Vaccine

Status of vaccine research and development of vaccines for malaria☆

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A R T I C L E   I N F O

A B S T R A C T

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

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.

3. Technical and regulatory assessment

The absence of robust biomarkers of protection for RTS,S/AS01, irradiated sporozoites/mosquitoes, infection-treatment vaccination (ITV), and naturally acquired blood-stage immunity hampers rapid progress in vaccine development. The identification of surrogate markers of protection and increased understanding of the mechanism(s) of protection are needed, which may be achieved via the increased interrogation from controlled human malaria infection and field efficacy studies.

In the absence of an available vaccine that is recommended for use, candidates must be evaluated in randomized, "placebo"-controlled, multicenter Phase III efficacy trials. RTS,S/AS01, the most advanced malaria vaccine candidate in development globally, completed Phase III evaluation, in January 2014, via a collaboration between GlaxoSmithKline Vaccines (GSK), the PATH Malaria Vaccine Initiative (MVI), and 13 clinical sites in eight sub-Saharan African countries. The co-primary efficacy objectives of the pivotal efficacy and safety trial (conducted at 11 sites in seven of the eight countries) were to evaluate the protective efficacy of RTS,S/AS01E against clinical malaria disease caused by *P. falciparum* in African children whose age at first dose will be from: 1) 6–12 weeks and will receive vaccine in co-administration with DTPwHepB/Hib antigens (Tritanrix HepB/Hib) and oral poliovirus vaccine (OPV); and 2) 5–17 months. The primary efficacy analysis for both of these age categories was for a duration of follow-up of a minimum of 12 months and a maximum of 18 months after completion of the primary course. Secondary objectives included evaluation of vaccine efficacy against severe malaria, anemia, malaria hospitalization, fatal malaria, all-cause mortality, and other serious illnesses including sepsis and pneumonia. Efficacy of the vaccine against clinical malaria under different transmission settings, the evolution of efficacy over time, and the potential benefit of a fourth dose were also evaluated. Safety of the primary course of immunization and the fourth dose were studied in both age categories [10]. In June 2014, GSK submitted an application for a scientific opinion by the Committee for Medicinal Products for Human Use (CHMP) on RTS,S through the European Medicine Agency's (EMA) Article 58 procedure. The EMA's CHMP evaluated data on the quality, safety, and efficacy of the RTS,S/AS01 vaccine candidate. On Friday July 24, 2015, the EMA announced CHMP's adoption of a positive opinion. This is not licensure, but will be helpful to African regulatory authorities as they receive submissions, knowing that a stringent regulatory authority has provided a positive assessment of quality, and risk/benefit. The EMA assessment does not include aspects such as feasibility of implementation, cost-effectiveness, and the role of RTS,S in the context of available malaria control measures all of which were considered during the WHO policy recommendation process.

The WHO's recommendations, published on January 29, 2016, call for large-scale pilot implementations in settings of moderate-to-high malaria transmission.

In recent years there has been an increased focus on development of a vaccine that interrupts malaria (parasite) transmission (VIMT) to support malaria elimination [5]. The two primary vaccine development strategies are to induce pre-erythrocytic immunity that prevents infection of humans or to induce sexual, sporogonic, and/or mosquito-stage (SSM) immunity to prevent transmission to mosquitoes [6]. While the focus of these vaccines is to prevent infection (as opposed to clinical disease), it is important to note that infection endpoints have historically not been sufficient to support vaccine licensure. Furthermore, SSM–VIMT would not confer direct, immediate clinical benefit to the recipient, but could be paired with an intervention that provides such a benefit. As such, the clinical benefit that SSM–VIMT provide is primarily a population-based long-term benefit associated with reduced incidence of new malaria parasite infections in humans. This absence of direct and immediate benefit to the recipient, together with the complexity of the *P. falciparum* lifecycle, make clinical development of SSM–VIMT challenging, particularly for use in the pediatric population.

Definition of regulatory pathways for next generation malaria vaccines that interrupt transmission to encourage the development of this important class of interventions – while at the same time safeguarding the health and well-being of the population that SSM–VIMT are intended to benefit – is urgently needed. One consideration under active discussion is the potential eligibility of SSM–VIMT for an Accelerated Approval (AA) method of licensure by FDA based on a proposed surrogate endpoint with confirmatory trials performed post-licensure. Resolving this important dilemma will require vaccine developers and other key stakeholders to work closely with regulatory authorities, including in endemic counties, and with the WHO. An important step forward in this regard was achieved at the inaugural convening of the WHO Product Development for Vaccines Advisory Committee meeting held in Geneva, September 8–10, 2014, where a specific recommendation was that identification of a feasible regulatory pathway for SSM–VIMTs be a priority area of work for the WHO [11].

The full exploration of the direct feeding assay (DFA), to demonstrate effective blocking of human-to-mosquito transmission at the level of the individual as a licensure endpoint will be important, as will standardization of key functional assays (standard membrane feedings assay [SMFA], direct membrane feeding assay [DMFA], and DFA) toward identification of correlates of transmission-blocking immunity.

4. Status of vaccine R&D activities

The current vaccine development pipeline is relatively diverse in terms of both the stage of parasite lifecycle targeted and the technology platforms being exploited. The global malaria vaccine portfolio is maintained at a website managed by WHO [12]. A summary of clinical-stage vaccine approaches, by lifecycle stage, is provided below and Table 1.

4.1. Pre-erythrocytic (PE) vaccines

The most advanced malaria vaccine candidate in development globally, RTS,S/AS01, completed Phase III clinical testing in 2014. Results of the co-primary endpoints of the Phase III study after a year of follow-up were published in November 2011 (for children aged 5–17 months) and in December 2012 (for infants aged 6–12 weeks) [13,14]. These results showed that three doses of RTS,S reduced clinical malaria by approximately half in children 5–17 months of age at first vaccination (Intention to Treat analysis). In infants 6–12 weeks of age at first vaccination with RTS,S, clinical malaria was reduced by approximately one-third. In a subsequent analysis after 18 months of follow-up, children aged 5–17 months at first vaccination with RTS,S experienced 45% fewer cases of clinical malaria, compared to children immunized with a control vaccine. Infants aged 6–12 weeks at first vaccination with RTS,S had 27% fewer cases of clinical malaria than infants in the control group and efficacy waned over time in both age categories [15].

The final study results, which analyzed vaccine efficacy, immunogenicity, safety, and impact of RTS,S/AS01 over a median of 38 and 48 months of follow-up (post-dose 1) in infants and young children, respectively, including the effect a booster dose of vaccine, were published in 2015 [15]. These final results demonstrated that vaccination with the three-dose primary series reduced clinical malaria cases over the length of the study by 28% in young children (over a median follow-up of 48 months after first dose across trial sites) and 18% in infants (over a median follow-up of 38 months

Table 1
Development status of current clinical-stage vaccine candidates (POC = proof of concept trial) (adapted from: WHO tables of malaria vaccine projects globally—"rainbow tables" [12].

Candidate name/identifier	Developer	Phase I	Phase II[a]	POC	Phase III
Pre-erythrocytic projects					
RTS,S/AS01 delayed fractional third dose	GSK	X[b]			
Adenovirus (Ad35) vectored CS and RTS,S/AS01 in heterologous prime-boost regimen	GSK	X[b]			
ChAd63/MVA ME-TRAP	University of Oxford		X		
ChAd63/MVA ME-TRAP/Matrix M™	University of Oxford	X[b]			
PfSPZ	Sanaria, Inc.	X[b]			
Polyepitope DNA EP1300	NIAID, NIH	X			
Adenovirus (Ad35) and adenovirus 26 (Ad26) vectored CS in heterologous prime-boost regimen	GSK	X[b]			
PfCelTOS FMP012/AS01B	Office of the Surgeon General (US), Department of the Army (US), USAMRMC	X[b]			
PfCelTOS FMP012/GLA-SE	Office of the Surgeon General (US), Department of the Army (US), USAMRMC	X[b]			
CSVAC	University of Oxford	X[b]			
RTS,S/AS01B + ChAd63/MVA (ME-TRAP)	University of Oxford	X[b]			
PfSPZ attenuated sporozoite	NIAID, NIH	X			
rCSP/GLA-SE	NIAID, NIH	X			
ChAd63/MVA (ME-TRAP) co-administered with RTS,S/AS01B	University of Oxford	X			
Blood stage projects					
EBA175 RII/aluminium phosphate	NIAID, NIH	X			
FMP2.1/AS01B (AMA-1 3D7 *E. coli*)	Office of the Surgeon General (US), Department of the Army (US), USAMRMC, University of Oxford	X[b]			
GMZ2/Alhydrogel®	European Vaccine Initiative (EVI)	X			
GMZ2 field/Alhydrogel®	AMANET, Statens Serum Institut		X		
PfAMA1-DiCo/GLA-SE or Alhydrogel®	Inserm	X			
P27A/GLA-SE or Alhydrogel®	Centre Hospitalier Universitaire Vaudois (CHUV)	X			
MSP3-LSP/AlOH	EVI, AMANET		X		
SE36/AlOH	Research Foundation for Microbial Diseases of Osaka University	X			
ChAd63 AMA1/MVA AMA1	University of Oxford	X			
NMRC-M3V-Ad-PfCA	Office of the Surgeon General (US), Department of the Army (US), USAMRMC	X[b]			
NMRC-M3V-D/Ad-PfCA prime/boost	Office of the Surgeon General (US), Department of the Army (US), USAMRMC	X[b]			
ChAd63/AMA MVA/AMA1 + Alhydrogel®/CPG7909	University of Oxford	X[b]			
PfPEBS-LSP/AlOH	Vac4All	X			
ChAd63 MSP1/MVA MSP1	University of Oxford	X[b]			
ChAd63 RH5 ± MVA RH5	University of Oxford	X			
Sexual stage projects					
Pfs25-EPA/Alhydrogel®	NIAID, NIH	X			
Pfs25-VLP/Alhydrogel®	Fraunhofer USA	X			
***P. vivax* project**					
ChAd63/MVA PvDBP	University of Oxford	X			

[a] Phase II comprises studies of a candidate vaccine that are intended to result in efficacy data in the target population to whom the vaccine would be administered should it eventually by licensed. A program of Phase II studies usually defines the preferred dose, route, and schedule of immunizations that are eventually evaluated for efficacy. Phase II studies also provide an expanded population assessment of the safety of the product.

[b] Controlled human malaria infection (CHMI) study.

after first dose across trial sites). A booster dose of RTS,S, administered 18 months after completion of the primary series, reduced the number of cases of clinical malaria in young children (aged 5–17 months at first vaccination) by 36% over the entire study period and in infants (aged 6–12 weeks at first vaccination) by 26% over the study period. These results were achieved on top of existing malaria interventions, such as ITNs, which were used by approximately 80% of the trial participants [15].

In both age categories, adverse events after vaccination included local reactions (such as pain or swelling) and fever, which were observed more frequently after RTS,S administration compared to the control vaccine (31% versus 21% of vaccine doses in the 6–12 week age category and 31% versus 13% in the older 5–17 month age category). Very few of the adverse events were severe. In the

younger age category (i.e. infants 6–12 weeks of age at first injection), injection site reactions were reported less frequently after RTS,S administration compared to the standard vaccines routinely used in the African EPI [14]. RTS,S continued to display a good safety profile during the entire study period.

In young children, the incidence of fever in the week after vaccination was higher in those who received the RTS,S vaccine compared to those who received the control vaccine. In some children this resulted in febrile reactions which were accompanied by generalized convulsive seizures, but all those affected fully recovered within seven days. The rates of serious adverse events seen in the trial (mainly medical events requiring hospitalization, regardless of whether they were considered to be caused by the study vaccine) were comparable between the trial's RTS,S

candidate vaccine recipients and those receiving a control vaccine, except for cases of meningitis, which were reported in low numbers, but more often in the RTS,S group compared to the control.

The meningitis signal previously reported remained in the older age category, including a small number of new cases reported after the fourth dose. This could be a chance finding as comparisons were made across groups for many different diseases, and because some of these cases happened years after vaccination without any obvious relationship to vaccination. If RTS,S is licensed, the occurrence of meningitis will be followed closely during Phase IV studies and has been flagged as important for the pilot implementations also. The pilot implementations are also being designed to determine whether additional safety concerns, identified by WHO, are of significance.

Strategies to directly build upon the success of RTS,S, via the induction of humoral and cell-mediated immune responses to the circumsporozoite protein (CSP) and other antigens, have been underway for many years. The scientific rationale for these studies is that a significant proportion of RTS,S-immunized volunteers not protected following controlled challenge display evidence for immunity, as determined by a delay to parasitemia that correlates with a >90% reduction in parasites exiting the liver. Currently, there is a significant focus on translational research studies to evaluate whether vaccine approaches that induce superior anti-CSP antibody responses and/or strong cell-mediated immune responses, directed at CSP and other antigens, are able to enhance protective efficacy.

In recent years, one of the most significant advances in the quest to develop highly efficacious pre-erythrocytic vaccines have been the demonstration that radiation-attenuated *P. falciparum* sporozoites, administered by five intravenous doses, protected 6/6 volunteers in the highest dose group from infection in CHMI studies [16]. Studies are ongoing to replicate these initial findings in larger numbers of volunteers, and to generate evidence for sustained protection (via delayed challenge) and cross-strain protection (via heterologous challenge). Heterologous prime-boost vaccine approaches, using different platforms and target antigens, have yielded modest levels of protection in CHMI studies [17–19].

4.2. Blood-stage (BS) vaccines

While immunity to asexual blood-stage antigens is an important mechanism of natural immunity to malaria in endemic regions, defined biomarkers of protection remain elusive. In recent years, preliminary evidence for vaccine-induced clinical efficacy from field studies has been generated using three blood-stage targets, *P. falciparum* AMA1, MSP3 and SERA5. However, as with similar preliminary findings for other antigens, such as MSP2, further studies are needed to confirm these initial findings. Additional antigens are currently undergoing Phase I and II development, with data expected in the coming years. Efforts to develop highly effective subunit vaccines targeting asexual blood stages has been buoyed by progress in deciphering the redundant network of merozoite invasion mechanisms for *P. falciparum*, revealing promising new vaccine targets. For *P. vivax*, the challenge of effectively targeting merozoite invasion ligands appears to be less complex, with the Duffy binding protein (DBP) representing the overwhelmingly dominant invasion ligand for ensuring reticulocyte invasion. Protein- and vector-based vaccines are expected to enter clinical testing over the coming years. Further, whole, attenuated blood-stage vaccines for *P. falciparum* are advancing toward clinical development based on promising preclinical data. The most advanced pregnancy-associated malaria vaccine approaches, although still at the preclinical stage, target var2CSA, which is preferentially expressed by placental parasites and is the target of acquired immunity over successive pregnancies.

4.3. Sexual, sporogonic, and/or mosquito (SSM) stage vaccines

Clinical studies to evaluate induction of antibodies to sexual, sporogonic, and/or mosquito-stage antigens, to block human-to-mosquito transmission, have to date focused on two antigens (*Pfs*25 and *Pvs*25) delivered as either recombinant proteins or via attenuated vaccinia virus; however, high levels of transmission-blocking activity have not been reported. Additional target antigens, including *Pfs*48/45, *Pfs*230, HAP2, and *An*APN1, have been associated with promising preclinical data.

5. Likelihood for financing

To ensure financing is available for vaccines that will support malaria eradication and elimination, it will be important to build strong support early on in its development. The Roadmap goal will be a good starting point for such a dialogue with potential financing organizations. Traditionally vaccine financing has gone to support children under age five to prevent disease and death, however, recently Gavi, the Vaccine Alliance, has supported the Global Polio Eradication Initiative, the MenAfriVac vaccine and HPV (both vaccines are provided outside of the EPI infant schedule), as well as Ebola (a commitment was made in December 2014 to purchase Ebola vaccines for at-risk populations). These relatively new commitments demonstrate that there is support for considering vaccination in a different context.

The Global Fund for AIDS, Tuberculosis and Malaria (GFATM) has been financing countries that are in the malaria pre-elimination phase with WHO-recommended tools. Although GFATM has yet to be involved in vaccine financing (there are no vaccines for AIDS or malaria, nor any new vaccines for TB), as vaccines become available for these diseases, GFATM will have to define its role in integrating vaccine use into broader efforts of preventing, treating, and/or interrupting transmission of these three major diseases. Dialogue between GFATM and Gavi on malaria vaccines has already started, as their financing mechanisms and models and areas of expertise are different. Their interactions on RTS,S will help to pave the way for future dialogue between these two key potential global-level financiers and help determine the optimal roles of the two organizations.

As part of the planning process to help secure financing, MVI will develop and update business and investment cases as a vaccine moves through the development pathway. As indicated in the Roadmap, "business cases would need to be developed prior to investment in each stage of development. Prior to proof of concept, a business case would include a value proposition (i.e. a statement that clearly identifies what advantages a customer will receive by purchasing the vaccine), PPCs, estimated development costs, options for financing, and an initial market assessment. Prior to entering into Phase III, the case would be more comprehensive and would be developed and agreed upon among manufacturers, donors, WHO, global-level financiers, and countries. This process will be especially important for an eradication agenda. The detailed business case prior to Phase III would include a value proposition, a TPP, late stage development costs, a financing plan, a strategic demand forecast, estimated capital costs, and pricing assumptions." The business and investment cases will be key documents to enable global-level financing bodies to understand their potential role in financing malaria vaccines for elimination and eradication.

Conflict of interest statement

The author declares no conflict of interests.

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