Vaccines: Tackling the world’s deadliest diseases, one shot at a time

Context
Infectious diseases are the leading cause of death of under-fives globally; they are responsible for nearly half of all child deaths annually.\textsuperscript{[1]} Immunisation against these illnesses is one of the most effective means of preventing their spread and severity and, thus, of saving lives; it is estimated to avert 2–3 million deaths every year.\textsuperscript{[2]} Vaccines also confer ‘herd immunity’ and socio-economic benefits such as direct medical savings, improved educational attainment and increased economic productivity.\textsuperscript{[3-4]}

Despite being one of the most cost-effective and relatively easy to deliver health interventions,\textsuperscript{[9]} uptake of essential vaccines has stagnated and there are still around 1.5 million vaccine-preventable deaths — due to measles, neonatal tetanus, pertussis, \textit{haemophilus influenzae} B, rotavirus diarrhoea and pneumococcal disease — annually.\textsuperscript{[5]} Demand and supply-side barriers include but are not limited to: low levels of awareness of vaccines’ value; prohibitive social/religious norms; safety-related hesitancy; difficulties accessing healthcare providers; affordability for governments; and insufficient domestic investment in national immunisation programmes.\textsuperscript{[6]}

While vaccines for many of the most life-threatening diseases exist, there is currently no commercially available vaccine against malaria, a disease that causes 405,000 deaths every year.\textsuperscript{[7]} Such a vaccine could complement the existing package of preventive, diagnostic and treatment tools being used to reduce the global malaria burden and, thereby, contribute to attaining global elimination targets by 2030.
Malaria vaccine development

All vaccines in use today protect people against either viral or bacterial illnesses. As malaria is caused by a parasite, a malaria vaccine would be one of the first vaccines to protect against a parasitic disease in humans.

However, the complex life cycle of malaria parasites (see Figure 1), coupled with limited understanding of the immune response to malaria infection (which varies by population and age group), has rendered the development of a vaccine incredibly challenging.[8] Not only are there thousands of potential antigens to tackle and harness, but exposure to malaria parasites also does not confer lifelong protection.

Despite these hurdles, the search for a vaccine — particularly one that contains antibodies that can attack the malaria parasite at multiple points in its life cycle[9] — remains a high priority. The most advanced candidate, RTS,S/AS01, targets the pre-erythrocytic stage of the *Plasmodium falciparum* parasite, the species responsible for the majority of malaria deaths.[9]

Developed through a partnership between GlaxoSmithKline and the PATH Malaria Vaccine Initiative, with funding from the Bill & Melinda Gates Foundation and others, RTS,S underwent a five-year (2009–2014) phase III clinical trial in seven sub-Saharan African countries. Involving around 15,000 young children (5–17 months at first dose) and infants (6–12 weeks at first dose), the trial sought to determine the vaccine’s efficacy at scale and in a range of malaria transmission settings, as well as collate data on safety, side effects and the potential added value of a fourth booster dose.

Promisingly, results published in April 2015 showed that RTS,S prevented a significant number of clinical malaria cases over a 3–4 year period.[9] Its efficacy was 26 and 18 percent in children and infants respectively with the three-dose vaccine schedule, and 39 and 27 percent in children and infants respectively with the booster dose — indicating that its efficacy is modest and short-lived. The vaccine’s effectiveness may have been lower in infants due to it being administered at the same time as other routine vaccinations, or because of the presence of passive immunity from antibodies passed through the placenta from the mother.[10] Positively, the vaccine also reduced the cases of severe malaria, severe anaemia, and malaria hospitalisations in older children. However, higher risks of meningitis, cerebral malaria, and female mortality seem to be associated with the vaccine.[9]

In July 2015, the European Medicines Agency officially supported the vaccine’s use in children aged 6 weeks to 17 months and in October 2015 the World Health Organization’s (WHO) Strategic Advisory Group of Experts on Immunization and its Malaria Policy Advisory Committee jointly recommended a pilot implementation in sub-Saharan Africa.

Then, in June 2016, a seven-year follow-up in Kenya (n= 447) showed that while a three-dose schedule of RTS,S was initially protective against clinical malaria in the first year after vaccination, efficacy waned over time and stood at just 3.6 percent by the seventh year.[11] It also found evidence of a ‘rebound effect’, whereby children living in areas with high transmission may be more susceptible to malaria as the vaccine’s efficacy fades because they have not built up any natural immunity to the parasite through exposure. This study did not, however, investigate the impact of the fourth booster dose.

Later that year, in November 2016, WHO announced that it would coordinate a pilot — the Malaria Vaccine Implementation Programme (MVIP) — in Kenya, Ghana and Malawi. Underway as of April 2019, this trial seeks to: assess the feasibility of delivering four doses of RTS,S; gauge the vaccine’s potential role in reducing childhood deaths; and evaluate its safety in the context of routine use. The country-led pilot aims to reach 360,000 children with RTS,S annually — delivered via national routine immunisation programmes — and is due to conclude in 2023/4. It will be complemented by a series of GlaxoSmithKline-led phase IV studies aiming to collect additional data on the vaccine’s effectiveness and on any side effects associated with routine use.[11]

In addition to RTS,S, there are currently more than 20 malaria vaccine projects in clinical trials, with the Malaria Vaccine Technology Roadmap guiding the priorities for vaccine development. By 2030, the goal is to have licensed vaccines targeting both *P. falciparum* and *P. vivax* that protect appropriate at-risk groups against clinical malaria and reduce transmission of the parasite.[13]

* Pre-erythrocytic vaccines prevent infection, blood-stage vaccines limit infection thereby reducing the severity of the disease, and transmission-blocking vaccines interrupt the spread of infection.
One particularly promising vaccine candidate that also targets the pre-erythrocytic stage of the *P. falciparum* parasite, Sanaria’s PSPZ, has been found to be safe, well tolerated and protective against malaria when administered intravenously to children and adults in Africa (Equatorial Guinea, Gabon, Kenya, Mali and Tanzania), Europe (Germany and Spain) and the United States. A phase III trial that seeks to provide the efficacy and safety data required for regulatory approval — comprising around 2,100 people aged 2–50 years — is due to commence in early 2020 on Bioko, an island off Equatorial Guinea.

Another vaccine candidate is MultiMalVax that, as its name suggests, targets several stages of the *P. falciparum* parasite’s life cycle concurrently.

**Our position**

As a leading technical organisation specialising in the prevention, control and treatment of malaria and other communicable diseases, we fully recognise the immense value of immunisation to controlling and eliminating some of the world’s deadliest diseases. To keep populations healthy and save lives, we believe it is crucial that the global community continues to support and invest in vaccine development.

- **We welcome efforts to develop an effective malaria vaccine**, which would provide an important additional tool for malaria control and elimination. We believe this is crucial given the growing resistance to insecticides and antimalarial drugs. We also recognise that any malaria vaccine should work alongside — rather than replace — the existing WHO-recommended package of preventive, diagnostic and treatment tools.

- **We feel that the progress made thus far has been positive and we look forward to the results of the MVIP trial and GlaxoSmithKline-led phase IV studies.** These will provide much needed safety-related data and will guide policy and recommendations on the optimal use of the RTS,S vaccine.

- **While the Malaria Vaccine Technology Roadmap has been invaluable for encouraging prioritisation of investment where there is greatest chance of success, we urge the scientific community to continue to promote the development of vaccines for other species of the *malaria parasite*, such as *P. vivax*. We also believe it is crucial that the resources needed to scale up existing malaria control measures — which have already been proven to be effective — are not diverted to address the additional research outlined in the Roadmap.

- **We believe that the practical challenges of rolling out vaccines and other malaria prevention initiatives to remote and hard-to-reach communities are considerable but not insurmountable, and require strong partnerships between national governments, non-governmental organisations, donors and other agencies, as well as careful addressing of caregivers’ perspectives. Further studies will be required on the acceptability and operational feasibility of rolling out RTS,S or similar malaria vaccine candidates at scale. These should consider: deployment issues (i.e. cold chains), possible co-delivery with other core interventions (e.g. national immunisation schedules, seasonal malaria chemoprevention etc.), messaging that promotes uptake despite relatively modest vaccine efficacy and short-lived immunity, and affordability for individuals and low- and middle-income country governments.**

**References**
