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Status of vaccine research and development of vaccines for malaria☆

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ABSTRACT

Despite recent progress in reducing deaths attributable to malaria, it continues to claim approximately 500,000 lives per year and is associated with approximately 200 million infections. New tools, including safe and effective vaccines, are needed to ensure that the gains of the last 15 years are leveraged toward achieving the ultimate goal of malaria parasite eradication. In 2015, the European Medicines Agency announced the adoption of a positive opinion for the malaria vaccine candidate most advanced in development, RTS,S/AS01, which provides modest protection against clinical malaria; in early 2016, WHO recommended large-scale pilot implementations of RTS,S in settings of moderate-to-high malaria transmission. In alignment with these advancements, the community goals and preferred product characteristics for next-generation vaccines have been updated to inform the development of vaccines that are highly efficacious in preventing clinical malaria, and those needed to accelerate parasite elimination. Next-generation vaccines, targeting all stages of the parasite lifecycle, are in early-stage development with the most advanced in Phase 2 trials. Importantly, progress is being made in the definition of feasible regulatory pathways to accelerate timelines, including for vaccines designed to interrupt transmission of parasites from humans to mosquitoes. The continued absence of financially lucrative, high-income markets to drive investment in malaria vaccine development points to continued heavy reliance on public and philanthropic funding.

1. About the disease and pathogen

Malaria is caused by five species of *Plasmodium* that infect humans (*Plasmodium falciparum, Plasmodium vivax*, *Plasmodium ovale* spp., *Plasmodium malariae* and *Plasmodium knowlesi*) and is transmitted by the bite of infected female Anopheline mosquitoes. The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment. In 2013, over 3 billion people were at risk of malaria; there were an estimated 198 million cases (uncertainty range 124–283 million) and 584,000 malaria deaths (uncertainty range 367,000–755,000) [1]. The vast majority of clinical cases (80%) and deaths (90%) occur in sub-Saharan Africa, with children under five years of age and primigravid pregnant women most affected [1]. However, Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2013, 97 countries and territories had ongoing malaria parasite transmission. According to the latest WHO estimates, malaria mortality rates were reduced by about 47% globally and by 54% in the WHO African Region between 2000 and 2013. During the same period, in sub-Saharan Africa, average infection prevalence in children aged 2–10 years fell from 26% to 14%—a relative decline of 48% [1]. Despite these encouraging gains, associated with the scale-up of preventive, diagnostic and treatment measures, new interventions, including vaccines to prevent clinical disease and transmission, are urgently needed [2].

Early diagnosis and treatment of malaria reduces disease and prevents deaths. It also contributes to reducing malaria parasite transmission. The best available treatment, particularly for *P. falciparum* malaria, is artemisinin-based combination therapy (ACT). In recent years, parasite resistance to artemisinins has been detected in four countries of the Greater Mekong subregion: Cambodia, Myanmar, Thailand and Viet Nam. In 2015 it was reported that

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resistance to artemisinins has spread across Southeast Asia much faster than expected and is now in regions of Myanmar close to its border with India [3]. If resistance to artemisinins develops and spreads to other large geographical areas, most notably sub-Saharan Africa, the public health consequences could be dire, as no alternative antimalarial medicines will be available for at least five years.

Vector control is the mainstay of reducing malaria parasite transmission at the community level from very high levels to close to zero. For individuals, personal protection against mosquito bites represents a first line of defence for malaria prevention. Two forms of vector control are effective in a wide range of circumstances: Insecticide-treated mosquito nets (ITNs) and indoor spraying with residual insecticides (IRS). Currently, vector control is highly dependent on the use of pyrethroids, which are the only class of insecticides currently recommended for ITNs. In recent years, mosquito resistance to pyrethroids has emerged in many countries. In some areas, resistance to all four classes of insecticides used for public health has been detected. Fortunately, this resistance has only rarely been associated with decreased efficacy, and ITNs and IRS remain highly effective tools in almost all settings. However, the use of ITNs does appear to be associated with selection for changes in mosquito biting behavior, such as time of day and location of biting, which could reduce their effectiveness.

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

Currently, there are no available malaria vaccines. The Malaria Vaccine Technology Roadmap (Roadmap) has guided vaccine development efforts since 2006 [4], and in 2013 was updated based on extensive consultations with scientists and public health experts from non-endemic and malaria-endemic countries, industry, non-governmental organizations, and funding agencies [5]. The revised Roadmap focuses on two strategic goals to be met by 2030: vaccines to achieve malaria elimination in multiple settings and vaccines that are highly efficacious against clinical malaria. The Roadmap also includes an updated set of priority areas in research, vaccine development, key capacities, and policy and commercialization, for which further funding and activities are likely to be crucial for success [5]. The original Roadmap contained a 2015 landmark goal for a modestly efficacious malaria vaccine yielding reductions in morbidity and mortality, which remains unchanged, and could be achieved by the RTS,S vaccine candidate now under regulatory and policy review.

There are three general approaches to developing malaria vaccines, targeting different stages of the parasite lifecycle, each of which is supported by biological evidence that protective immune responses are attainable. Pre-erythrocytic vaccines aim to induce antibodies that block hepatocyte invasion by sporozoites and/or cell-mediated immune responses that target infected hepatocytes. Whole parasite and subunit vaccine approaches, evaluated in controlled human malaria infection (CHMI) and/or field efficacy studies, have proven to successfully induce PE-stage immunity. The scientific rationale supporting the development of asexual blood-stage vaccines is rooted in the observation that naturally acquired immunity can be passively transferred to susceptible individuals. A specialized asexual blood-stage vaccine approach targeting pregnancy-associated malaria aims to leverage observations that parasite prevalence is highest in first pregnancy and falls profoundly with each subsequent pregnancy. Finally, development of vaccines to interrupt human-to-mosquito transmission is based on studies in avian and primate models where immunization with extracellular gametes totally suppressed parasite infectivity to mosquitoes on a subsequent blood meal.

2.2. General approaches to vaccine development for this disease for low and middle income country markets

Vaccines are needed that target all *Plasmodia* species that cause human disease, but most notably *P. falciparum* and *P. vivax* [6]. *P. falciparum* is most prevalent on the African continent, and is responsible for most deaths from malaria. *P. vivax* has a wider geographic distribution, with an estimated 2.5 billion people at risk, although it is largely absent from the African continent due to the widespread Duffy-negative phenotype that renders red blood cells resistant to parasite invasion. The lack of homology between *P. falciparum* and *P. vivax* antigens will likely necessitate the development of species-specific vaccines.

Vaccines to prevent clinical disease target pre-erythrocytic and/or asexual blood-stage antigens, and are primarily intended for those enduring the greatest burden of disease; whereas vaccines interrupting malaria (parasite) transmission (VIMT) primarily target pre-erythrocytic and/or sexual, sporogonic and/or mosquito-stage (SSM) antigens, and are targeted to populations at risk of endemic transmission. While it may be possible to develop vaccines that are highly effective at both preventing clinical disease (i.e. cases averted, toward saving lives and preventing disease) and interrupting the cycle of transmission (i.e. transmission interrupted, to support control and elimination), they are associated with distinct clinical endpoints, overlapping but different target populations, discrete Target Product Profiles (TPP), regulatory approval processes, and implementation strategies [6]. In 2015, WHO published Preferred Product Characteristics (PPCs) for disease reducing and transmission reducing malaria vaccines. WHO PPCs describe preferences for parameters of vaccines from a public health, rather than a return on investment perspective; in particular their indications, target groups, and possible immunization strategies, as well as the clinical data desired related to safety and efficacy in low and middle income countries [7]. PPCs are meant to provide early guidance for the development of new products or the improvement of existing ones. Each PPC addresses early-stage vaccine research and development (R&D) generally at least five to ten years from vaccine availability, and will be reviewed every five years, at least, and updated if necessary. PPCs are not static exit criteria, but are structured in such a way so as to drive innovation toward meeting public health needs [7]. In addition to PPC criteria, vaccine developers targeting WHO prequalification should consider programmatic suitability criteria defined by WHO and updated in 2014 [8].

The absence of financially lucrative, high-income markets to justify investment in malaria vaccine development has led to a heavy reliance on public and philanthropic funding. According to the 2014 G-Finder Report, which reports 2013 global investment for research and development (R&D) of new products for neglected diseases, and identifies trends and patterns across the seven years of global G-FINDER data, funding for malaria R&D in 2013 was $549 million, the lowest level since 2007 [9]. Basic research accounted for more than a third ($193 million, 35%) of malaria funding, with $119 million (22%) allocated to vaccine development [9].

While different funding agencies have their own priority focus areas, they are generally aligned with one of the two Roadmap goals associated with *P. falciparum* and with one or more of the four priority areas. That said, there continues to be a chronic lack of support for the development of *P. vivax* vaccines, whether to prevent clinical disease or to prevent transmission, and a lack of support in all four priority areas of the Roadmap.