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The impact of heterogeneous transmission on the establishment and spread of antimalarial drug resistance

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HIGHLIGHTS

- We embedded within-host competition in an agent-based model of malaria.
- We examined the role of heterogeneous biting on the establishment and spread of drug resistance.
- We find that heterogeneous transmission slows the establishment of resistance in a population.
- We find that heterogeneous transmission speeds the spread of resistance once established.

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ABSTRACT

Despite the important insights gained by extending the classical models of malaria, other factors, such as immunity, heterogeneous biting, and differential patterns of drug use have not been fully explored due to the complexity of modeling multiple simultaneous malaria infections competing within a host. Understanding these factors is important for understanding how to control the spread of drug resistance to artemisinin which is just emerging in Southeast Asia. The emergence of resistance plays out at the population level, but is the result of competition within individuals for transmission events. Most studies of drug resistance evolution have focused on transmission between hosts and ignored the role of within-host competition due to the inherent complexity of modeling at multiple scales. To embed within-host competition in the model, we used an agent-based framework that was developed to understand how deviations from the classical assumptions of the Ross-MacDonald type models, which have been well-described and analyzed, impact the dynamics of disease. While structured to be a stochastic analog to classical Ross-Macdonald type models, the model is nonetheless based on individuals, and thus aspects of within-host competition can be explored. We use this framework to explore the role of heterogeneous biting and transmission on the establishment and spread of resistance in a population. We find that heterogeneous transmission slows the establishment of resistance in a population, but once resistance is established, it speeds the spread of resistance through the population. These results are due to the skewed distribution of biting which makes onward transmission a low probability and suggests that targeting the "core" group of individuals that provide the vast majority of bites could significantly slow the spread of resistance.

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1. Introduction

Effective antimalarial drugs have saved millions of lives since their use became widespread in the 1950s. Unfortunately the emergence of resistance to the first-line drugs chloroquine (Payne, 1987) and then sulphadoxine-pyrimethamine (Nair et al., 2003; Roper et al., 2003) significantly undermined the ability to control the disease (Wongsrichanalai et al., 2002) and increased morbidity and mortality (Snow et al., 2001; Trape et al., 1998). In recent years, global efforts have been directed at maintaining the effectiveness of the artemisinin drugs, which in combination with another drug are the current recommended first-line therapy for uncomplicated malaria. While strategies, such as combination therapy, can serve to delay emergence (Smith et al., 2010a; White, 1999a, 1999b), the evolution of resistance is likely inevitable. In fact, an artemisinin delayed clearance phenotype has already been reported (Dondorp et al., 2010), suggesting that resistance to artemisinin drugs

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may already be emerging. As such, a better understanding of how resistance becomes established and spreads through a population is necessary for devising future policies and interventions to deal with the inevitable.

Since the early 1900s mathematical models of malaria have been used to understand the dynamics of the disease and guide policy (Smith et al., 2012). In recent years a number of different models have elucidated important aspects of the evolution of resistance, particularly regarding the role of transmission intensity, superinfection (i.e. multiple simultaneous malaria infections (Macdonald, 1950)), and clinical immunity (Artzy-Randrup et al., 2010; Chiyaka et al., 2009; Hastings, 1997, 2006; Hastings and D'Alessandro, 2000; Klein et al., 2008; Pongtavornpinyo et al., 2008). However, most of these theoretical studies of drug resistance evolution have focused on transmission between hosts and ignored the role of within-host competition (Klein, 2013; Reiner et al., 2013), which, while simplifying the dynamics, makes it difficult to understand how the dynamics are impacted by competition within the host. In an agent-based framework, it is possible to embed within-host competition; however this creates a degree of complexity that makes it difficult to analyze the model. To bridge this difference, we have developed an individual-based model that is a direct analog of a mathematical model of mosquito-borne pathogen transmission based on the assumptions of the Ross-MacDonald model. The model builds on prior epidemiological models of vector-borne transmission (Bailey, 1982; Dietz et al., 1974; Macdonald, 1950), and takes a stepwise approach to incorporating both competition and drug resistance. This makes the analysis tractable and allows for a careful examination of how deviations from the orthodoxy of the Ross-Macdonald framework, in particular the role of heterogeneous biting, impacts the dynamics of infection and the establishment and spread of drug resistance.

2. Methods

Malaria is a vector-borne disease transmitted by the bite of an anopheles mosquito. Individuals living in malarious regions of the world are bitten regularly by infected mosquitoes. This continuous re-exposure results in simultaneous infection, or superinfection (Macdonald, 1950), with multiple parasites. The number of genetically distinct parasite genotypes, called the multiplicity of infection (MOI), generally increases on average in the population with transmission (Bendixen et al., 2001; Sama et al., 2006), but varies based on mosquito biting patterns (Smith et al., 2005) and the age of the individual (Bendixen et al., 2001; Sama et al., 2006), which likely has to do with the level of acquired immunity (Klein, 2013). We base our assumptions of how parasites compete within the host on a Markov-Chain model for superinfection and clearance developed by Bailey (Bailey, 1982) based on work by MacDonald, Irwin, Fine and Walton (Dietz et al., 1974; Fine, 1975; Macdonald, 1950; Walton, 1947). We first describe a class-based deterministic model that will serve as the basis for comparison to an agent-based model.

2.1. Mosquito dynamics

To ensure that our formulation will be analogous to an individual based version, we explicitly model the mosquito population's contribution to transmission following classical malaria notation (Smith and McKenzie, 2004). Susceptible mosquitoes (M_s) emerge at a constant rate per human (m) and are assumed to die at a constant rate (g), which generates an equilibrium mosquito density per human (m/g). The rate that mosquitoes become latently infected (M_L) is dependent on the density of mosquitoes, the biting rate (a) and the efficiency of transmission from human to mosquito (c). Mosquitoes that become infected must then survive sporogony (n) before becoming infectious (M_I). The dynamics of the mosquito population are described by the following set of ordinary differential equations:

$$\dot{M}_S = mN_H - gM_S - \frac{acI_H}{N_H}M_S$$
$$\dot{M}_L = \frac{acI_H}{N_H}M_S - (g+n)M_L$$
$$\dot{M}_I = nM_L - gM_I \quad (1)$$

where N_H is the total number of humans and I_H is the total number of infected humans.

2.2. Human dynamics

The human dynamics are formulated so that $\sum_i I_i = 1$ and $\sum_i \dot{I}_i = 0$, where I_0 are susceptible individuals. Thus, the values of the state variables describe the distribution of susceptible and infected individuals in the population over time. Humans are infected by infectious mosquitoes at a rate dependent upon the mosquito density, the biting rate, and the infectivity rate (b), or the fraction of bites on humans that produce a patent infection. The equation describing the dynamics of the population of susceptible humans is,

$$\dot{S} = \dot{I}_0 = B - \left(\frac{abM_I}{N_H} + \mu\right)I_0 + \gamma I_1 + \psi\rho\sum_{j=1}^{n} I_j \quad (2)$$

and the equations describing infected humans is,

$$\dot{I}_j = \frac{abM_I}{N_H}I_{j-1} - \left(\frac{abM_I}{N_H} + \mu + \gamma j + \psi\rho + \delta\right)I_j + \gamma(j+1)I_{j+1}, j \geq 1 \quad (3)$$

where μ is the background mortality rate, γ is the rate infections are cleared, and δ is the disease induced death rate. We also assume that deaths are balanced by births (B). Lastly, drug use is assumed to be associated with clinical symptoms (primarily fever), which develops at rate ψ. The rate that clinical symptoms arise is assumed to be independent of MOI. A fraction of symptomatic patients, ρ, are assumed to use drugs and successfully clear all sensitive parasites immediately upon treatment. Treatment of resistant parasites is assumed to be ineffective. For numerical simulations we assume that the max MOI is 100, thus to avoid a population leak, the equation for the maximum MOI differs slightly,

$$\dot{I}_{j_{max}} = \frac{abM_I}{N_H}I_{j_{max}-1} - (\mu + \gamma j_{max} + \psi\rho + \delta)I_{j_{max}} \quad (4)$$

though this has negligible impact because of the high assumed MOI. See Fig. 1 for a schematic of the model.

2.3. Computationally efficient individual-based model

Our individual model of malaria was developed to be, in its base form, a stochastic analog of the deterministic model described above.

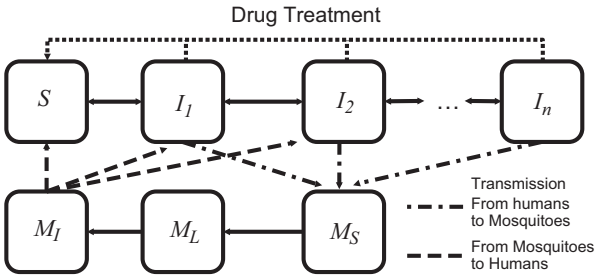

Fig. 1. Schematic of Deterministic Model. S refers to susceptible individuals, I_i is individuals infected with i genetically distinct clones, and M_S, M_L, M_I refer to susceptible, latent and infectious mosquitoes, respectively.

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