Vaccine approaches to malaria control and elimination: Insights from mathematical models

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Article history:
Available online 23 October 2015

Keywords:
Malaria
Vaccine
Trial design
Mathematical model
Transmission

A R T I C L E   I N F O

A licensed malaria vaccine would provide a valuable new tool for malaria control and elimination efforts. Several candidate vaccines targeting different stages of the malaria parasite’s lifecycle are currently under development, with one candidate, RTS,S/AS01 for the prevention of Plasmodium falciparum infection, having recently completed Phase III trials. Predicting the public health impact of a candidate malaria vaccine requires using clinical trial data to estimate the vaccine’s efficacy profile—the initial efficacy following vaccination and the pattern of waning of efficacy over time. With an estimated vaccine efficacy profile, the effects of vaccination on malaria transmission can be simulated with the aid of mathematical models.

Here, we provide an overview of methods for estimating the vaccine efficacy profiles of pre-erythrocytic vaccines and transmission-blocking vaccines from clinical trial data. In the case of RTS,S/AS01, model estimates from Phase II clinical trial data indicate a bi-phasic exponential profile of efficacy against infection, with efficacy waning rapidly in the first 6 months after vaccination followed by a slower rate of waning over the next 4 years. Transmission-blocking vaccines have yet to be tested in large-scale Phase II or Phase III clinical trials so we review ongoing work investigating how a clinical trial might be designed to ensure that vaccine efficacy can be estimated with sufficient statistical power. Finally, we demonstrate how parameters estimated from clinical trials can be used to predict the impact of vaccination campaigns on malaria using a mathematical model of malaria transmission.

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1. Introduction

Following the declaration of the Millennium Development Goals in 2000, increased funding for malaria control has resulted in an estimated 42% reduction in global malaria mortality [1]. This success has been largely attributed to the increased scale up of coverage of long-lasting insecticidal nets (LLINs) and expanded access to effective treatment with Artemisinin Combination Therapies (ACT) [1]. Despite this, the burden of malaria remains high, with an estimated 584,000 (367,000–755,000) deaths in 2013, the majority in young children in sub-Saharan Africa [1]. Therefore, there remains a pressing need to build on the gains made with existing interventions through the development and deployment of novel tools. Malaria vaccines may provide a wide range of benefits: providing personal protection from infection and episodes of clinical malaria to vaccinated individuals; reducing population level transmission in a community, and achieving and sustaining elimination in areas of low transmission.

Malaria vaccine candidates have conventionally been classified according to the stage of the life-cycle targeted [2]. Pre-erythrocytic Vaccines (PEV) target sporozoites and hepatic forms in the liver, potentially providing protection from infection. Blood-stage Vaccines (BSV) target merozoites and infected red blood cells, preventing episodes of symptomatic clinical malaria and helping to clear blood-stage infections. Sexual-stage Mosquito-transmission-blocking vaccines (SSM-TBV) target the sexual stages of the Plasmodium parasite in the human or mosquito preventing onwards transmission but not necessarily providing direct protection to the vaccinated individual. Both PEVs and SSM-TBVs are a major focus of current research efforts [2]. PEVs and SSM-TBVs are likely to have similar effects on a population level, causing reductions in transmission in the community [3]. However, on an individual level, it will be possible to measure the effect of PEVs, but not the effect of SSM-TBVs which do not provide direct protection to vaccinated individuals.

A number of candidate Plasmodium falciparum PEVs are currently under development based either on sub-unit approaches
where vaccination induces immune responses to targeted antigens \[4–6\], or whole parasite approaches where exposure to attenuated sporozoites may induce strong, broad-spectrum immune responses \[7–9\]. RTS,S/AS01, which induces strong immune responses targeting the circumsporozoite protein (CSP), is the most advanced vaccine candidate having recently completed Phase III trials. Efficacy against clinical malaria over one year of follow-up was 55.8% (97.5% CI: 50.6–60.4%) in children age 5–17 months \[4\], but was significantly lower in infants aged 6–12 weeks (31.3%, 97.5% CI: 23.6–38.3%) \[5\]. A number of candidate SSM-TBVs are also in development against both \emph{P. falciparum} and \emph{P. vivax}, albeit at a much earlier stage \[10\]. These can be divided into vaccines which target parasite surface antigens expressed either in the pre-fertilisation stages within the human (for example Pf48/45 and Pf5230) or the post-fertilisation stage within the mosquito (for example Pf525 and Pf528) \[11\]. Only one of these candidates has gone through Phase I human clinical trials (Pf525 \[10\] for \emph{P. falciparum} and Pvs25 \[12\] for \emph{P. vivax}).

The key parameters that must be measured in order to assess the impact of both PEV and SSM-TBV malaria vaccines are their efficacy (against infection, clinical disease, or onwards transmission) and the duration of protection (often measured in terms of half-life). For PEV clinical trials, vaccine efficacy against both infection (through active detection) and against clinical disease has been estimated with a high degree of statistical power \[4,5,13\]. However, in these trials it has been more challenging to estimate the duration of vaccine-induced protection \[14,15\]. For SSM-TBVs, studies to date have estimated the decrease in either the intensity or prevalence of onward infection to mosquitoes, using membrane or direct feeds \[16,17\]. The challenges with measuring efficacy in a field setting are considerable and no other trials of malaria interventions have as yet attempted to directly measure impact on onward transmission in the community. A further challenge is to translate estimates of vaccine efficacy and duration of protection into their potential public health impact. Although direct measurement can be made from PEV clinical trials, these are restricted by the characteristics of the trial (transmission intensity, age profiles, duration of follow up), and cannot be easily extrapolated to other areas where vaccination is being considered. For SSM-TBVs, there is unlikely to be a direct estimate of public health impact from a trial. In both cases, mathematical models of malaria transmission provide the most rational approach to estimate the public health impact of malaria vaccines across a wide range of settings \[18–21\].

Here, we present an overview of these challenges with a focus on determining the public health impact of future malaria vaccines.

2. Mathematical models of malaria transmission

Mathematical models can provide valuable tools for interpreting the results of malaria vaccine trials, and for estimating the effectiveness of malaria vaccination campaigns beyond trial settings. They can account for the dynamics of transmission of malaria between humans and mosquitoes, and the non-linear effects of reducing transmission through vaccination. A number of approaches of varying complexity for modelling malaria transmission have been successively pursued \[19,20,22\]. In this manuscript, we utilize a previously published model that accounts for the effect of vaccination on the acquisition of immunity to malaria \[23\]. The model is based on the Ross–MacDonald models \[22\] and accounts for the age and exposure dependent acquisition of immunity, heterogeneity and seasonality in exposure, and the impact of a range of interventions.

3. Pre-erythrocytic vaccine efficacy profiles

The safety, immunogenicity, and efficacy of candidate vaccines are estimated in clinical trials. Controlled human malaria infection (CHMI) studies can be used to obtain an initial estimate of efficacy in naive volunteers. CHMI studies played a key role in the development of the RTS,S malaria vaccine, providing early demonstrations of safety \[24\], immunogenicity \[25\], and efficacy against infection \[26\]. Similarly, most second generation vaccine candidates will be first tested in CHMI trials \[27\].

The primary efficacy endpoint for PEV CHMI studies has been efficacy against infection in the first month after vaccination. Estimates of efficacy are conventionally presented as point estimates, for example based on the proportion of vaccinated individuals protected following challenges with \emph{P. falciparum} infectious mosquito bites \[6,7,26\]. Several studies have tested the duration of vaccine-induced protection from infection via re-challenge after vaccination \[8,26\]. However the design of these studies often involves selection of individuals for re-challenge conditional upon being protected after a primary challenge. For example, when Kester et al. \[26\] re-challenged RTS,S vaccinated participants 5 months after vaccination, participants were selected conditional upon being protected during their first challenge. Thus, care must be taken when interpreting estimates of efficacy at re-challenge from CHMI trials, as individuals who were protected following primary challenge are not necessarily representative of the population as a whole.

Once efficacy has been established in CHMI studies, field trials are needed to establish efficacy under natural exposure conditions in partially immune individuals residing in endemic areas. When evaluating the efficacy of a PEV, a number of endpoints are generally considered, including \emph{P. falciparum} infection, episodes of clinical malaria, and episodes of severe malaria \[28\]. In clinical trials of PEVs under conditions of natural malaria exposure, efficacy is evaluated by comparing the number of events in a vaccinated and a control cohort over a given period of time. Point estimates of efficacy can be calculated as the rate ratio based on the number of episodes in each cohort or as the hazard ratio based on time to episodes in each cohort \[29,30\].

If there is substantial waning of vaccine efficacy over time, then a single point estimate of efficacy will provide only part of the picture. This is particularly important in the case of malaria vaccines where components of naturally acquired and vaccine-induced immune responses have been observed to be short-lived \[15,31\]. Fig. 1 provides an example of how vaccine efficacy against infection may wane over time, and the associated limitations of point estimates of efficacy. In particular point estimates of efficacy against infection from CHMI trials at primary challenge may differ from point estimates from field trials measured over a long time window due to waning of efficacy. We define the vaccine efficacy profile as the combination of the initial efficacy against infection immediately following vaccination and the pattern of waning of efficacy over time.

A number of statistical methods for assessing waning vaccine efficacy over time have been utilized. These include testing for parametric or non-parametric patterns of waning \[32,33\], or methods for incorporating time-dependent covariates in proportional hazards models such as Schoenfeld residuals or Anderson Gill modification \[14,29,34\]. Such estimation of patterns of waning has predominantly been done in post hoc analyses. Future malaria vaccine candidates should therefore incorporate statistical methods for estimation of duration of protection into earlier stages of their trial design.

4. Example: The vaccine efficacy profile of RTS,S

Fig. 2 shows an example of how RTS,S-induced anti-CSP antibody titres, efficacy against infection, and efficacy against clinical malaria change over time based on model estimates from data from nine Phase II trials \[15\]. Similarly to naturally-acquired antibody
responses [31], RTS,S-induced anti-CSP antibody titres wane over time (Fig. 2a). In particular waning titres follow a bi-phasic exponential pattern with rapid waning in the first 6 months followed by a much slower rate of waning over the next 5 years. The short-lived nature of the RTS,S induced antibody responses is in contrast to vaccine-induced responses to other pathogens which can be very long-lived [35]. It has been hypothesized that boosting of vaccine-induced immune responses due to natural exposure may occur [36], although this has never been observed for a malaria vaccine in clinical trials.

RTS,S induced anti-CSP antibodies have been observed to be associated with (i) protection from P. falciparum infection in controlled human malaria infection (CHMI) studies in the laboratory [26,37]; (ii) protection from P. falciparum infection under conditions of natural exposure in field trials [38,39]; and (iii) protection from episodes of clinical malaria in field trials [40]. Fig 2b shows the dose–response relationship between anti-CSP antibody titres and protection from infection based on model estimates from data from Phase II trials [15]. Notably, it is assumed that the dose–response relationship is the same for all vaccinees and remains constant over time. Given the anti-CSP antibody dynamics and the dose–response relationship, the vaccine efficacy profile against infection for RTS,S can be estimated (Fig. 2c). This results in a bi-phasic exponential pattern with rapid waning in the first 6 months followed by a slower rate of waning over the next 5 years. There is substantial variation in efficacy between individuals due to the variation in vaccine-induced antibody titres.

Efficacy against clinical malaria will change over time due to waning efficacy against infection (caused by waning anti-CSP antibody titres), and due to the different rates of acquisition of natural immunity in the vaccine and control cohorts [41,42] (Fig. 2d). Individuals in the control cohort tend to experience more episodes of clinical malaria than individuals in the vaccine cohort, and hence develop natural immunity at a faster rate [43]. This differential acquisition of immunity between cohorts means that efficacy against clinical malaria decays faster than the underlying profile of efficacy against infection. The prediction of negative efficacy after approximately 4 years is due to the higher incidence at that time in the vaccine group compared to the control group as a consequence of the delayed acquisition of clinical immunity. However, the total number of cases averted by vaccination over the child’s lifetime is always predicted to be positive, in agreement with data from the Phase III trial of RTS,S [44]. We define the decay of vaccine efficacy to be the combination of waning of vaccine-induced immune responses and the higher levels of natural immunity in the control cohort compared to the vaccine cohort. As such, the decay of vaccine efficacy will depend on transmission intensity, with more rapid decay in high transmission settings [45]. This pattern is clear in site-specific analyses of data from Phase III trials of the RTS,S vaccine [45], although there was insufficient statistical power to demonstrate statistical significance.

5. Estimating the efficacy of transmission-blocking vaccines

A range of laboratory methods have been developed to assess the effectiveness of SSM-TBV candidates [46]. The current gold standard is the mosquito feeding assay whereby laboratory reared mosquitoes are fed on infectious blood, either directly or through a membrane feeder, before being dissected 8–10 days later to determine the number of parasites (oocysts) that have developed on the midgut wall [16]. The difference in prevalence of oocyst between the control (untreated) mosquitoes and those exposed to the SSM-TBV candidate blood is used to estimate SSM-TBV efficacy. Care should be taken when analysing the results of these assays as the efficacy is thought to vary with the human-to-mosquito force of infection [17].

Once a SSM-TBV has been shown to be safe and there is evidence of transmission reducing ability from mosquito feeding studies, field trials are needed to demonstrate impact on onward transmission. In contrast to the Phase Ib/III trials undertaken for PEVs, a trial for SSM-TBV will need to be designed to estimate the impact on onward transmission. One approach is to use mosquito infection as a trial endpoint as a surrogate for onward infection. This would involve feeding studies using either membrane or direct feeding on trial participants [16]. A key advantage to such studies is their relative simplicity compared to the more complex designs needed to estimate impact on transmission (see below). However, the relationship between human and mosquito infection is not straightforward and may vary between settings [47]. It therefore remains unclear whether regulatory agencies would accept mosquito endpoints when granting licensure.

As for PEVs, early Phase II trials tend, by their design, to focus on estimates of initial efficacy, and not duration of protection. Here, exactly the same principles apply as those outlined for PEVs and a similar decay profile may be predicted (Fig.1). To provide an estimate of the duration of efficacy, a subset of those enrolled in the full field trials should be repeatedly sampled over a longer time period.

If it is decided that a Phase III clinical trial is required to prove effectiveness then a cluster-randomised control trial (CRCT) will be needed. It is unclear exactly what scale a CRCT should be carried out at to ensure the community benefits of a SSM-TBV are adequately captured [48]. Ultimately it will depend on the population density of the area (small compact versus sparsely populated villages), the availability of mosquito breeding sites (whether they are ubiquitous or concentrated in one place) and the degree of human movement. One approach to try and mitigate the impact of human and mosquito migration would be for each cluster to be surrounded by a buffer-zone (the so called “fried-egg” design) where the intervention is given but whose residences do not contribute to the primary endpoint of the study [48].
From a statistical point of view, the objective when designing a trial is to maximize statistical power. Low transmission areas are therefore generally not appropriate since only a small number of individuals are expected to become infected. Statistical power in general increases as the incidence of malaria increases. However, participants that develop disease during the trial will need to be treated, and it has been proposed that these treated individuals should be subsequently censored (removed) from the trial for a period of a few weeks to prevent the prophylactic effects of the drug from biasing estimates of susceptibility to malaria [48]. Hence, if effectiveness is measured as a reduction in clinical incidence then statistical power is likely to plateau at moderate to high transmission (Fig. 3). This means that the most suitable place to conduct a trial based on clinical incidence endpoints may be in a moderate transmission setting. Although the effects of censoring mean that moderate transmission settings are likely to be optimal for the evaluation of SSM-TBVs, from a public health point of view the effectiveness will be based on the total number of clinical cases averted.

In a SSM-TBV trial, participants receiving the vaccine acquire no direct protection from infection, and hence the appropriate endpoint is some measure of infection in the community. Whilst the time to the first clinical episode is the easiest endpoint to measure, its interpretation is complicated by the differential rates of acquisition of natural immunity by age and transmission site. An alternative is to use a direct measure of incidence of infection, for example, through active detection of infection in order to include new asymptomatic infections. However if all participants in the trial are treated following infection, then transmission in the community as a whole is likely to be modified, necessitating the same procedure to be carried out in both arms of the study to prevent biased estimates of vaccine efficacy. To overcome the problems of the clinical trial protocol in itself causing a change in transmission it has been suggested that only a small percentage of the cluster, a sentinel population, is monitored over time [48]. This would reduce the epidemiological impact of active case detection and treatment, though comes at the cost of substantially increasing cluster size and overall financial costs.

An important consideration when designing a Phase III trial is ensuring that the results are representative of the settings in which implementation is likely to occur. For SSM-TBVs, this results in a number of conundrums. Firstly, variation in transmission, seasonality, past history of interventions, immune status of the population, and genetic variation of individuals may all affect the ultimate efficacy of a vaccine. Capturing this variation in a trial is important for safety reasons, as well as for obtaining accurate efficacy estimates. However, variation between clusters decreases statistical power and hence necessitates more enrolled individuals,
increasing the cost of such a trial. Secondly, the setting where a partially efficacious TBV is likely to have the greatest impact is at low transmission, since in such settings the vaccine could potentially interrupt transmission leading to community benefit through herd immunity (whereby unvaccinated people are protected from infection by vaccinated individuals). However, the statistical power of trials in such settings is very low. Thus, it is likely that the true value of TBVs will only become apparent following licensure and Phase IV follow-up.

6. Predicting population impact

The population impact of a vaccine is dependent on the epidemiological setting in which it is deployed. Early phase clinical trials can estimate vaccine efficacy in individuals, but the effectiveness at reducing transmission and the number of cases in non-trial populations will be modified by factors such as transmission intensity, seasonality, mosquito species, coverage, compliance patterns, and the use of other control interventions. Financial constraints will limit the range of epidemiological settings where clinical trials can be undertaken. Mathematical models are therefore needed to extrapolate the effectiveness of a vaccine candidate to other settings where they are likely to be utilized. Equally it should be realized that Phase III clinical trials are dependent on the epidemiological and healthcare setting in which they took place and that vaccine effectiveness once deployed in the general population may be higher or lower than previously measured.

Key to understanding the population level impact of vaccination is the current level of transmission. The appropriate measure of transmission intensity to use will depend on the type of vaccine under investigation, but in most settings, the entomological inoculation rate (EIR, the number of infectious bites per person per year) provides a good metric and the malaria prevalence (as measured by microscopy, RDT, or PCR) a convenient alternative. Crucially, both are related to the basic reproductive number, $R_0$, which provides an indication of the vaccine effectiveness required to interrupt transmission [49]. One important consequence of the correlation between public health impact and transmission intensity is that there is no single “target” vaccine efficacy to achieve a given goal. For example, for RTS,S, whilst the lowest efficacy against disease was observed in the highest transmission settings, the greatest public health impact was also observed in these settings due to the higher underlying burden [45]. Similarly, the minimum efficacy required to achieve elimination will be lower in very low transmission settings, with vaccines alone unlikely to interrupt transmission in moderate or high settings.

The current transmission intensity will depend on the coverage of other interventions (e.g., vector control and first-line treatment) in place. Therefore, an area might have low transmission intensity either because there was low endemicity at baseline due to low mosquito densities or because other interventions have successfully reduced transmission [50]. It is not immediately clear whether it is just the current level of transmission that will determine vaccine effectiveness or whether the population’s history of infection will have an influence due to the previous acquisition of immunity (which may or may not interact with the vaccine induced immunity). Regardless, any new vaccine will need to be assessed in light of the ongoing background of other interventions and access to first-line treatment.

The effectiveness of vaccines with relatively short periods of protection will also vary according to the seasonality in malaria transmission. This seasonality could be driven by fluctuations in mosquito numbers or the use of other time-varying interventions such as indoor residual spraying. In areas of high seasonality, the shorter the period of optimal vaccine protection the more important it will be to time vaccination appropriately, with the maximum impact on the number of cases typically occurring immediately prior to the peak in transmission. Other facets of mosquito behaviour such as heterogeneity in biting will also influence population level effectiveness. For example, if there are hotspots of transmission and some people are bitten substantially more than others, then the relationship between disease prevalence and transmission intensity becomes increasingly non-linear [47,51]. Thus the ability of a vaccine campaign to reduce transmission also varies according to whether the people that are bitten the most had received the vaccine. It is therefore important to assess these heterogeneities as far as possible in clinical trials.

Integral to the effectiveness question is the potential delivery strategy for a new vaccine and the likely coverage of the target population that can be achieved. This will depend on whether
the goal of the programme is to reduce morbidity or to interrupt transmission. The latter will require a more comprehensive regimen and the minimum population coverage needed will vary between settings and according to vaccine profile. Cost will clearly be important for both of the vaccine itself, but also of the delivery strategy. For example, vaccines can be added to the WHO Expanded Program on Immunisation (EPI) to directly protect young children from disease, but the limited age range might not be suitable for all types of vaccines if the aim is to reduce population-level transmission. As such, EPI delivery is appropriate for PEVs but it is unlikely to be suitable for TBVs as older children and adults contribute significantly to the human reservoir of infection [52].

Fig. 4 shows a comparison using a mathematical model [23] of vaccination campaigns with PEVs and SSM-TBVs in a setting of moderate and seasonal malaria transmission intensity. Despite providing substantial protection to vaccinated children, a PEV administered through the EPI is expected to have limited impact on population level transmission. Mass vaccination campaigns with PEVs or SSM-TBVs may cause large reductions in population level malaria transmission, although the effect size will depend on transmission intensity, campaign coverage, vaccine efficacy and duration of protection.

7. Conclusions

The wide range of potential roles for malaria vaccines is a consequence of the diversity of approaches for targeting the Plasmodium parasite, which has multiple life stages in both the human and vector hosts. This is in contrast to viral pathogens such as measles with much simpler lifecycles. In the past, the complex nature of the Plasmodium lifecycle has been viewed as a challenge to the malaria vaccine development effort. However, it also provides opportunities to target the malaria parasite on multiple fronts. One area in which research is perhaps lacking is how best to combine PEVs, BSVs, and TBVs. Future research into the potential synergies of such an approach could prove valuable [53,54].

Development of malaria vaccines has been rapid over the last decade, with a wide range of candidates in the current pipeline [2]. Furthermore, the first malaria vaccine to complete Phase III trials, RTS.S, could become available to endemic countries within the next three years. Much has been learned during the development of the RTS.S vaccine, in particular in relation to the variability in vaccine efficacy between individuals and between individuals residing in different epidemiological settings. The implementation of Phase II and Phase III trials of RTS.S in greater than 20,000 participants in *P. falciparum* endemic countries has come at considerable financial cost, but at the same time provides a solid research basis to speed the development and evaluation of the next generation of malaria vaccines.

Acknowledgements

MTW is supported by a Population Health Scientist fellowship from the Medical Research Council (MRC) (Grant No. MR/L012170/1). RV and TSC are supported by PATH Malaria Vaccine Initiative. ACG acknowledges support from the Bill and Melinda Gates Foundation and MRC Centre funding. The authors would like to thank the UK MRC/UK Department for International Development (DFID) under the MRC/DFID Concordat agreement.

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