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Perspective

Development of a transmission-blocking malaria vaccine: Progress, challenges, and the path forward

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ABSTRACT

New interventions are needed to reduce morbidity and mortality associated with malaria, as well as to accelerate elimination and eventual eradication. Interventions that can break the cycle of parasite transmission, and prevent its reintroduction, will be of particular importance in achieving the eradication goal. In this regard, vaccines that interrupt malaria transmission (VIMT) have been highlighted as an important intervention, including transmission-blocking vaccines that prevent human-to-mosquito transmission by targeting the sexual, sporogonic, or mosquito stages of the parasite (SSM-VIMT). While the significant potential of this vaccine approach has been appreciated for decades, the development and licensure pathways for vaccines that target transmission and the incidence of infection, as opposed to prevention of clinical malaria disease, remain ill-defined. This article describes the progress made in critical areas since 2010, highlights key challenges that remain, and outlines important next steps to maximize the potential for SSM-VIMTs to contribute to the broader malaria elimination and eradication objectives.

1. Introduction

The 2013 update to the Malaria Vaccine Technology Roadmap (Roadmap) expanded the vision to develop "safe and effective vaccines against *Plasmodium (P.) falciparum* and *P. vivax* that prevent disease and death and prevent transmission to enable malaria eradication" and introduced an important new strategic goal: "The development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria (parasite) infection" [1]. This complemented the original 2006 Roadmap strategic goal of developing a highly efficacious vaccine to prevent clinical disease [2] and highlighted the definitive shift of the broader malaria community to a focus on the development of tools to accelerate elimination and eventual eradication of malaria. The leadership of the Bill & Melinda Gates Foundation (Gates Foundation), along with the World Health Organization (WHO), the Roll Back Malaria Partnership, and other key stakeholders, have challenged the malaria community to renew its efforts to eradicate malaria [3], therefore leading to a significant refocusing of associated product development efforts [4].

Over the last several years, as the malaria community began to embrace the challenge of eradication, questions arose about the

Abbreviations: CDP, clinical development plan; CHMI, controlled human malaria infection; CRT, cluster-randomized trial; DFA, direct feeding assay; DMFA, direct membrane feeding assay; malERA, Malaria Eradication Research Agenda; MALVAC, malaria vaccine advisory committee; MESA, Malaria Eradication Scientific Alliance; MVI, PATH, Malaria Vaccine Initiative; Roadmap, Malaria Vaccine Technology Roadmap; SMFA, standard membrane feeding assay; SSM-VIMT, sexual, sporogonic, mosquito stage vaccine to interrupt malaria transmission; TBV, transmission-blocking vaccine; TM&E, transmission measures and epidemiology; TPP, target product profile; VIMT, vaccine to interrupt malaria transmission.

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feasibility of such an endeavor, the tools and strategies that would enable it, and the gaps that would need to be addressed in order to support eradication as a long-term goal. A number of meetings and consultations took place in and around 2010 to define the research agenda for malaria eradication, including those associated with the development of a malaria vaccine to interrupt malaria (parasite) transmission (VIMT) [5–16]. Initially *P. falciparum* and *P. vivax* were prioritized, with the recognition that to truly eradicate malaria, all species that infect humans must eventually be addressed. This article describes the progress that has since been made in critical focus areas identified during those meetings (Clinical development pathway and regulatory strategy; Assays; Transmission measures and epidemiology; Communications and ethics; Policy and access; Process development and manufacture; specific challenges associated with targeting *P. vivax*), and highlights the next steps that will be critical to developing the classes of vaccines needed to support the community's malaria-eradication goals, as laid out in the revised Roadmap.

While vaccines have the potential to interrupt malaria transmission at multiple points in the parasite lifecycle, this paper will focus on strategies targeting the sexual, sporogonic, and mosquito (SSM) stages of the parasite (hereafter referred to as an SSM-VIMT), which are involved in the transmission of malaria parasites from an infected person to a female mosquito, rather than those involved in parasite infection of the human host or causing malaria disease. While not a novel concept, as evidenced by the 2000 meeting report on transmission-blocking vaccines (TBVs), "an ideal public good" [17], the product development resources now available to apply to the development of such products have created significant new opportunities. Unique development challenges associated with this class of VIMT, most notably the delayed as opposed to immediate benefit conferred to immunized individuals, require special consideration.

2. Ideal characteristics of an SSM-VIMT

The availability of a target product profile (TPP), in which key preferred and minimally acceptable characteristics of the vaccine have been defined, at an early stage in development helps ensure alignment between the product developed and the developing-country context in which its use is intended [18,19]. The PATH Malaria Vaccine Initiative (MVI) presented a draft TPP for a stand-alone SSM-TBV against both *P. falciparum* and *P. vivax* that was used as the basis for discussion at the MVI-sponsored TBV workshop in 2010 and the malaria vaccine advisory committee (MALVAC) meeting the same year [15]. There was consensus among participants on a number of key elements, including that the vaccine would need to be amenable to campaign administration, and therefore safe for administration to all who may transmit malaria parasites, effective in as few doses as possible for as long as possible, and low cost [16]. The WHO is currently leading an effort to develop consensus preferred product characteristics to guide the community's progress toward developing a VIMT that meets the updated Roadmap goals; the characteristics with outstanding questions are described below.

A critical gap in the TPP is the required vaccine effect (a combination of factors including efficacy and coverage) [20] needed to support elimination efforts. Preliminary modeling data indicate that efficacy and coverage are equally important in the impact of a TBV [21]. Although the implications of this relationship on the required level of vaccine efficacy are not yet known, it is of critical importance to identify the minimally required efficacy (and coverage) to support defining stage-gate criteria that will inform early clinical decision-making. In addition to mathematical models (reviewed in the Malaria Eradication Research Agenda [malERA] Consultative Group on Modeling, 2011 [8]), biological and population models may also help to inform these criteria [20].

There is general agreement that a vaccine designed to contribute to elimination would need to be suitable for use in campaigns; however, it is still too early to have consensus on its exact formulation. In addition to the development of a stand-alone SSM-VIMT, which would not confer an immediate, direct benefit to the vaccine recipient, a vaccine targeting both SSM and other stage malaria antigens, a vaccine co-formulated with one targeting a different disease, and/or co-administration with another health intervention that targets the same population have been proposed. Strategies of combining antigens from different stages of the parasite lifecycle (such as RTS,S [22]) or of co-administering the vaccine with a transmission-blocking drug are some of those currently being explored and could prove to be synergistic, while leveraging the successes in product development to date.

There has been significant debate on the merits of targeting antigens that are expressed while the parasite resides in the human, thus creating opportunity for an anamnestic immune response upon subsequent infection. As elimination is approached, fewer and fewer infections will occur, perhaps making natural boosting of a protective immune response a less impactful attribute of a product's TPP. Furthermore, expression in the human increases the possibility that immune selection will lead to the proliferation of escape mutants. Additional data are therefore needed to support whether endemic boosting should be a critical attribute of an ideal SSM-VIMT.

3. Clinical development plan and regulatory pathway

The clinical development plan (CDP) and the basis of regulatory approval for an SSM-VIMT will likely be different from those applied to pre-erythrocytic and blood-stage malaria vaccines due to the methods in which vaccine effect will be established at the level of the community rather than the individual. In 2010, the major points of discussion on CDP/regulatory pathway were on the acceptability to regulatory authorities of a vaccine acting via delayed clinical benefit, the appropriate CDP and regulatory pathway, including the potential need for a cluster randomized trial (CRT), and the required level of efficacy.

A critical outcome of the 2010 MVI TBV workshop was that the US Food and Drug Administration (FDA) indicated that there is no legal bar to prevent a vaccine such as an SSM-TBV from being considered for licensure in the context of their review process. The FDA has the authority to license biological products that are demonstrated to be "safe, pure, and potent" (Section 351 of the Public Health Service Act & Section 505(b) of the Food, Drug, and Cosmetic Act), regardless of whether the disease occurs in the United States [23]. This feedback has encouraged the malaria vaccine development community to consider product development pathways for vaccine approaches exclusively targeting parasite transmission from human to mosquito. In 2012, moreover, the report on the MALVAC meeting states, "great progress has been made in recent years with a general acceptance in malaria vaccine circles that the issue of community benefits for TBV is not a major hurdle for clinical or regulatory pathways" [24]. The challenge moving forward will be to further define both the CDP and regulatory pathways and seek specific feedback from regulators, such as the FDA, European Medicines Agency, or another stringent regulatory authority.

Another important outcome of the VIMT research agenda-setting meetings and consultations was the preliminary definition of two potential clinical development pathways for an SSM-VIMT (Fig. 1). One involves a large-scale, Phase 3 efficacy trial, which, in the case of an SSM-VIMT, has been proposed by regulators to be a CRT to demonstrate vaccine impact on incidence of infection

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