Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Review

Design of a Phase III cluster randomized trial to assess the efficacy and safety of a malaria transmission blocking vaccine

Isabelle Delrieu[a,*], Didier Leboulleux[b], Karen Ivinson[c], Bradford D. Gessner[a], Daniel Chandramohan[d], Thomas Churcher[e], Chris Drakeley[d], Elizabeth Halloran[f], Gerry Killeen[g,h], Immo Kleinschmidt[d], Paul Milligan[d], Vincent Robert[i], Christophe Rogier[j], Allan Saul[k], Robert Sinden[l], Thomas Smith[m], For the Malaria Transmission Blocking Vaccine Technical Consultation Group

[a] *Agence de Médecine Préventive, 13 Chemin du Levant, 01210 Ferney-Voltaire, France*
[b] *PATH, Bâtiment Avant Centre, 13 Chemin du Levant, 01210 Ferney-Voltaire, France*
[c] *PATH, 207 Route de Ferney, 1218 Grand Saconnex, Geneva, Switzerland*
[d] *LSHTM, Keppel Street, London WC1E 7HT, United Kingdom*
[e] *Imperial College, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom*
[f] *University of Washington and Hutchinson Research Center, 1100 Fairview Ave N, Seattle, WA 98109, United States*
[g] *Liverpool School of Tropical Medicine, Liverpool L35QA, United Kingdom*
[h] *Ifakara Health Institute, PO Box 53, Ifakara, Tanzania*
[i] *Institut de Recherche pour le Développement, BP 64501, 34394 Montpellier cedex 5, France*
[j] *Institut Pasteur de Madagascar, B.P. 1274, Ambatofotsikely, 101 Antananarivo, Madagascar*
[k] *Vaccines Institute for Global Health, Via Fiorentina 1, 53100 Siena, Italy*
[l] *Imperial College, South Kensington Campus, Exhibition Road, London SW7 2AZ, United Kingdom*
[m] *Swiss Tropical and Public Health Institute, Socinstr. 57, 4051 Basel, Switzerland*

ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form 16 January 2015
Accepted 20 January 2015
Available online xxx

Keywords:
Transmission blocking vaccine
Malaria
Trial design
Cluster randomized trial

ABSTRACT

Vaccines interrupting *Plasmodium falciparum* malaria transmission targeting sexual, sporogonic, or mosquito-stage antigens (SSM-VIMT) are currently under development to reduce malaria transmission. An international group of malaria experts was established to evaluate the feasibility and optimal design of a Phase III cluster randomized trial (CRT) that could support regulatory review and approval of an SSM-VIMT. The consensus design is a CRT with a sentinel population randomly selected from defined inner and buffer zones in each cluster, a cluster size sufficient to assess true vaccine efficacy in the inner zone, and inclusion of ongoing assessment of vaccine impact stratified by distance of residence from the cluster edge. Trials should be conducted first in areas of moderate transmission, where SSM-VIMT impact should be greatest. Sample size estimates suggest that such a trial is feasible, and within the range of previously supported trials of malaria interventions, although substantial issues to implementation exist.

1. Introduction

Over the past decade, with the scale-up of preventive, diagnostic and treatment measures, significant progress has been achieved in reducing malaria burden (Fig. 1). However, during 2012 an estimated 3.4 billion people remained at risk of malaria, most of them in sub-Saharan Africa. Existing measures may not be sufficient to achieve effective control and possible elimination; these measures are limited by less than optimal implementation of World Health Organization (WHO) policies and recommendations at country level, stagnation in international malaria control funding [1], increasing mosquito resistance to insecticides [2], and drug-resistance of malaria parasites [3]. In this context, additional interventions, such as malaria vaccines, may constitute a key component of a global malaria eradication package [4,5].

During 2013, the Malaria Vaccine Technology Roadmap was updated, and included among other strategic goals for 2030 development of vaccines interrupting malaria parasite transmission (VIMTs) [6]. VIMTs are under development, which can, in principle,

* Corresponding author. Tel.: +33 153 86 89 22.
E-mail addresses: idelrieu@aamp.org (I. Delrieu), dleboulleux@path.org (D. Leboulleux), kivinson@path.org (K. Ivinson), bgessner@aamp.org (B.D. Gessner).

http://dx.doi.org/10.1016/j.vaccine.2015.01.050
0264-410X/

Fig. 1. Trial participant mother sets up mosquito netting.
Photo by John Michael Maas, Darby Communications.

block different stages of the malaria parasite lifecycle. VIMTs targeting sexual, sporogenic, or mosquito-stage antigens (SSM-VIMT) (Fig. 2) aim to prevent human malaria infection in vaccinated communities by inhibiting parasite development within the mosquito after a blood meal taken from a human carrier with circulating gametocytes [7,8]. Hence, vaccination does not provide the vaccinees with immediate direct protection against infection or disease; instead, vaccination blocks maturation of gametocytes ingested by a mosquito into oocysts and sporozoites, which in turn blocks transmission from the mosquito to other humans [9]. By this means, the vaccine recipient and his or her community receive protection against secondary infection.

Before embarking on a time-consuming and expensive clinical development of an SSM-VIMT, investigators and regulators need to agree on the regulatory requirements and most efficient acceptable clinical development pathway. One option is to follow a clinical regulatory pathway that would include Phase I and Phase II trials followed by a large scale population-based Phase III trial evaluating efficacy against infection and clinical endpoints. The current manuscript presents the results of a working group whose objective was to identify key design issues, preferred methodology, and technical and operational requirements for the Phase III trial of such a pathway. The goal was to develop a plan sufficiently detailed for agencies such as the US Food and Drug Administration (FDA) to assess whether this design could, in principle, lead to licensure.

To achieve these objectives, the Malaria Vaccine Initiative (MVI; a program of the international public health organization PATH), with the help of the Agence de Médecine Préventive (AMP), established a working group of international experts across a broad range of malaria disciplines relevant to an SSM-VIMT Phase III trial. This paper provides a synopsis of the conclusions drawn from the evaluation process conducted by this group.

2. Methods

2.1. Technical consulting group

MVI organized a working group (all included as authors of the current manuscript) with the objectives to develop and define key design aspects for an SSM-VIMT Phase III cluster randomized trial (CRT); document study feasibility; and provide sufficient details for the US FDA to discuss the constraints and limitations of a prelicensure CRT, and to assess whether this design could in principle lead to licensure. To achieve these objectives, MVI brought together 13 experts on clinical trial design, malaria epidemiology, malaria entomology, and statistics, for a face-to-face meeting at the PATH Europe office in Ferney-Voltaire, France. External observers were included in the discussions, with participants from the WHO, PATH, MMV (Medicines for Malaria Venture), AMP, and GlaxoSmithKline (GSK), which has malaria vaccines in development. We concentrated our efforts on designing a Phase III trial, working from predefined assumptions on the outcomes of Phase I and Phase II trials.

Because the US FDA had previously indicated a preference for a CRT, and because an SSM-VIMT is by definition a community rather than an individual intervention, we focused on this design. This a priori bias has a scientific basis as well. The TBV coverage needed to interrupt transmission in any particular setting of malaria transmission and mosquito dynamics is unknown. In this context, any selected ratio of vaccinated to unvaccinated persons in an individually randomized trial may lead to substantial protection of

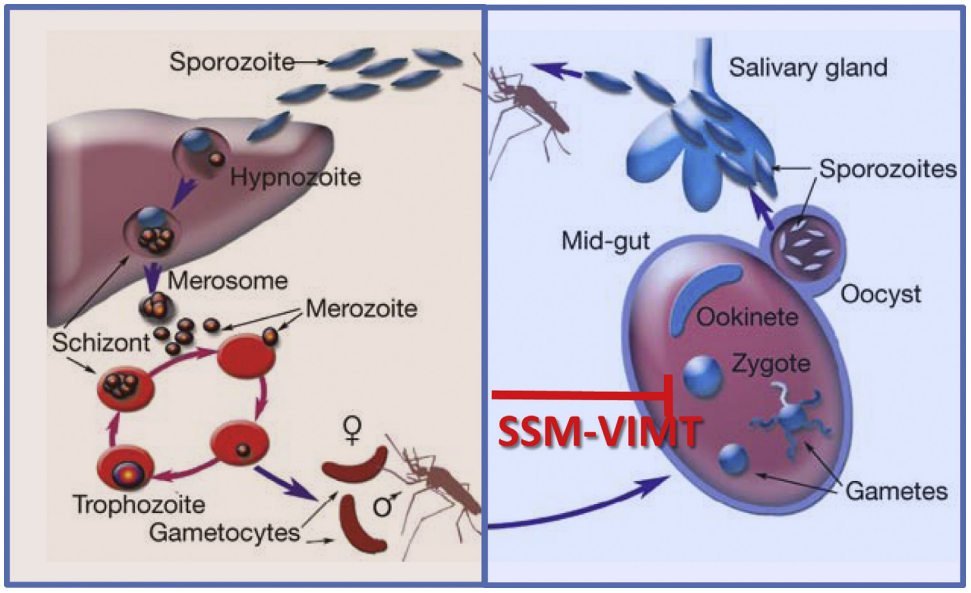

Fig. 2. Steps in the parasite life cycle affected by sexual, sporogenic, or mosquito antigen vaccines that interrupt malaria transmission (SSM-VIMTs). When ingested by a mosquito, antibodies produced by an SSM-VIMT vaccinated individual could interrupt maturation of gametocytes into oocysts and sporozoites
Adapted from Winzeler [7].

Please cite this article in press as: Delrieu I, et al. Design of a Phase III cluster randomized trial to assess the efficacy and safety of a malaria transmission blocking vaccine. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.01.050