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Preparing for future efficacy trials of severe malaria vaccines

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Abstract

Severe malaria is a major cause of mortality in children, but comprises only a small proportion of *Plasmodium falciparum* infections in naturally exposed populations. The evaluation of vaccines that prevent severe falciparum disease will require clinical trials whose primary efficacy endpoint will be severe malaria risk during follow-up. Here, we show that such trials are feasible with fewer than 1,000 participants in areas with intense malaria transmission during the age interval when severe malaria incidence peaks.

Keywords

severe malaria; vaccine; clinical trial; immunity; sample size

Introduction

Clinical trials of malaria vaccines have used different endpoints to measure activity or efficacy, in part because malaria vaccines might reduce the number of malaria-related deaths through a variety of mechanisms. As examples, vaccines that prevent infection by targeting pre-erythrocytic parasites [1], or that block transmission to mosquitoes [2] and hence subsequent human infections, will ultimately have the effect of reducing burden of parasitemia and hence severe disease. Further, recent studies indicate that immunity against severe malaria can be acquired rapidly [3, 4] without reducing parasitemia [3], supporting

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

efforts to develop vaccines that prevent severe falciparum syndromes [5] by targeting factors involved in disease pathogenesis, such as parasite sequestration or virulence.

Despite these encouraging results, the experience of the multicenter RTS,S trial [6] has left the impression that many thousands of children are required to test the efficacy of vaccines against severe malaria, creating pessimism that future such trials will be undertaken. Here, we estimated the risk of severe malaria during infancy in an intensively followed Tanzanian birth cohort [3], and calculated sample sizes for future vaccine trials.

Material and Methods

We analyzed data from Mother-Offspring Malaria Studies (MOMS) Project at Muheza Designated District Hospital, Muheza. The study design and population are described in detail elsewhere [3]. Briefly, children were enrolled at birth, then seen every 2 weeks during infancy and every 4 weeks post-infancy for clinical and blood smear examinations, regardless of the presence or absence of fever and other symptoms. Whenever children became symptomatic, they were also examined by a study clinician. Study participants who developed severe malaria according to WHO criteria [7] were treated with parenteral quinine.

Ethics

Protocols for procedures used in this study were approved by the International Clinical Studies Review Committee of the Division of Microbiology and Infectious Diseases at the US National Institutes of Health. Ethical clearance was obtained from the Institutional Review Boards of Seattle BioMed and the National Medical Research Coordinating Committee in Tanzania. Written informed consent was obtained from mothers prior to enrollment.

Statistical analysis

Only children followed for at least one year (N=688), or for less than a year if they developed severe malaria during infancy (N=4), were included in our estimation of severe malaria risk in the first year of life. We performed sample size calculations for comparisons of severe malaria risk by tests of two proportions (power=80%; two-sided significance level=0.05). Data analyses were conducted using Stata 11.1 (StataCorp, Texas, United States).

Results

In this longitudinal study with active surveillance for infection and disease, 67/692 (9.7%) children experienced at least one severe malaria episode during infancy. A clinical trial of a vaccine that prevents severe malaria with 50% efficacy and with 1 year follow-up in a population where severe malaria risk is similar to ours would have required ~1,000 infants (479 in each study arm). In areas with low severe malaria risk (for example, 1%) during the same age period, the sample size required would be much higher (Figure 1). Very few infants (6/67, 8.9%) suffered their severe malaria episode during the first 4 months of life, suggesting that before this age children enjoy some form of intrinsic or passively transferred

immunity, and the optimal age to start an active post-vaccination follow-up is after this period.

Discussion

In our study, severe malaria risk during the age interval when its incidence peaks [3] is high: 1 in 10 study children developed at least one episode of severe malarial illness during infancy. The overall severe malaria incidence in our study [3] is similar to [8] or higher than [9] rates observed at other east African sites, however those studies used passive case detection which will underestimate severe malaria incidence. Our intensive follow-up and timely provision of treatment were expected to reduce the incidence of severe malaria and yet risk remained high. Taken together, our results indicate that vaccine trials designed to measure efficacy against life-threatening malaria are feasible with fewer than 1,000 children if performed in areas with intense transmission and during the age range when severe malaria peaks, even with frequent follow-up and prompt treatment of clinical cases.

The recent RTS,S Phase 3 trial enrolled 15,460 children and was powered (90%) to detect vaccine efficacy of 30% against clinical malaria [10] over a wide range of malaria transmission intensities. Severe malaria risk was a secondary efficacy endpoint and, although that trial involved more than 10 study centers, three sites (Siaya, Kintampo, and Kombewa) comprising roughly one third of the study population contributed more than two thirds of all severe malaria events in the first year of the study [11]. A vaccine trial using severe malaria risk as primary endpoint in an area where the baseline risk is similar to that observed in the RTS,S Phase 3 trial (~2.5%) would be feasible, assuming 80% power, with a study population < 2,000 individuals, one year of follow-up and vaccine efficacy of 70% or more. This baseline risk is probably much higher in some study sites (Siaya, for example), which implies that trials undertaken in these areas would probably need to enroll < 1,000 individuals to test highly effective vaccines against severe malaria.

In this study, we did not observe cerebral malaria episodes. The incidence of this syndrome is inversely related to malaria transmission intensity [12] and in areas with high levels of transmission, similar to our study site, this clinical presentation is uncommon. Trials to test malaria vaccines that specifically target pathogenic processes related to cerebral malaria would need to be undertaken in areas with moderate or low transmission, where this syndrome represents a higher proportion of severe malaria events. A similar pattern has been observed in areas where falciparum epidemiology is transitioning from high to low transmission intensity [13]: while the total number of malaria-related hospitalizations might remain stable for several years, an increasing proportion of life-threatening malaria presents as cerebral malaria. In low transmission areas, severe malaria incidence peaks at older ages and over a wider age range, and thus vaccine trials would need to recruit older children and likely require a larger sample size or longer follow-up to measure efficacy against cerebral malaria.

Over the last 15 years, malaria burden has decreased in Sub-Saharan Africa [14]. As exposure to malaria parasites becomes infrequent, the overall risk of developing severe disease might not decrease [13, 15] and interventions that specifically prevent severe malaria

will become even more important. Vaccines that prevent severe malaria by blocking parasite egress from erythrocytes, by neutralizing parasite virulence factors, or by inhibiting parasite sequestration in deep vascular beds might play an important role in reducing malaria-related mortality. Our observations suggest that trials designed to test these vaccines are feasible in areas with high malaria incidence, although setting-specific factors need to be considered: incidence might vary from year to year and sample size calculations should be conservative and allow for fluctuations in the risk of severe malaria; as transmission declines, the total number of severe malaria events might also decline, remain stable or even increase. Therefore, clinical trials should be powered for scenarios where life-threatening malaria rates decrease with infection incidence, as often happens when trial activities begin. Additionally, sample size calculations would be facilitated by realistic expectations of vaccine efficacy, but unfortunately animal models do not exist for that purpose. Epidemiological studies that measure variations in risk based on hypothetical mechanisms of severe disease immunity, such as antibodies against parasite virulence factors, may be useful for estimating efficacy of vaccines that target these mechanisms.

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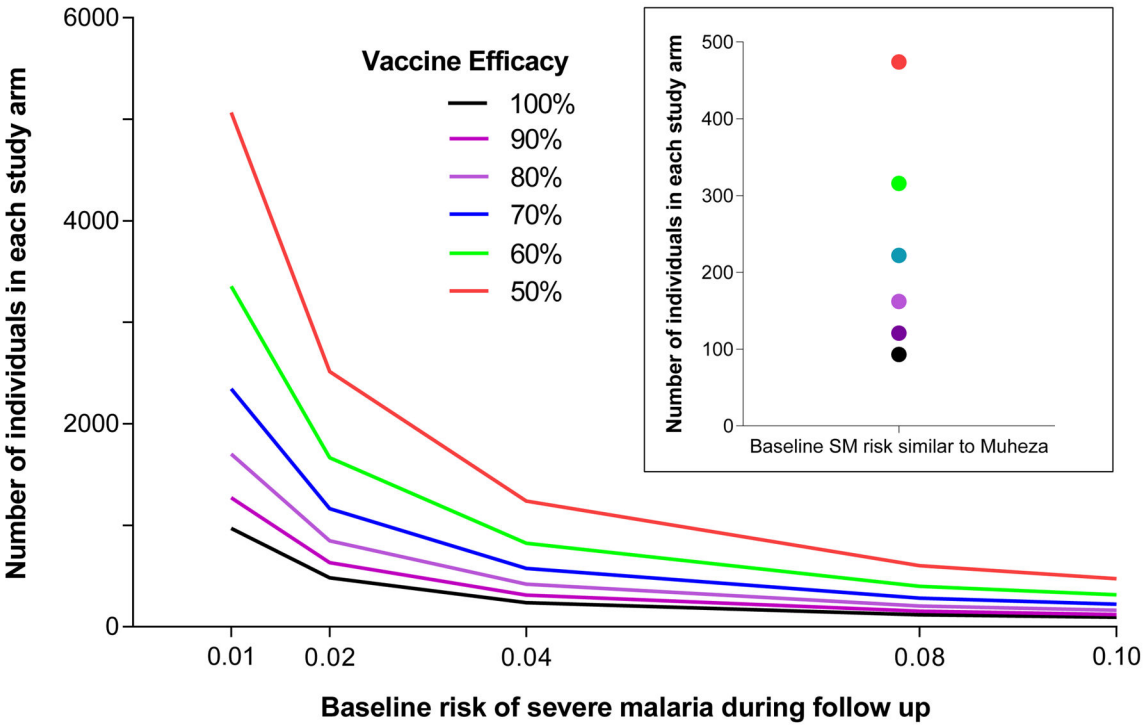

Figure 1.

Sample sizes (per study arm; y-axis) for trials that test efficacy against severe malaria by baseline severe malaria risk (x-axis) and vaccine efficacy. Calculations for trials in areas with risk similar to Muheza (9.7%) are presented in the inset.