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Could Low-Efficacy Malaria Vaccines Increase Secondary Infections in Endemic Areas?

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Summary. Recent breakthroughs in malaria vaccines have given new hope that a safe, effective malaria vaccine may be found. The following epidemiological questions are addressed: 1. What level of vaccination coverage is required to offset the limitations of an imperfect disease-modifying vaccine? 2. Could the introduction of a low-efficacy malaria vaccine lead to an increase in the number of secondary infections? 3. What characteristics of such a vaccine will have the greatest effect on the outcome? A mathematical model is developed for a disease-modifying malaria vaccine that is given once prior to infection, and the minimum coverage level for disease eradication is established. There is a threshold depending on the relative rate of infection, the efficacy of the vaccine and the duration of infection. Vaccines which reduce the rate and duration of infection will always result in a decrease in secondary infections. More surprisingly, there is a duration "shoulder," such that vaccines that increase the duration of infection slightly will still lead to a decrease in secondary infections, even if the rate of infection is unchanged. Beyond this, the number of secondary infections will increase unless the rate of infection is sufficiently lowered. This is critical for low-efficacy vaccines.

Key words: Malaria, vaccines, coverage, rate of infection, duration of infection, efficacy.

1.1 Introduction

Malaria remains one of the most important human diseases throughout the tropical and subtropical regions of the world and causes more than 300 million acute illnesses and at least one million deaths annually [18]. 90% of deaths due to malaria occur in sub-Saharan Africa, mostly among young children [17]. The search for a malaria vaccine is now over seventy years old [6], and a great deal of effort and funding has been put into the task [11]. Recent vaccine findings [1] have renewed the interest in the potential role of vaccines within malaria-control programs by focusing on the possibility of an anti-malarial vaccine delivered to infants prior to infection.

In this chapter, a model of malaria infection is developed which combines the classic Aron models [2,3] with those of vaccine models [8], but includes disease-modifying effects based on theoretical HIV vaccine models [4, 15]. The following epidemiological questions are addressed: 1. What level of vaccination coverage is required to offset

the limitations of an imperfect disease-modifying vaccine? 2. Could the introduction of a low-efficacy malaria vaccine lead to an increase in the number of secondary infections? 3. What characteristics of such a vaccine will have the greatest effect on the outcome?

1.2 The Model

A malaria vaccine could have different potential effects, including (a) reducing mortality due to malaria, (b) increasing the recovery rate, (c) increasing the acquired immunity rate or d) reducing the rate of infection. Possible limitations of a vaccination program include (i) the vaccine may only be delivered to a proportion p of the population, (ii) the vaccine may only "take" in a proportion ϵ of people vaccinated, (iii) the vaccine may wane over time (ω is the rate of waning of immunity) and (iv) the vaccine may have a suboptimal efficacy ψ. It is assumed that all vaccinated individuals are vaccinated before infection, reflecting the situation in [1]. Furthermore, unlike in HIV models (but in common with other models of vaccination; eg pertussis [16]), the vaccine may wane before, during or after infection.

It follows that *"successfully vaccinated"* individuals consist of those who received the vaccine, for whom the vaccine "took" and for whom the vaccine did not wane prior to infection. All other individuals shall be referred to as *unprotected individuals*, regardless of whether they received the vaccine or not, since the net effect prior to infection is identical. (See [4] and [15] for more detailed discussions.) Note that "successfully vaccinated" individuals have the potential to become infected (if the vaccine efficacy ψ is less than 100%, or if vaccine-induced immunity wanes subsequently) and cause secondary infections. These individuals may have a reduced rate of infection, but will have an increased life expectancy. They may recover faster from the disease and their disease-induced mortality will be lower. Consequently, their total duration of infection may either decrease (due to higher recovery rates) or increase (due to fewer deaths from infection).

It can be assumed that mosquitos are either susceptible (M) or infected (N), have birth rate Ω and that their death rate (μ_M) does not vary significantly if they are infected. Individuals who have experienced infection may recover (without substantial gain in immunity) at *recovery rate* h_k ($k = U, V$; U = unvaccinated, V = vaccinated) or may become temporarily immune at *acquired immunity rate* α_k ($k = U, V$). See [5,9,10,12] for further details. Temporarily immune individuals will become susceptible again at rate δ_k ($k = U, V$). The rate of infection of an infected individual in class X_k is β_k ($k = U, V$) and the rate of infecting a mosquito is β_M (assumed identical from either class of individual, since mosquitos are not vaccinated). The birth rate is π, the background death rate is μ and γ_k is the death rate due to malaria ($k = U, V$). Thus, the model is

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \Omega - \beta_M Y_U M - \beta_M Y_V M - \mu_M M$$
$$\frac{\mathrm{d}N}{\mathrm{d}t} = \beta_M Y_U M + \beta_M Y_V M - \mu_M N$$

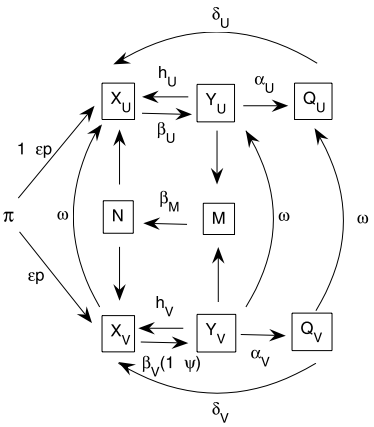

Fig. 1.1. Schematic representation of the model, representing both unprotected and "successfully vaccinated" individuals, as well as mosquitos. The background mortalities for humans μ (in all compartments) and mosquitos μ_M (in both compartments), as well as disease-induced mortality for humans γ_U, γ_V (in the infected compartments) are not drawn in, for conciseness.

$$
\begin{aligned}
\frac{\mathrm{d}X_U}{\mathrm{d}t} &= (1-\epsilon p)\pi - \mu X_U - \beta_U N X_U + \omega X_V + h_U Y_U + \delta_U Q_U \\
\frac{\mathrm{d}X_V}{\mathrm{d}t} &= \epsilon p\pi - \mu X_V - (1-\psi)\beta_V N X_V - \omega X_V + h_V Y_V + \delta_V Q_V \\
\frac{\mathrm{d}Y_U}{\mathrm{d}t} &= \beta_U N X_U - (\mu + \gamma_U + \alpha_U + h_U) Y_U + \omega Y_V \\
\frac{\mathrm{d}Y_V}{\mathrm{d}t} &= (1-\psi)\beta_V X_V - (\mu + \gamma_V + \alpha_V + h_V) Y_V - \omega Y_V \\
\frac{\mathrm{d}Q_U}{\mathrm{d}t} &= \alpha_U Y_U - (\mu + \delta_U) Q_U + \omega Q_V \\
\frac{\mathrm{d}Q_V}{\mathrm{d}t} &= \alpha_V Y_V - (\mu + \delta_V) Q_V - \omega Q_V \,.
\end{aligned}
$$

The model is illustrated in Fig. 1.1.

With the notation $\xi_k = \mu + \gamma_k + \alpha_k + h_k$ $(k = U, V)$, $1/\xi_K$ is the total duration of the infectious period for unprotected and "successfully vaccinated" individuals, respectively. It is expected that the recovery rates α_V, h_V will increase due to the vaccine, but that the disease-induced death rate γ_V will decrease. It follows that the total duration of the infectious period for vaccinated individuals may either increase or decrease. It is also expected that the rate of infection β_V will not increase.

1.3 Analysis

The disease-free equilibrium satisfies $\bar{M} = \Omega/\mu_M$, $\bar{X}_U = [\pi(\mu(1-\epsilon p)+\omega)]/[\mu(\mu+\omega)]$, $\bar{X}_V = \epsilon p\pi/(\mu+\omega)$ and $\bar{N} = \bar{Y}_U = \bar{Y}_V = \bar{Q}_U = \bar{Q}_V = 0$.

Thus, the proportion of the population that is successfully vaccinated, S, satisfies $S = \bar{X}_V/(\bar{X}_U + \bar{X}_V) = \epsilon p\mu/(\mu + \omega)$. In particular, $\bar{X}_U = (\pi/\mu)(1 - S)$ and $\bar{X}_V = (\pi/\mu)S$.

At the disease-free equilibrium, the Jacobian matrix is $J =$

$$\begin{bmatrix} \mu_M & 0 & 0 & 0 & -\beta_M\bar{M} & -\beta_M\bar{M} & 0 & 0 \\ 0 & -\mu_M & 0 & 0 & \beta_M\bar{M} & \beta_M\bar{M} & 0 & 0 \\ 0 & -\beta_U\bar{X}_U & -\mu & \omega & h_U & 0 & \delta_U & 0 \\ 0 & -(1-\psi)\beta_V\bar{X}_V & 0 & -\mu-\omega & 0 & h_V & 0 & \delta_V \\ 0 & \beta_U\bar{X}_U & 0 & 0 & -\xi_U & \omega & 0 & 0 \\ 0 & (1-\psi)\beta_U\bar{X}_V & 0 & 0 & 0 & -\xi_V-\omega & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_U & 0 & -\mu-\delta_U & \omega \\ 0 & 0 & 0 & 0 & 0 & \alpha_V & 0 & -\mu-\delta_V-\omega \end{bmatrix} .$$

Thus, $\det(J - \Lambda I) = -(\mu_M + \Lambda)(\mu + \Lambda)(\mu + \omega + \Lambda)(\mu + \delta_U + \Lambda)(\mu + \delta_V + \omega + \Lambda) \det M$, where

$$M = \begin{bmatrix} -\mu_M - \Lambda & \beta_M\bar{M} & \beta_M\bar{M} \\ \beta_U\bar{X}_U & -\xi_U - \Lambda & \omega \\ (1-\psi)\beta_V\bar{X}_V & 0 & -\xi_V - \omega - \Lambda \end{bmatrix} .$$

Thus, the largest eigenvalue for J will be the largest eigenvalue for M. The vanishing determinant condition gives $-\mu_M\xi_U(\xi_V + \omega) + (1 - \psi)\beta_V\beta_M\omega\bar{X}_V\bar{M} + (1 - \psi)\xi_U\beta_V\beta_M\bar{X}_V\bar{M} + (\xi_V + \omega)\beta_U\beta_M\bar{X}_U\bar{M} = 0$. Hence,

$$\frac{(1-\psi)\beta_V\beta_M\bar{M}(\xi_U + \omega)}{\mu_M\xi_U(\xi_V + \omega)}\bar{X}_V + \frac{\beta_U\beta_M\bar{M}}{\mu_M\xi_U}\bar{X}_U = 1 .$$

Individuals who are vaccinated with disease-modifying vaccines have the potential to become infected and cause secondary infections. Such individuals may have a reduced rate of infection, but will have an increased survival time. The reproduction number in a population with vaccination is R_V, in contrast to R_0, the basic reproduction number in an unvaccinated population.

If there is no vaccine, $S = 0$, so $\bar{X}_V = 0$, $\bar{X}_U = \pi/\mu$ and hence the vanishing determinant condition gives $R_0 = \pi\Omega\beta_U\beta_M/\mu\mu_M^2\xi_U$. If the entire population is successfully vaccinated, $S = 1$ and $\omega = 0$, so $\bar{X}_V = \pi/\mu$, $\bar{X}_U = 0$ and hence the vanishing determinant condition gives $R_V = (1 - \psi)(\pi\Omega\beta_V\beta_M/\mu\mu_M^2\xi_V)$. Thus, the population reproduction number is $R_P = (1 - S)R_0 + SR_V$. See [4,7,13–15].

To estimate the minimum coverage levels p_c for an imperfect disease-modifying vaccine, when $R_P = 1$, this last equation can be rearranged to produce

$$S = \frac{\epsilon p_c\mu}{\mu + \omega} = \frac{1 - R_0}{R_V - R_0} .$$

Thus, the threshold disease-modifying vaccine coverage level is

$$p_c = \frac{(\mu + \omega)(\mu + \gamma_V + \alpha_V + h_V)[\mu\mu_M^2(\mu + \gamma_U + \alpha_U + h_U) - \beta_U\beta_M\Omega\pi]}{\epsilon\mu\beta_M\Omega\pi[(1-\psi)\beta_V(\mu + \gamma_U + \alpha_U + h_U) - \beta_U(\mu + \gamma_V + \alpha_V + h_V)]} . \quad (1.1)$$

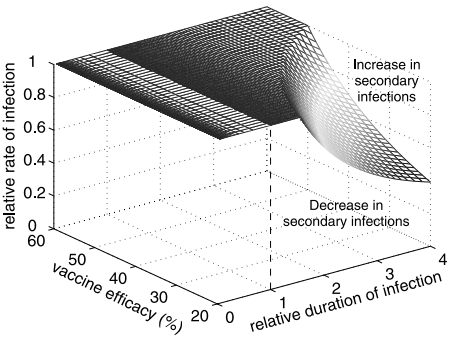

Fig. 1.2. The relationship between the relative rate of infection, the relative duration of infection and the vaccine efficacy. A disease-modifying vaccine which reduces the duration of infection will always lead to a decrease in secondary infections, regardless of the efficacy of the vaccine. More surprisingly, a vaccine which increases the duration of infection can still result in an overall decrease in secondary infections, but the outcome depends on the rate of infection and the efficacy of the vaccine. There is a duration "shoulder," such that vaccines that increase the duration of infection slightly will still result in a net decrease in secondary infections. However, as the duration of infection increases, the number of secondary infections will increase, unless the rate of infection is lowered accordingly. This is critical for low-efficacy vaccines.

Vaccination programs whose coverage levels exceed this proportion of the population are likely to eradicate the disease.

Once a vaccine is introduced, the number of secondary infections will increase if $R_P > R_0$ (i.e., if the population reproduction number after the introduction of a vaccine is greater than the reproduction number currently). This occurs when

$$\begin{aligned}(1-S)R_0 + SR_V &> R_0\\ \frac{\beta_V}{\beta_U} &> \frac{\xi_V}{(1-\psi)^2\xi_U}\,.\end{aligned}$$

This is illustrated in Fig. 1.2.

Clearly, if the rate of infection and the duration of infection both decrease, then there will always be a decrease in the number of secondary infections. More surprisingly, for a given efficacy of the vaccine, there is a duration "shoulder," such that a small increase in the duration of infection will still decrease the number of secondary infections, even if the rate of infection is unchanged. However, if the duration of infection is increased beyond this shoulder, then it is crucial that the rate of infection be decreased accordingly. This is critical for low-efficacy vaccines.

The "shoulder" occurs when the relative duration of infection satisfies

$$\frac{1/\xi_V}{1/\xi_U} = \frac{1}{(1-\psi)^2}$$

for a given vaccine efficacy ψ. For example, a 20% efficacious vaccine could accomodate an increase in the duration of infection by as much as 1.5625 times the current

duration of infection, with no reduction in the rate of infection and still result in a decrease in secondary infections. However, a 20% efficacious vaccine that increased the duration of infection by a factor of 4 would lead to an increase in secondary infections unless the rate of infection for the vaccinated population were reduced to 40% of the current rate of infection.

1.4 Discussion

A vaccination program implementing a disease-modifying malaria vaccine in an endemic area should have a minimum coverage level p_c, as estimated by (1.1). If the proportion of the population that can be vaccinated exceeds p_c, then such a vaccination program is likely to result in the eradication of the disease.

Furthermore, reducing the transmission probability of such a disease-modifying vaccine is crucial, for vaccines whose duration of infection increases significantly. While it is expected that a disease-modifying vaccine would increase the recovery rates, it would also decrease the rate of disease-induced mortality, so the total duration of the infectious period for a vaccinated individual may either increase or decrease. If this duration decreases, then the number of secondary infections will always decrease, regardless of the vaccine efficacy, so long as the rate of infection does not increase.

There is a duration "shoulder," such that the number of secondary infections will always decrease if the duration increases within this shoulder. However, an increase beyond the "shoulder" will lead to an increase in secondary infections, unless the rate of infection of the vaccine is lowered accordingly. This is critical for low-efficacy vaccines.

It should be noted that these results primarily apply to areas in which malaria is endemic. A disease-modifying malaria vaccine with a high duration of infection (for example, one which drastically reduced disease-induced mortality, but which had negligible effect on the recovery rates) might be quite desirable for a temporary outbreak of malaria in the developed world, if the prospect of reinfection is negligible. In endemic areas however, such a vaccine would likely make the situation worse. It follows that low-efficacy vaccines which result in high durations of infection but which do not significantly lower the rate of infection should not be used in endemic areas.

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