Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Michael T. White*, Robert Verity, Thomas S. Churcher, Azra C. Ghani

MRC Centre for Outbreak Analysis & Modeling, Department of Infectious Disease Epidemiology, Imperial College London, Norfolk Place, London W2 1PG, UK

ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form
14 September 2015
Accepted 15 September 2015
Available online xxx

Keywords:
Malaria
Vaccine
Trial design
Mathematical model
Transmission

ABSTRACT

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.

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

* Corresponding author. Tel.: +44 2075943946.
E-mail address: m.white08@imperial.ac.uk (M.T. White).

http://dx.doi.org/10.1016/j.vaccine.2015.09.099
0264-410X/

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 *P. falciparum* and *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 Pfs48/45 and Pfs230) or the post fertilization stage within the mosquito (for example Pfs25 and Pfs28) [11]. Only one of these candidates has gone through Phase I human clinical trials (Pfs25 [10] for *P. falciparum* and Pvs25 [12] for *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 naïve 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 *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 *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

Please cite this article in press as: White MT, et al. Vaccine approaches to malaria control and elimination: Insights from mathematical models. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.09.099