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Optimal vaccination and bednet maintenance for the control of malaria in a region with naturally acquired immunity

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HIGHLIGHTS

- We present a malaria vaccination model with naturally acquired immunity (NAI).
- We derive a necessary and sufficient condition for subthreshold endemic equilibria.
- We determine optimal vaccination and bednet control policies under two scenarios.
- In first scenario, increase vaccination efforts when NAI and prevalence are low.
- In second scenario, bednet efforts can eliminate malaria, but epidemic risk is high.

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ABSTRACT

Following over two decades of research, the malaria vaccine candidate RTS,S has reached the final stages of vaccine trials, demonstrating an efficacy of roughly 50% in young children. Regions with high malaria prevalence tend to have high levels of naturally acquired immunity (NAI) to severe malaria; NAI is caused by repeated exposure to infectious bites and results in large asymptomatic populations. To address concerns about how these vaccines will perform in regions with existing NAI, we developed a simple malaria model incorporating vaccination and NAI. Typically, if the basic reproduction number (R_0) for malaria is greater than unity, the disease will persist; otherwise, the disease will become extinct. However, analysis of this model revealed that NAI, compounded by a subpopulation with only partial protection to malaria, may render vaccination efforts ineffective and potentially detrimental to malaria control, by increasing R_0 and increasing the likelihood of malaria persistence even when $R_0 < 1$. The likelihood of this scenario increases when non-immune infected individuals are treated disproportionately compared with partially immune individuals – a plausible scenario since partially immune individuals are more likely to be asymptomatically infected. Consequently, we argue that active case-detection of asymptomatic infections is a critical component of an effective malaria control program. We then investigated optimal vaccination and bednet control programs under two endemic settings with varying levels of naturally acquired immunity: a typical setting under which prevalence decays when $R_0 < 1$, and a setting in which subthreshold endemic equilibria exist. A qualitative comparison of the optimal control results under the first setting revealed that the optimal policy differs depending on whether the goal is to reduce total morbidity, or to reduce clinical infections. Furthermore, this comparison dictates that control programs should place less effort in vaccination as the level of NAI in a population, and as disease prevalence, increases. In the second setting, we demonstrated that the optimal policy is able to confer long-term benefits with a 10-year control program by pushing the system into a new state where the disease-free equilibrium becomes the attracting equilibrium. While this result suggests that one can theoretically achieve long-term benefits with a short-term strategy, we illustrate that in this second setting, a small environmental change, or the introduction of new cases via immigration, places the population at high risk for a malaria epidemic.

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1. Background

Due in part to the proliferation of artemisinin-resistant malaria, alternative strategies for controlling and reducing malaria burden have received much attention. Using multiple strategies simultaneously has proven remarkably effective at reducing malaria burden (de Castro et al., 2004), and part of the recent reduction in malaria burden worldwide can be attributed to the integrated use of treatment and vector control strategies (Raghavendra et al., 2011). Vaccination is often cited as a promising tool for augmenting these integrated malaria control programs (Killeen et al., 2000), though a malaria vaccine has yet to become available for large-scale use. Some vaccines are nearing certification, such as the RTS,S/AS01 vaccine being developed by GSK with a multinational consortium of government and non-governmental agencies (Agnandji et al., 2012). The vaccines in development confer immunity and reduce the likelihood of transmission and infection through a variety of methods, and can be placed into one of three broad categories (Halloran and Struchiner, 1992): blood-stage targeting vaccines that increase the recovery rate of infected humans, gametic-stage targeting vaccines that reduce infectivity of humans to mosquitoes, and sporozoite-targeting vaccines (including RTS,S) that decrease susceptibility of humans to infection. Most malaria vaccines in development do not confer perfect immunity for the duration of immunity, however, and can be classified as leaky vaccines (Halloran et al., 1989). While leaky vaccines reduce an individual's infection risk, they do not prevent transmission entirely. For RTS,S, recent trials have suggested that vaccinated individuals are 40% less likely to become infected over a 6-month period, and are protected for roughly 2 years (Maire et al., 2006). As a result, vaccines such as RTS,S alone are unlikely to eliminate malaria from areas with high malaria transmission. Balancing limited funding between vaccination and other controls to most efficiently reduce malaria burden is an important policy concern, and previous models have explored the possibility of using multiple controls concurrently (Griffin et al., 2010). Optimal control theory has been useful in addressing similar issues (Jung et al., 2002), and can be applied to optimize an objective (for example, reducing malaria deaths or overall malaria burden) by manipulation of controls (Lenhart and Workman, 2007), including vaccination and bednet usage. In regions of high malaria endemicity, immunity can occur naturally even in the absence of vaccination (Gupta et al., 1999). After an individual is exposed to malaria parasites repeatedly, infections no longer cause acute malaria and instead result in asymptomatic cases, though these individuals are still able to transmit parasites to mosquitoes (Langhorne et al., 2008). While multiple inoculations are required for this natural immunity to develop, people commonly receive enough inoculations to develop natural immunity to malaria before age 10 in areas with very high entomological inoculation rates; the exact mechanism for this phenomenon, however, remains unknown (Langhorne et al., 2008; Doolan et al., 2009). Mathematical models have previously shown that naturally acquired immunity affects transmission dynamics, potentially influencing the utility of leaky vaccines (Halloran and Struchiner, 1992). In other disease systems, natural immunity has been shown to potentially cause a backward bifurcation (Reluga et al., 2008), or a phenomenon where the disease can persist despite the basic reproductive number being under the typical critical threshold of unity. Backward bifurcations are important facets of disease systems, as backward bifurcations can lead to catastrophic reintroduction, and have been shown to be a property of some malaria models (Chiyaka et al., 2008; Aguas et al., 2008). Catastrophic reintroductions occur in settings where the introduction of a small number of cases when $R_0 < 1$ would not lead to reintroduction of the disease, but once R_0 increases above unity, a small reintroduction event causes a rapid move to an equilibrium with a high proportion of people infected (Dushoff et al., 1995). Despite enthusiasm for malaria vaccine development, there is some skepticism about the ability of these leaky vaccines to reduce malaria burden, especially in areas with high rates of naturally acquired immunity (Halloran and Struchiner, 1992). If leaky vaccines reduce the amount of exposure individuals have to malaria, then vaccinated individuals may not develop natural immunity as quickly as without vaccination. Because infection remains possible for these vaccinated individuals, it is possible that they will be more likely to exhibit severe malaria when infected, as vaccination may prevent the development of natural immunity. Some modeling efforts have examined the impact of leaky vaccines on malaria burden in highly endemic areas, and the previous models have suggested that in areas with very high rates of malaria transmission, using leaky vaccines may not reduce malaria burden appreciably, and may even cause increased rates of symptomatic malaria (Halloran and Struchiner, 1992).

Because of the potentially complex interactions between immunity, vaccination, and malaria dynamics, predicting the outcome of a vaccination program and determining effective vaccination policy are important concerns. In this study, we determine the optimal vaccination policy in the presence and absence of naturally acquired immunity. We also determine the effect of naturally acquired immunity on the basic reproductive number and the endemic equilibrium of malaria prevalence. Under Section 2, we first present a malaria vaccination model with naturally acquired immunity, followed by the extension of this model to include vaccination and bednet control efforts. A thorough analysis of the original model in Section 3 reveals that naturally acquired immunity can render vaccination efforts counter-productive, and moreover, may lead to backward bifurcation at $R_0 = 1$. Lastly, using the optimal control construction, we present optimal vaccination and bed-net control strategies in populations with differing levels of naturally acquired immunity. The analytic and numerical analyses of our malaria vaccination model can help predict under which circumstances vaccination will be most effective at reducing malaria burden, and under which circumstances vaccination will be ineffective, or even counterproductive.

2. Methods

2.1. Model

We consider human and mosquito populations of constant sizes in a closed, homogeneous environment using a system of differential equations. The human population of size N is divided into five compartments: susceptible (S), infectious (I), recovered from clinical malaria (R), susceptible but partially protected (S_p), and individuals with partial protection who are infected and recovering (R_p). The infected mosquito population is modeled as a proportion z.

The system of ordinary differential equations in System (1) describes the disease dynamics in humans and mosquitoes. Initially, humans are susceptible (S). These susceptible individuals can either become vaccinated at a rate ν and progress to S_p, or they can become infected at the rate βz, where β is the product of the ratio of mosquitoes to humans, the mosquito biting rate, and the mosquito-to-human-transmission efficiency. Once infected, the S-individual progresses to the infectious stage, I, and displays clinical symptoms. Individuals ultimately leave the I stage of the infection and enter R at a rate α, at which point they are no longer clinically ill, cannot move back to the clinical infection stage I, and are less infectious to mosquitoes. These asymptomatic, temporarily immune, partially infectious individuals have been previously incorporated into mathematical models of malaria (Aron, 1987;