We predict the effects of introduction of a pre-erythrocytic vaccine against *Plasmodium falciparum* into malaria-endemic populations in Africa. We use a stochastic simulation model that includes components of transmission, parasitology, and clinical epidemiology of malaria and was validated using the results of field trials of the RTS,S/AS02A vaccine. The results suggest that vaccines with efficacy similar to that of RTS,S/AS02A have a substantial impact on malaria morbidity and mortality during the first decade after their introduction, but have negligible effects on malaria transmission at levels of endemicity typical for sub-Saharan Africa. The main benefits result from prevention of morbidity and mortality in the first years of life. Vaccines with very short half-life or low efficacy may have little overall effect on incidence of severe malaria. A similar approach can be used to make predictions for other strategies for deployment of the vaccine and other types of malaria vaccines and interventions.

INTRODUCTION

The development of a safe and effective vaccine against *Plasmodium falciparum* is recognized as one of the major unmet medical needs in non-industrialized countries. As a result of recent funding initiatives, various candidate vaccines targeting different stages of the parasite are in pre-clinical and clinical development. The most advanced vaccine development program is currently that of the pre-erythrocytic vaccine, RTS,S/AS02A, which recently demonstrated an efficacy of 45% in preventing *P. falciparum* infection in children in Mozambique.

Partially protective vaccines have complex effects on the dynamic interactions between the host and an infectious agent. It is generally acknowledged that a malaria vaccine is unlikely to be 100% effective and the effects of imperfectly protective malaria vaccines may be particularly complex. To make predictions of the likely public health impact of a range of malaria vaccines, we have developed a stochastic simulation model of the epidemiology of *P. falciparum* in endemic areas. We have now used this model to simulate the likely health impact of introducing the RTS,S/AS02A into malaria-endemic populations via the expanded program on immunization (EPI). The model considers both the short- and long-term effects of a vaccination program on the burden of disease, allowing for the temporal dynamics of effects on immunity and transmission.

MATERIALS AND METHODS

**Epidemiologic model.** The epidemiologic model is a stochastic individual-based simulation of *P. falciparum* malaria in endemic settings that uses a five-day time step with the pattern of transmission as the input. For every individual in the simulated population, each discrete *P. falciparum* infection is characterized by simulated duration, parasite densities, infectivity, and anemia risk. At each time point, clinical episodes of malaria or malaria attributable mortality may occur with probabilities depending on the simulated parasite density and recent exposure. For the present analyses we simulate populations of 100,000 individuals, with an approximately stationary age distribution matching that of the demographic surveillance site in Ifakara in southeastern Tanzania in 1997–1999.

We run the model under a series of assumed transmission patterns (Table 1). Each simulation assumes a recurring annual pattern of the vectorial capacity. The simulated population has been subjected to this pattern for a lifetime at the start of the vaccination program to ensure that the level of acquired immunity is correct for all ages. We then consider the transient behavior of the model during a follow-up period of 20 years. We simulate case-management and the effects on malaria transmission using a reference scenario as described in an accompanying paper. This reflects a typical rural setting in Tanzania with mesoendemic malaria transmission.

**Reference vaccine scenario.** The simulated vaccine is a pre-erythrocytic vaccine that protects vaccinated individuals by reducing the force of infection. Relevant characteristics of the simulated vaccine were chosen to match the data from a phase 2b clinical trial in children 1–4 years of age in Mozambique. We have simulated the action of the vaccine in this trial and fitted the efficacy to the trial data. These simulations suggested that pre-existing semi-immunity leads to a slight underestimation of the underlying efficacy of the vaccine in such a trial. After this, we therefore assume that the vaccine provides an initial reduction in the force of infection of 52% corresponding to the 45% efficacy in extending time to first infection after three doses. There are no data available on the efficacy after one or two doses of RTS,S/AS02A. We assume a reduction in the force of infection of 40% and 46% after the first and the second dose. The Manhiça trial did not demonstrate any decay of the efficacy against infection. However, decay in protection is possible when longer time periods are considered and is likely to have important implications for vaccine effectiveness. We assume an exponential decay of the primary efficacy of the vaccine and set the half-life to 10 years for the reference vaccine.

We expect that the protection provided by the vaccine is not homogenously distributed among the vaccinated individuals. We assign initial values for the efficacy of the vaccine that are drawn from a beta distribution with parameter $b = 10$ (a justification is given in an accompanying paper).
Simulation approach. We simulate the introduction of vaccination at the target ages of one, two, and three months in a random sample of infants. A total of 95% of the infants receiving the first dose, 95% of those receiving the second dose, and 99% of those receiving the first two doses complete the course of vaccination. We assume all vaccines to be delivered at the target age, and that no infant received dose 2 without receiving dose 1, or dose 3 without receiving dose 2. This results in a cohort effect because the proportion of the population who have received the full vaccination course gradually increases throughout the 20 year follow-up (Figure 1). Since by the end of this period vaccination coverage in older age groups is still zero, we do not consider the equilibrium that would eventually be reached if vaccination continued indefinitely.

The introduction of vaccination leads to transient behavior that may in principle modify the level of *P. falciparum* transmission. We consider the effects after periods of 5, 10, and 20 years after initiation of the vaccination program. We plot the cumulative numbers of events averted. Where the cumulative number of episodes averted increases approximately linearly over time, (indicating constant effectiveness), we compute the effectiveness of vaccination over the whole 20-year follow-up as

\[
\text{Cumulative Effectiveness} = \frac{1}{\text{Cumulative number of events in comparison scenario}} \left( \text{Cumulative number of events in vaccine scenario} \right)
\]

where the comparison scenario is identical to the vaccination scenario in all respects other than the inclusion of vaccination. In addition, we present age-prevalence of parasitemia and anemia as well as age-incidence of different clinical outcomes averaged over one year of simulated follow-up starting 4, 9, and 19 years into the follow-up period.

Effects of vaccine characteristics. We expect the predictions about the effectiveness of the vaccine to depend on assumptions about the key properties of the vaccine. In addition, effectiveness depends on the proportion of the population that has been vaccinated. Effectiveness may be an accelerating function of coverage if vaccination has a community effect through reduction of the infectivity of the human hosts. We therefore modeled a range of different assumptions about the proportion of infections that are prevented after an individual has received one, two, or three doses of the vaccine, the rate of decay of protection against infection, and the variation in efficacy between individuals. To keep the number of simulated scenarios manageable we start from the reference scenario described above and vary one assumption at a time (Table 1).

Effects of transmission intensity and seasonality. In addition to the reference scenario we also generate simulation results corresponding to a range of transmission intensities. There are characteristic shifts in the ages distributions of clini-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
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<tbody>
<tr>
<td>Coverage</td>
<td>Proportion of eligible individuals who receive all 3 vaccine doses. (coverage with first, second, and third dose)</td>
<td>50% (70%, 85%, 85%)</td>
</tr>
<tr>
<td>Initial efficacy of the vaccine</td>
<td>Efficacy in fully vaccinated individuals immediately after third dose. Numbers in brackets show efficacy after first and second dose</td>
<td>0.3 (0.2, 0.25)</td>
</tr>
<tr>
<td>Decay of the efficacy of the vaccine</td>
<td>Time after vaccination at which the vaccine efficacy is 50% of initial value, assuming exponential decay of protection</td>
<td>6 months</td>
</tr>
<tr>
<td>Variation in vaccine efficacy between hosts</td>
<td>b is the parameter of the beta distribution used to describe inter-host variation</td>
<td>All or nothing (b = 0.01), Intermediate (b = 10), Homogeneity (b = 100,000)</td>
</tr>
<tr>
<td>Intensity of transmission</td>
<td>Infectious bites per year prior to the introduction of the vaccine</td>
<td>High transmission: 82</td>
</tr>
<tr>
<td>Seasonality</td>
<td>Source of data for seasonal distribution on inoculations</td>
<td>Namawala, Tanzania</td>
</tr>
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</table>

* Each level of each variable defines a scenario that was compared with the reference. In each scenario, the variables not being evaluated were fixed at the reference levels (indicated in bold).
cal events in *P. falciparum* at different transmission intensities and we wanted to explore how these would modify vaccine effectiveness. Starting from the reference scenario described above, we explore the effect of increasing or decreasing the annual entomologic inoculation rate (EIR) prior to the introduction of the vaccine within a range found in areas of stable endemic malaria. In addition, we study the impact of different seasonal patterns of EIR by simulating the case of a completely non-seasonal environment with the same yearly average EIR as in the reference scenario.

**RESULTS**

**Reference vaccination scenario.** In the reference vaccination scenario the introduction of vaccine leads to lower parasite prevalence for all age groups that had received the vaccine, resulting in a cohort effect with the effect gradually moving into older age groups (Figure 2a). Corresponding to the reduction in parasite prevalence, anemia prevalence is also reduced but because the anemia is concentrated in the first few years of life, anemia prevalence becomes stable within the first few years of vaccination (Figure 2b).

The incidence of malaria episodes and mortality decrease for children less than five years of age within the first few years of vaccination and remain reduced over the 20-year time span (Figure 3). These dynamic effects resulted almost entirely from the cohort effect of introducing vaccination gradually into the population and hardly at all from community effects due to reduction in transmission. The level of transmission was reduced only very slightly in the vaccine scenario compared with the reference. None of the scenarios we studied resulted in major effects on transmission to the vector within the 20-year time span. After 10 years of vaccination, the incidence of uncomplicated episodes in 5–9-year-old children remains lower than in unvaccinated children, while severe episodes and mortality incidence have slightly increased in incidence in this age group (Figure 3). This is because the prevention of infections reduces the acquisition of asexual blood stage immunity. By the end of the 20-year follow-up period, all incidence measures are somewhat higher in the 10–19-year-old age group of the vaccinated population, although the cumulative number of events they have experienced over the whole 20-year period is reduced.

The approximately linear increase in cumulative numbers of deaths averted (Figure 4c) indicates that the vaccine reduces mortality by a more or less constant amount throughout the 20-year intervention period. Overall, vaccination also leads to substantial reductions in the incidence of uncomplicated episodes of malaria over the 20-year follow-up (Figure 4), but the benefit of the vaccination program in preventing uncomplicated episodes decreases over time, as indicated by a reduction in the gradient of the curve over time (Figure 4a).

The decay in the benefit was even more marked when assessed in terms of numbers of severe episodes (Figure 4b). After 10 years of vaccination the overall incidence of severe episodes returns to a level similar to that in the absence of
vaccination. This is due to the shift in incidence to older ages (Figure 3b).

The average effectiveness of the vaccine over the 20-year follow-up period differed for the different clinical outcomes. The average effectiveness in preventing uncomplicated episodes and death were 0.067, and 0.12, respectively (Figure 5). The overall effectiveness of 0.052 in preventing severe episodes is difficult to interpret because of the heterogeneity in the effect over time.

**Effect of vaccine efficacy.** We considered four different values for the initial efficacy of the vaccine (Table 1). An efficacy of 30% corresponds approximately to the lower limit that phase IIb clinical trials have so far been powered to detect. Vaccines with lower efficacy than this are unlikely to be considered for further development. An efficacy of 52% corresponds to our best estimate of the initial efficacy of the RTS,S/AS02A vaccine in a recent trial in Mozambique\(^1\) (this is higher than the average efficacy measured during the trial\(^3\)). An efficacy of 80% corresponds to a rule of thumb often used to evaluate partially efficacious vaccines, while an efficacy of 100% corresponds to a perfect vaccine, and thus allows us to assess the maximum possible effect achievable by our model of vaccine delivery.

An increase in the vaccine efficacy (defined as the proportion of infections averted) results in a near-proportional increase in effectiveness over the whole 20-year follow-up, whether this is measured in terms of prevention of uncomplicated, severe, or fatal episodes (Figures 4 and 5a). The cumulative number of events averted is highest for the most efficacious vaccine with effects on uncomplicated episodes and mortality approximately proportional to the initial efficacy, but only a vaccine with a very high efficacy remains effective in reducing the incidence of severe episodes in the latter part of the 20-year follow-up period (Figure 4). The effects of changes in efficacy on age-prevalence of parasitemia or anemia or in the age-incidence of clinical events in the low and high-efficacy scenarios are similar to those in the reference scenario.

**Effects of waning of the protective effect of the vaccine.** Assuming a faster decay of the vaccine effect leads to a reduction in all effectiveness measures, and the converse is observed when the rate of decay is decreased. The effectiveness against uncomplicated episodes is roughly proportional to the half-life (Figures 5b and 6a). However, effectiveness for the other clinical outcomes does not increase linearly with half-life (Figure 5). An increase of the half-life from six months to...
one year has little effect on the effectiveness against severe episodes or mortality, but there is a marked increase in effectiveness if the half-life increases to two years (Figure 6b and c). There is only a small further improvement in increasing half-life from 2 to 5 or 10 years.

Effect of vaccination coverage. The effect of varying the values of coverage is similar to the effect of varying the initial efficacy, with a low coverage resulting in similar epidemiologic patterns to that of a reduced vaccine efficacy. Although increasing coverage to high levels can be of crucial importance with fully protective vaccines when the objective is to eliminate transmission, the impact of 100% coverage is more or less proportional to that of the 89% coverage in our reference scenario (Figure 7).

Effect of variation in efficacy between individuals. An all-or-nothing response to the vaccine (b = 0.01) results in a higher number of illness episodes and deaths averted than are found in a scenario with the same mean efficacy, but less variation between individuals. With such a vaccine, the population is equivalent to a mixture of individuals vaccinated with a 100% effective vaccine, together with unvaccinated individuals. As with the simulation of the 100% effective vaccine, however, the number of severe episodes averted decreases over time. This is due to the decay in the efficacy (simulated with a half-life of 10 years). If there is no decay in efficacy we expect the effectiveness of such a vaccine to increase with the coverage throughout the follow-up period.

When there is no heterogeneity in vaccine efficacy (b = 100,000), (Figure 8), the pattern is very similar to that of the reference vaccine (b = 10), in which the degree of heterogeneity was chosen to match the data of the RTS.S/AS02A vaccine trial in Mozambique.14

Effect of transmission intensity and seasonality. The absolute number of clinical episodes and deaths averted by a vaccine is affected by the transmission intensity in ways that changed over the course of the simulated vaccination program (Figure 9). For the first few years of follow-up, the number of events averted was lowest at low transmission intensity due to the lower numbers of events in the vaccinated age group. Protection against uncomplicated episodes increased over time, the effect on mortality remained approximately constant, and that on severe morbidity decayed at a much slower rate than in the reference scenario. A net reduction in incidence of severe episodes was consequently still evident after 20 years of follow-up, while the total number of deaths averted over the 20-year period was lower than in the reference scenario.

At high transmission the initial gains were similar to those seen for the reference scenario, but the overall incidence of
uncomplicated episodes became higher than that in the unvaccinated scenario after about 10 years of the vaccination program (Figure 9a and b). There was no such adverse effect on mortality rates, but the initial gain seen during the first 10 years of the program did not continue (Figure 9c).

Although the degree of seasonality hardly affects the cumulative number of deaths averted, the number of uncomplicated episodes averted is lower in the absence of seasonality than in the reference scenario. The cumulative efficacy against uncomplicated episodes is reduced from 0.067 to 0.050 in the absence of seasonality.

**DISCUSSION**

We use a stochastic simulation model of the transmission dynamics and epidemiology of *P. falciparum* malaria in endemic areas to assess the likely impact of a pre-erythrocytic vaccine introduced via the EPI. This is the first major attempt to combine dynamic modeling of malaria transmission with predictions of parasitologic and clinical outcome, using models that have been fitted to field epidemiology data from a range of sites across Africa.

We have based our simulations as much as possible on field data, but many uncertainties and approximations remain, both in our epidemiologic models and our model of vaccination. The uncertainty in the field estimate of efficacy of RTS,S/AS02A is substantial; the efficacy of incomplete courses of vaccination is unknown, as is the rate of waning of vaccine efficacy.

We agree with previous dynamic models of the impact of malaria vaccination\(^ {15-18}\) that a leaky anti-infection vaccine will have little effect on transmission in endemic areas. Our estimates of transmission effects are even smaller than those in most previous models because we predict that reduction in human infection will have little effect on infectiousness to vectors (except in the case of complete protection of a sub-set of the population). We nevertheless identify substantial potential public health benefits of vaccination because severe disease is largely concentrated in the first years of life (in our model this arises largely because of age-dependent cofactors\(^ 9\)) and can be averted by delaying exposure to blood-stage parasites.

We would expect a pre-erythrocytic vaccine to have much more effect on transmission in areas of unstable malaria such as highland areas of east Africa,\(^ {19}\) KwaZulu-Natal,\(^ {20}\) or areas of low transmission outside Africa. This raises the issue of whether the best delivery strategy in such areas might then be a mass vaccination campaign, contributing to local elimination. Mathematical models of the impact of such a vaccination program need not consider the complexities of acquired clinical immunity, and so might reasonably be based on conventional compartment models.\(^ {17}\) Extension of these models to
allow appropriately for heterogeneities in transmission would be of critical importance.

In our model, the dynamics result mainly from a cohort effect on coverage and from the dynamics of immunity, rather than from effects on transmission. Since the effectiveness of vaccination (the proportion averted of all the events in the population) cannot reach equilibrium until after the oldest people are vaccinated, even 20-year simulations do not approach equilibrium. Effectiveness in the initial years of a program is likely to be much lower than vaccine efficacy because only a small proportion of the people will be vaccinated.

The 20-year time horizon allows us to see that the effect of a vaccine program on illness incidence will change over time, although we predict a roughly constant reduction in the crude mortality rate throughout the follow-up. After approximately 10 years, there is a net reduction in cumulative numbers of clinical episodes only in low transmission scenarios, with a predicted increase in high transmission. This is due to an increase in severe malaria incidence in children greater than five years of age who have accrued less immunity to asexual blood stage parasites during their childhood. This partly results from the models used for predicting uncomplicated episodes and severe malaria, which are fitted to data that suggest the lifetime number of clinical episodes and the incidence of hospital admissions for severe malaria are highest at intermediate levels of transmission.

With a vaccine with high efficacy in a proportion of the population (i.e., with a low value of b), effectiveness continues to increase as the vaccinated proportion increases, although in our simulations this effect is gradually lost due to decay in vaccine efficacy. With vaccines with partial efficacy in all individuals (the model we propose for RTS.S/AS02A), the factors attenuating the efficacy such as interactions with the epidemiologic effects of acquired immunity become more important as the vaccination program proceeds. In very low transmission settings, we predict initial increases in effectiveness because the proportion vaccinated increases before the first vaccinees leave the age range of high vulnerability. At higher transmission, there is little evident increase in effectiveness as the number of fully vaccinated individuals increases.

Since no vaccinated child reached more than 20 years of age in our simulations, very long-term effects of vaccination are not captured. This is important when comparing different decays or initial efficacies because the relationship between the duration during protection and the life expectancy of the vaccinated individual may be important in determining the effectiveness. However, we are very uncertain about the risk of severe malaria that such adults would experience. There are few data available from which to estimate severe malaria risk in adolescents or adults with limited previous exposure.

Vaccination reduces the incidence of uncomplicated episodes because it leads to fewer successful infections. The reduced exposure to parasites leads to less acquired asexual stage immunity; thus, the longer-term level of clinical protection is lower than the initial efficacy. In our models, the pyrogenic threshold, which determines the parasite density that leads to acute illness, also depends on the recent exposure to parasites and is therefore lower in vaccinated individuals. Vaccination can also modify the proportion of acute episodes that are severe by leading to a shift in clinical episodes to an older age, when the host is protected from co-morbidity and from other age-dependent factors enhancing susceptibility. With an efficacious vaccine, efficacy against severe malaria may be greater than that against infection. Conversely, if the vaccine does not offer a sufficiently high level of protection for a long enough time, the lower level of asexual stage immunity means that an increased proportion of clinical attacks result in severe malaria.

The application of our models can be extended not only to include other means of deployment (including regimens with booster doses of vaccines), to other types of vaccines (asexual blood stage and transmission blocking), and to consider the inclusion of vaccination within integrated control programs. We have seen that a pre-erythrocytic vaccine will be most effective at low transmission intensities, but that on its own it is unlikely to reduce transmission very much except possibly when this is already low. It may be that such a vaccine will be most effective if deployed in conjunction with vector control measures that reduce the vectorial capacity at the same time.

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REFERENCES