves the combined therapy with gametocytocidal ($\nu = 10^{24}$ and $\varphi = 0, 95$). The parameter values used in the simulation are in Table 2

effective than the campaigns against *P. falciparum* because the proportion of infected by *P. vivax* were greater in all the scenarios.

The emergence of the resistant strain started around the 20^{th} year, when only monotherapy is applied. Also, in this case the proportion of I_{vs} was 42% and L_{vs} was 45%. Actually, the campaign effectiveness is poor in terms of the prevalence reduction because the large proportion of asymptomatic cases ($1 - \sigma_v = 0.66 \rightarrow 66\%$) does not let the use of an effective drug coverage and it produces an underestimate of the real disease prevalence. Moreover, $\gamma_{fs} < \gamma_{vs}$ produces a greater infectious period in an *P. vivax* infected due to the premature relapse of gametocytes [12]. This situation allows the surveillance of the sensitive strain and the delayed emergence of the resistant strain.

On the other hand, the inclusion of the gametocytocidal decreased the proportion of humans in latent state but it increased the amount of infected cases by the greater

amount of susceptible humans. The reason of this behaviour is the initial assumption of removing the superinfection of humans in latent state because it decreases the amount of susceptible humans.

The combination therapy delayed the emergence of the resistant strain as the combined therapy used in *P. falciparum* results. Moreover, the gametocytocidal inclusion with the combined therapy brought a similar effect than the monotherapy where the humans in latent state decreased while the infected humans rise up. Besides the increment in the resistant emergence period, the combined therapy showed a limited performance in the prevalence reduction as it happened in the monotherapy campaign.

Finally, when involving the superinfection of humans in latent state (Figure 7), the emergence of the resistant strain is accelerated reducing the period before the emergence of drug resistance in 5 years to the monotherapy and 10 years to the combination therapy. Furthermore, the superinfection increased the proportion of infected near to the 80% while it was decreasing the humans in latent state under the 10%. Moreover, the humans in infected and latent states did not have a significant reduction in its proportion with the gametocytocidal due to the most of cases are asymptomatic. This result support the suggestion of the WHO for use primaquine only in low transmission settings where the superinfection unlikely.

4 Discussion

The emergence of drug resistance in *P. falciparum* and *P. vivax* has happened with different patterns in time and efficacy. For instance, Chloroquine remains as the first-line treatment for malaria caused by the *P. vivax* parasite [20, 23], though it has not been recommended for treatment of *P. falciparum* infections. Nevertheless, the *P. vivax* resistance to chloroquine has been widespread in some endemic zones, as an evidence that this parasite has this selection possibility in a different rate from *P. falciparum* parasite [24].

In order to explain the pattern of resistance evolution, we studied the differences between life cycles, the kind of therapy, the resistance cost, the infectious period, the window of selection and the asymptomatic cases. Our results show that the drug

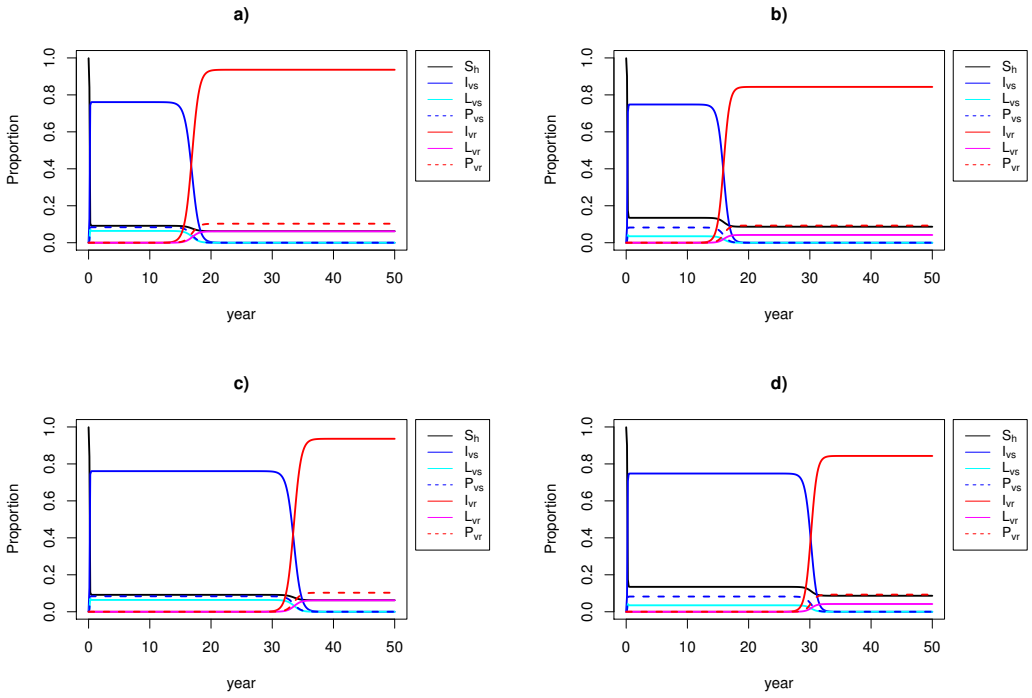

Figure 7. Simulating the inclusion of campaigns with monotherapy, combined therapy and gametocytocidal against the malaria caused by *P. vivax* allowing the superinfection effect. The figure a) shows the monotherapy use alone ($\nu = 10^{-12}$ and $\varphi = 0$), b) represents the monotherapy plus gametocytocidal ($\nu = 10^{12}$ and $\varphi = 0,95$), c) develops the implementation of combined therapy ($\nu = 10^{24}$ and $\varphi = 0$) and d) involves the combined therapy with gametocytocidal ($\nu = 10^{-24}$ and $\varphi = 0,95$). The parameter values used in the simulation are in Table 2

resistance in *P. falciparum* appears faster than in *P. vivax* using the same treatment line.

First, we found that a resistance cost of 30% or less in the transmission allows a resistant strain to have a greater reproduction number than a sensitive strain where the emergence of drug resistance is imminent for both *Plasmodium* species. Our estimate value is within the range of the estimated resistant cost of previous research in the field of within host dynamics and transmission intensity [18, 19, 25, 26]. Thus, resistance costs under transmission above 30% produces an imminent spread of drug resistance in a similar proportion to *P. falciparum* and *P. vivax*. Nevertheless, the period before the emergence of the resistant strain depends on the other factors as we can see in the previous section where we used a fixed resistance cost obtaining different emergence times in the resistant strain.

Our results show that the infectious period in infected humans is the most

important factor that enables a premature emergence of drug resistance in *P. falciparum*. An infected human by *P. vivax* has an infectious period, longer than the one for *P. falciparum*, before receiving treatment, permitting transmission of sensitive parasites, and delaying the emergence of a resistant strain [12, 27]. However, this infectious period before the treatment decreased the effectiveness of the drug therapy trials as we can appreciate in the reproduction numbers in *P. vivax*. Moreover, this statement implies that a reduction in a infectious periods before the treatment caused by the successful therapies, rapid attention and the rapid diagnostic test allows the increase of the risk in the spread of drug resistance.

As result of the evaluation between monotherapy and combined therapy, we remark the best effect of a combined therapy against the spread of drug resistance [20, 28]. The explanation is the lower mutation probability against multiple components in a combined therapy than a monotherapy [21]. Currently, the first-line treatment against *P. falciparum* is the use of artemisinin based combination therapy (ACT) that has been administrated since the first decade of the 21^{st} century besides the resistance reports in the Greater Mekong sub-region [29]. Therefore, ACT is highly recommended after the emergence of CQ resistance to treat malaria caused by *P. vivax*. In fact, accelerating the development of triple combination therapies to use against *P. falciparum* malaria deserves attention, due to reduction in the mutation probabilities [30].

The variation of the window of selection (WoS) did not have a relevant effect in the emergence of a resistant strain because it had the same impact against the reproduction numbers in both sensitive and resistant strains of both *Plasmodium* species. However, the competence between multiple strains in a single host could make differences between the strains development in presence of the drug administration but the current research do not achieve multiple infection and it can explain the obtained behaviour with respect at the WoS [26].

On the other hand, the inclusion of gametocytocidal produces in an acceleration in the emergence of resistant strain in overall simulated campaigns whereas it obtained a different performance against disease prevalence between the malaria species. In the *P. falciparum* case, the gametocytocidal reduced the prevalence of infected humans, suggesting that the WHO recommendation of a single dose of primaquine (PQ) to

avoid the transmission of sexual stages has a beneficial effect in the malaria control [20]. By contrast, the gametocytocidal accelerates the emergence of the resistant strain in *P. falciparum* due to the reduction in the transmission of sensitive parasite during the prophylactic period. Moreover, premature drug resistance was also present in *P. vivax* but in this case primaquine has an additional effect to clear hypnozoites. The results in *P. vivax* shows the increase in the population of infected humans by the inclusion of gametocytocidal because the reduction in the humans in latent state produces a rise up in susceptible humans using the model structure.

On the other hand, the asymptomatic cases decreased the drug coverage and the effectiveness against the sensitive strain in both *Plasmodium* species. Thus, an elevated drug coverage would imply a less pronounced effect against the resistant strain producing the spread of drug resistance and the asymptomatic cases supports the transmission of the sensitive strain delaying the drug coverage outcome. Furthermore, our results are in accordance that control of *P. vivax* using drug administration is difficult since most cases are asymptomatic [9]. Although the contribution of asymptomatic infections remains unclear and previous research shows a variable potential of asymptomatic in the transmission, our results achieve an estimation of the contribution in the parasite transmission [33, 34].

Our findings suggest that the emergence of drug resistance can be delayed to the *P. vivax* parasite but the malaria control against it is more difficult to achieve than to the *P. falciparum* parasite. We observe that more effectiveness in the campaign for reducing the prevalence of *P. falciparum* reaches a premature spread of drug resistance. By contrast, the simulated campaigns against *P. vivax* parasite shows less effectiveness in the reduction of the infection prevalence than *P. falciparum* but this result produces a delayed spread of drug resistance.

In order to compare the emergence of drug resistance, we found previous works that have monitored drug resistance in specific regions [46, 47]. In Kenya CQ resistance is near 100% after more than ten years of administration, in accordance with our results showing monotherapy coverage against *P. falciparum*. Moreover, the artemether-lumefantrine (AL) was implemented in Kenya as the first antimalarial treatment in 2006 and the mutations related with artemisinin drug resistance have increased their frequency to around 60% in ten years and the mutant related with AL

resistance would replace the wild type *P. falciparum* parasite in five years as the simulation with the combination therapy showed. In the other hand, the mutations related with artemisinin resistance in *P. falciparum* in Thailand have evolved with a genetic diversity where the new mutants are replacing the wild type along the course of the 21^{th} century. These evolution periods are comparable with the simulation results despite the genetic diversity and the geographical conditions.

In concert with validate the results with the available data, the main limitation is associated at the diversity of fields that the modelling involves: disease prevalence, resistance frequency, treatment performance and transmission conditions. Some available data bases such as the Malaria Atlas Project (MAP) and the World Wide Antimalarial Resistance Network (WWARN) have limited spatial information of disease incidence and studies for monitoring the drug resistance according with the methodologies proposed by the WHO [45]. However, several factors such as the differences in the frequencies of clinical trials to measure the drug resistance, variables sample sizes, the short periods of monitoring, geographical variations in the information about the drug coverage, the different mutant alleles, the less amount of studies in *P. vivax* parasites and the still unclear effect of asymptomatic infected humans produce a set of disturbances that do not allow adjusting the expected conditions to the model parameters and structure. Additionally, parameters reported in previous studies have variations according with the different field conditions.

In conclusion, the current study shows that the drug resistance evolves faster in *P. falciparum* because the treatment on the infected population decreases the transmission of sensitive parasites allowing a competitive advantage in resistant parasites. On the other hand, the slower spread of drug resistant in *P. vivax* was due to the transmission of sensitive parasites before the treatment and the higher proportion of asymptomatic infections than *P. falciparum*. Nevertheless, this behaviour in *P. vivax* implied that the campaigns against the disease prevalence were less effective than *P. falciparum*. Thus, the improvements in the rapid testing, drug coverage, primaquine use, treatments to asymptomatic cases can increase the risk of drug resistant and the development of new combination therapies is necessary to delay the spread of resistant strains.

Table 1. Model parameters

Parameter	Description
m	Number of mosquitoes per human N_m/N_h
a	Biting rate
b	Transmission probability from an infected mosquito to a susceptible human
η	Drug coverage to infected humans
σ_f	Proportion of symptomatic humans infected by *P. falciparum*
σ_v	Proportion of symptomatic humans infected by *P. vivax*
r_{fs}	Recovery rate for untreated infected humans by sensitive strain of *P. falciparum*
r_{vs}	Recovery rate for untreated infected humans by sensitive strain of *P. vivax*
γ_{fs}	Recovery rate for treated infected humans by sensitive strain of *P. falciparum*
γ_{vs}	Recovery rate for treated infected humans by sensitive strain of *P. vivax*
r_{fr}	Recovery rate for untreated infected humans by resistant strain of *P. falciparum*
r_{vr}	Recovery rate for untreated infected humans by resistant strain of *P. vivax*
γ_{fr}	Recovery rate for treated infected humans by resistant strain of *P. falciparum*
γ_{vr}	Recovery rate for treated infected humans by resistant strain of *P. vivax*
μ_h	Human death rate
φ	Proportion of humans treated with gametocytocidal drug
κ	Average clearance time of drug
ϱ	Resistance cost in the transmission
n	Recurrences produced by the resistant strain
Λ_h	Human birth rate
Λ_m	Mosquito birth rate
μ_m	Mosquito death rate
c_a	Transmission probability from an infected asymptomatic human to susceptible mosquito
c_s	Transmission probability from an infected symptomatic human to susceptible mosquito
ν	Transmission probability of a resistant strain from a human in prophylactic state by sensitive strain to a susceptible mosquito.
ψ	Hypnozoite relapse rate
ρ_{sr}	Probability of developing sensitive infection by the contact between an infected mosquito by sensitive strain and a human in latent state of the resistant strain
ρ_{rs}	Probability of developing resistant infection by the contact between an infected mosquito by resistant strain and a human in latent state of the sensitive strain
ϕ_t	Probability of a human in prophylaxis state of going to latent state
ϕ_u	Probability of an untreated infected human of going to latent state
μ_{vl}	Clearance rate of hypnozoites

References

1. Ross R. 1911. The prevention of malaria. *London: John Murray*. pp. **651-686**.

2. Macdonald G. 1956. Epidemiological basis of malaria control. *Bull World Health Org* **15: 613-626**.

3. O. Diekmann, J. A. P. Heesterbeek, and M. G. Roberts. 2010. The construction of next-generation matrices for compartmental epidemic models. *The Royal*

Table 2. Parameter values

Parameter	Value	Source
N_h	625	[6]
N_m	2435	[6]
m	N_m/N_h	[6]
a	$0.21 day^{-1}$	[5]
b	0.5	[7]
σ_f	0.9	[8]
σ_v	0.33	[9]
r_{fs}	$1/287\ day^{-1}$	[6]
r_{vs}	$1/60\ day^{-1}$	[10]
γ_{fs}	$1/2\ day^{-1}$	[6]
γ_{vs}	$1/9\ day^{-1}$	[11, 12]
r_{fr}	r_{fs}	Assumed
r_{vr}	r_{vs}	Assumed
n	1	Assumed one recurrence [20]
γ_{fr}	$\gamma_{fs}/(n+1)$	
γ_{vr}	$\gamma_{vs}/(n+1)$	
η	0-1	Proportion
φ	0-1	Proportion
κ	8 *days* (*P. falciparum*), 3 *days* (*P. vivax*)	[12, 13]
ϱ	0-0,6	[18]
μ_m	$0.033\ day^{-1}$	[6]
Λ_m	$0.033\ day^{-1}$	Assumed constant population
c_s	0.4	[15]
c_a	0.12	[15]
ν	10^{-12}, 10^{-24}	Monotherapy and combination therapy [21]
ψ	$1/60\ day^{-1}$(tropical)	[16]
ρ_{sr}	0.5	Assumed
ρ_{rs}	0.5	Assumed
ϕ_t	0.29	[17]
ϕ_u	0.40-0.90	[4]
μ_{vl}	$1/425\ day^{-1}$	[5]

Society Interface **7: 873-885**

4. Michael T. White, George Shirreff, Stephan Karl, Azra C. Ghani and Ivo Mueller. 2011. Variation in relapse frequency and the transmission potential of *Plasmodium vivax* malaria. *Proc. R. Soc.* **B 283:20160048**.

5. Michael T White, Stephan Karl, Katherine E Battle, Simon I Hay,Ivo Mueller and, Azra C Ghani. 2014. Modelling the contribution of the hypnozoite reservoir to *Plasmodium vivax* transmission. *ELife* **3: e04692**.

6. Chitnis N, Hyman JM, Cushing JM. 2008. Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model.

Bull Math Biol **70(5):1272-96**.

7. David L. Smith, Chris J. Drakeley, Christinah Chiyaka, and Simon I. Hay. 2010. A quantitative analysis of transmission efficiency versus intensity for malaria. *Nat Commun* **1:108**.

8. Kim A Lindblade, Laura Steinhardt, Aaron Samuels, S Patrick Kachur and Laurence Slutsker. 2013. The silent threat: asymptomatic parasitemia and malaria transmission. *Expert Rev Anti Infect Ther* **(6):623-39**.

9. Anne C. G. Almeida, Andrea Kuehn, Arthur J. M. Castro, Sheila Vitor-Silva1, Erick F. G. Figueiredo,Larissa W. Brasi, Marcelo A. M. Brito, Vanderson S. Sampaio, Quique Bassat, Ingrid Felger,Wanderli P. Tadei, Wuelton M. Monteiro, Ivo Mueller, and Marcus V. G. Lacerda. 2018. High proportions of asymptomatic and submicroscopic *Plasmodium vivax* infections in a peri-urban area of low transmission in the Brazilian Amazon. *Parasites and vectors* **11:194**.

10. Collins WE, Jeffery GM, and Roberts JM. 2003. retrospective examination of anemia during infection of humans with *Plasmodium vivax*. *Am J Trop Med Hyg* **(4):410-2**.

11. M. Nacher, U. Silachamroon, P. Singhasivanon, P. Wilairatana, W. Phumratanaprapin, A. Fontanet, S. Looareesuwan. 2004. Comparison of artesunate and chloroquine activities against *Plasmodium vivax* gametocytes. *Antimicrob Agents Chemother* **48 (2004) 2751**.

12. Kristan A Schneider, and Ananias A Escalante. 2013. Fitness components and natural selection: why are there different patterns on the emergence of drug resistance in *Plasmodium falciparum* and *Plasmodium vivax*?. *Malaria Journal* **12:15**.

13. Katherine Kay and Ian M Hastings. 2015. Measuring windows of selection for anti-malarial drug treatments. *Malaria journal* **14:292**.

14. François Blanquart, Sonja Lehtinen, Marc Lipsitch, and Christophe Fraser. 2018. The evolution of antibiotic resistance in a structured host population. *J. R. Soc. Interface* **15: 20180040**.

15. Jamie T. Griffin, T. Deirdre Hollingsworth, Lucy C. Okell, Thomas S. Churcher, Michael White, Wes Hinsley, Teun Bousema, Chris J. Drakeley, Neil M. Ferguson, María-Gloria Basáñez and Azra C. Ghani. 2010. Reducing *Plasmodium falciparum* Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. *Plos medicine* **8e1000324**.

16. Olivia Prosper and Maia Martcheva. 2013. Impact of enhanced malaria control on the competition between *Plasmodium falciparum* and *Plasmodium vivax* in India. *Mathematical Biosciences* **242 33-50**.

17. T. Adak, V.P. Sharma and V.S. Orlov. 1998. Studies on the *Plasmodium vivax* relapse pattern in Delhi, India. *Am. J. Trop. Med. Hyg* **59 (1998) 175**.

18. Klein EY, Smith DL, Boni MF, Laxminarayan R. 2008. Clinically immune hosts as a refuge for drug-sensitive malaria parasites. *Malar J* **7:67**.

19. Silvie Huijben, Brian H.K. Chan, William A. Nelson and Andrew F. Read. 2018. The impact of within-host ecology on the fitness of a drug-resistant parasite. *Evolution, Medicine, and Public Health* **pp. 127-137**.

20. World Health Organization. 2015. Guidelines for the treatment of malaria. Third edition. *World Health Organization* **316 pages**.

21. Nicholas J. White. 2004. Antimalarial drug resistance. *J. Clin. Invest* **113:1084-1092**.

22. Michael T. White, Patrick Walker, Stephan Karl, Manuel W. Hetzel, Tim Freeman, Andreea Waltmann, Moses Laman, Leanne J. Robinson, Azra Ghani and Ivo Mueller. 2018, Mathematical modelling of the impact of expanding levels of malaria control interventions on *Plasmodium vivax*. *Nature Comunications* **9:3300**.

23. Robert G. Ridley. 2002. Medical need, scientific opportunity and the drive for antimalarial drugs. *Nature* **vol 415**.

24. Price, R. N., von Seidlein, L., Valecha, N., Nosten, F., Baird, J. K., and White, N. J. 2014. Global extent of chloroquine-resistant *Plasmodium vivax*: a

systematic review and meta-analysis. *The Lancet. Infectious diseases*, **14(10), 982-91**.

25. Artzy-Randrup Y, Alonso D, Pascual M. 2010. Transmission intensity and drug resistance in malaria population dynamics: implications for climate change. *PLoS One* **5:e13588**.

26. Legros M, Bonhoeffer S. 2016. A between-hosts and within-host combined modeling framework for the evolution of resistance to antimalarial drugs. *J R Soc Interface* **13:20160148**.

27. Boyd MF, Kitchen SF. 1937. On the infectiousness of patients infected with *Plasmodium vivax* and *Plasmodium falciparum*. *Am J Trop Med Hyg*, **17:253-262**.

28. Miriam K. Laufer, Abdoulaye A. Djimdé, and Christopher V. Plowe. 2007. Monitoring and Deterring Drug-Resistant Malaria in the Era of Combination Therapy. *Am. J. Trop. Med. Hyg* **77(Suppl 6), pp. 160-169**.

29. Didier Menard and Arjen Dondorp. 2018. Antimalarial Drug Resistance: A Threat to Malaria Elimination. *Cold Spring Harb Perspect Med*, **7:a025619**.

30. Margaret A. Phillips, Jeremy N. Burrows, Christine Manyando, Rob Hooft van Huijsduijnen, Wesley C. Van Voorhis and Timothy N. C. Wells. 2017. Malaria. *Nature reviews*, **vol(3), article number 17050**.

31. Deepika Fernando, Chaturaka Rodrigo and Senaka Rajapakse. 2011. Primaquine in vivax malaria: an update and review on management issues.*Malaria Journal*, **10:351**.

32. Hannah C. Slater, Lucy C. Okell, and Azra C. Ghani. 2017. Mathematical Modelling to Guide Drug Development for Malaria Elimination. *Trends in Parasitology*, **Vol. 33, No. 3**.

33. Amélie Vantaux, Reingsey Samreth, Eakpor Piv, Nimol Khim, Saorin Kim, Laura Berne, Sophy Chy, Dysoley Lek, Sovannaroth Siv, Walter R Taylor, Didier Ménard. 2018. Contribution to Malaria Transmission of Symptomatic and

Asymptomatic Parasite Carriers in Cambodia. *The Journal of Infectious Diseases*, **Volume 217, Issue 10, Pages 1561-1568**.

34. Kiattibutr K, Roobsoong W, Sriwichai Pet al. 2017. Infectivity of symptomatic and asymptomatic *Plasmodium vivax* infections to a Southeast Asian vector, Anopheles dirus. *Int J Parasitol*, **47:163-70**.

35. World Health Organization WHO. 2018. *World Malaria Report*. WHO Library Cataloguing-in-Publication Data, printed in France.

36. World Health Organization WHO. 2010. *Global report on antimalarial efficacy and drug resistance: 2000-2010*. Drug Resistance and Containment Unit, Global Malaria Program,World Health Organization: Geneva, Switzerland.

37. Payne D. 1987. Spread of chloroquine resistance in *Plasmodium falciparum*. *Parasitol Today*, **vol. 3 (pg. 241-6)**.

38. Peters W. 1987. Resistance in human malaria IV: 4-aminoquinolines and multiple resistance, Chemotherapy and drug resistance in malaria. *London Academic Press*, **vol.2 (pg. 659-786)**.

39. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F, Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegardh N, Socheat D and White NJ. 2009. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*, **361:455-467**.

40. Liwang Cui, Sungano Mharakurwa, Daouda Ndiaye, Pradipsinh K. Rathod, and Philip J. Rosenthal. 2015. Antimalarial Drug Resistance: Literature Review and Activities and Findings of the ICEMR Network. *Am. J. Trop. Med. Hyg.*, **93(Suppl 3), pp. 57-68**.

41. Ric N Price, Lorenz von Seidlein, Neena Valecha, Francois Nosten, J Kevin Baird and Nicholas J White. 2014. Global extent of chloroquine-resistant *Plasmodium vivax: a systematic review and meta-analysis*. *Lancet Infect Dis*, **14: 982-91**.

42. Escalante AA, Cornejo OE, Rojas A, Udhayakumar V and Lal AA. 2004. Assessing the effect of natural selection in malaria parasites. *Trends Parasitol*, **20:388-395**.

43. Hamza A.Babiker, Amal A.H.Gadalla, Lisa C.Ranford-Cartwright. 2013. The role of asymptomatic *P. falciparum* parasitaemia in the evolution of antimalarial drug resistance in areas of seasonal transmission. *Drug Resistance Updates1*, **6 (2013), 1-9**.

44. Aleisha R Brock, Carole A Gibbs, Joshua V Ross and Adrian Esterman. 2017. The Impact of Antimalarial Use on the Emergence and Transmission of *Plasmodium falciparum* Resistance: A Scoping Review of Mathematical Models. *Tropical Medicine and Infectious Disease*, **October 15, 2 (4)**.

45. World Health Organization WHO. 2009. *Methods for Surveillance of antimalarial drug efficacy*. Global malaria programme ,World Health Organization: printed in France.

46. Elizabeth Hemming-Schroeder, Emuejevuoke Umukoro, Eugenia Lo, Becky Fung, Pedro Tomás-Domingo, Guofa Zhou, Daibin Zhong, Amruta Dixit, Harrysone Atieli, Andrew Githeko, Anne Vardo-Zalik, and Guiyun Yan. 2018. Impacts of Antimalarial Drugs on *Plasmodium falciparum* Drug Resistance Markers, Western Kenya, 2003-2015. *Am. J. Trop. Med. Hyg*, **98(3), pp. 692-699**.

47. Theerayot Kobasa, Eldin Talundzic, Rungniran Sug-aram, Patcharida Boondat, Ira F. Goldman, Naomi W. Lucchi, Pratin Dharmarak, David Sintasath, Mark Fukuda, Toni Whistler, John MacArthur, Venkatachalam Udhayakumar, Preecha Prempree and Nipon Chinanonwait. 2018. Emergence and Spread of *kelch13* Mutations Associated with Artemisinin Resistance in *Plasmodium falciparum* Parasites in 12 Thai Provinces from 2007 to 2016. *Antimicrobial Agents and Chemotherapy*, **Volume 62 Issue 4 e02141-17**.

48. Smith DL, Battle KE, Hay SI, Barker CM, Scott TW, McKenzie FE. 2012. Ross, Macdonald, and a Theory for the Dynamics and Control of Mosquito-Transmitted Pathogens. *PLoS Pathog*, **8(4): e1002588**.

49. P. Pongsumpun and I.M. Tang. 2007. Transmission Model for *Plasmodium Vivax* Malaria: Conditions for Bifurcation. *International Journal of Bioengineering and Life Sciences*, **Vol:1, No:5**.

50. Diekmann O., Heesterbeek J.A.P., Metz J.A.J. 1990. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, **vol 28, issue 4, pp. 365-382**.

51. P. van den Driessche, James Watmough. 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, **180 (2002) 29-48** .

52. JC Koella and R Antia. 2003. Epidemiological models for the spread of anti-malarial resistance. *Malar J.*, **2003, 2:3**.

53. Tchuenche JM, Chiyaka C, Chan D, Matthews A, Mayer G. 2011. A mathematical model for antimalarial drug resistance. *Math Med Biol*, **Dec; 28(4):335-55**.

54. Mario Cañón, Hernando Diaz, Andrés Olarte. 2017. Mathematical model for the spread of drug resistance in *Plasmodium falciparum* parasite considering transmission conditions. *J. Theor. Biol.*, **vol 435, dec 1-11**.

55. Nick Scott, Ricardo Ataide, David P. Wilson, Margaret Hellard, Ric N. Price, Julie A. Simpson and Freya J. I. Fowkes. 2018. Implications of population-level immunity for the emergence of artemisinin-resistant malaria: a mathematical model. *Malar J.*, **2018 17:279**.

56. Jamie T. Griffin. 2016. Is a reproduction number of one a threshold for *Plasmodium falciparum* malaria elimination? *Malar J*, **15:389**.

57. Eli Schwartz. 2012. Prophylaxis of Malaria. *Mediterr J Hematol Infect Dis,* **4(1): e2012045**.

58. Keillen M. Martins-Campos, Andrea Kuehn, Anne Almeida, Ana Paula M. Duarte, Vanderson S. Sampaio, et al. 2018. Infection of *Anopheles aquasalis* from

symptomatic and asymptomatic *Plasmodium vivax* infections in Manaus, western Brazilian Amazon. *Parasites & Vectors*, **11:288**.