

## Editorial

### Development & licensing of first ever vaccine against malaria

Malaria has played a key role in shaping human history. Tropical areas of the world would not have been colonized but for the acquisition and use of knowledge of Indian remedy, the cinchona bark, and world would have looked a great deal different from what we see now; no colonial empires would have been set up. Discovery of cheap and effective insecticides and synthetic drugs like chloroquine and their use in malaria endemic countries post world war II led to a belief that malaria was finally conquered, leading to much decreased attention and inaction. Malaria struck back following vector's resistance to insecticides and in fact, re-emerged with a vengeance due to fast spreading drug resistant strains of the disease causing parasites. Developing and poor countries paid heavy price for the neglect. But in the past few years increased attention has been paid by the WHO, major donor agencies like the Wellcome Trust and Bill & Melinda Gates Foundation that fund research in infectious diseases and the governments. These efforts have led to the development of new tools for detection and therapeutic interventions as well as efforts in prevention of the disease, but the battle against malaria has clearly not been won yet. It is generally believed that without an effective vaccine as an additional tool, effective control and eradication of this disease may remain an elusive goal. In this regard the recent announcement of licensure of a partially protective malaria vaccine which can potentially save many lives particularly in Sub Saharan Africa is both an exciting and welcome news.

It is not that efforts to develop vaccine(s) against malaria have lacked intent, support and scientific vigor. In fact, many research groups around the world have spent their life time trying to work up rationale and basis for vaccines against this highly complex, multi-stage disease. The malaria parasite is transmitted by an infective female *Anopheles* mosquito and once

in the host, it goes through its life cycle, and huge multiplication, in distinctly different stages. This deadly parasite does not have an easy life for itself, but causes a great deal of grief and often fatal damage to the host.

Vaccines against all the three stages of the life cycle of the parasite are being pursued. The liver stage vaccine(s) have potential to stop malaria infection from going on to the blood stages, which are responsible for the clinical disease. Blood stage vaccine(s) have the potential of reducing morbidity and further transition to sexual stages whereas vaccines(s) against the sexual stage parasites can block the cycle of transmission, killing the parasite during this stage and are hence called transmission blocking vaccines. All three kinds have their place in malaria control, and its eradication. In this context the recent announcement of licensure of a pre-erythrocytic stage vaccine called RTS,S is an exciting and long awaited development<sup>1</sup>. This vaccine, developed by some of the major players in malaria vaccine development enterprise, namely Walter Reed Army Institute of Research (WRAIR) and Glaxo Smith Kline (GSK), continuously supported by the WHO and other funding sources like Bill and Melinda Gates Foundation among others, has taken more than 20 years to come to this stage<sup>2-9</sup>. It has been an amazing and sustained effort and it is important to trace back the story of its development. More so, because it also underscores the scientific and organizational problems encountered in the development of vaccines against complex diseases like malaria, TB, HIV and dengue viral infection.

It has been known for a while that immunization with irradiated liver stage parasites (sporozoite) can protect the host against malaria infection<sup>7</sup>. The story of development of RTS, S began with the identification of the circumsporozoite protein (CS protein) as a key antigen involved in the protection observed after

immunization with irradiated sporozoites. A team of scientists from the GSK and WRAIR decided to develop a malaria vaccine based on the CS protein which contains an immunodominant tetrapeptide repeat region in the middle of its structure and was an obvious choice for the design of a subunit vaccine<sup>2</sup>. Although initial experiments with constructs based solely on the repeat region or on the flanking regions were unsuccessful, the quest for inducing high level of antibodies to CS protein to neutralize sporozoites continued. Use of highly immunogenic hepatitis virus surface protein (HBsAg) as a carrier for CS protein to enhance its immunogenicity, led to the development of a fusion protein (R16 HBsAg) that assembled into virus like particles (VLPs). This was soon followed by another CS protein construct that was to include a C-terminal flanking region containing T-cell epitopes along with tetrapeptide repeat region, fused with HBsAg and co-expressed with HBsAg(S). However, VLPs of the fusion protein were not immunogenic in human compatible alum based adjuvants which was a big setback<sup>3,4</sup>. However, not giving up on this construct these researchers who had access to many adjuvant formulations being developed at GSK, tried various combinations of novel adjuvants (the ASO series) leading to stable VLPs of RTS,S that comprised only 25 per cent of the fusion protein containing CS protein (RTS) and the rest 75 per cent made up of HBsAg(S). A randomized trial in Gambia with a new adjuvant formulation ASO2 established safety of RTS, S as well as the ASO2.

These safety and phase II proof of concept trials that began in 1992 were finally completed in 2007 demonstrating that children and infants immunized with RTS, S vaccine formulations were partially protected against malaria<sup>5,6</sup>. Encouraged by the demonstrated safety and efficacy, although only partial (lower prevalence of parasites, lower episodes of malaria and of severe malaria - all in the range of 25 to 40% of cases) RTS, S vaccine phase III clinical trials were planned. This in itself was an amazing exercise and involved all major players and stakeholders including GSK as the sponsor, the scientists represented by the clinical trials partnership committee, with financial support from MVI/PATH and the Bill & Melinda Gates Foundation and in many ways was an unprecedented exercise in its intent, scope, and financial implication. These phase III trials were finally conducted in 11 different locations in seven malaria endemic African countries, starting in 2009 and finishing in 2014<sup>8,9</sup>. However, in the final analysis, in children and in infants who received three

doses of RTS, S vaccine and a booster, the risk of clinical episodes reduced only up to 36 per cent in children and up to 26 per cent in infants over a period of three to four years of observation with no remarkable protection against severe disease in infants<sup>9</sup>. By any standards of prevention of disease by immunization these are very modest outcomes, even for a first generation vaccine. Be that as it may, following recommendations by the European Medicines Agency, the WHO decided in July 2015 that RTS,S vaccine with a trade name of Mosquirix be approved for use in young children in Africa<sup>1</sup>. While questions about its mode of action and concerns about its low efficacy remain, RTS,S is the first ever vaccine against any parasitic disease. Scientists involved in malaria vaccine development and major funding agencies should be encouraged with the licensure of first ever vaccine against malaria and continued efforts will yield vaccine with much higher efficacy in coming years. In fact, another liver stage vaccine based on irradiated sporozoites has been reported recently by Sanaria, a company launched by Dr Stephen L. Hoffmann that has successfully produced sporozoites weakened by irradiation from infective mosquitoes; but initial results in human trials were disappointing<sup>10</sup>. However, intravenous immunization with five doses of this vaccine called PfSPZ, has shown complete protection in human volunteers<sup>11,12</sup>. This is an exciting development but serious challenges including preparation and storage of weakened sporozoites in liquid nitrogen, delivery of five doses of the vaccine in infants by intravenous route and efficacy trials in the field remain to be addressed.

Malaria vaccines against the blood and sexual stages of the parasite are also being pursued by several research groups around the world including India. A number of vaccine target antigens have been characterized, greatly facilitated by advances in genomics and proteomic techniques. Although early experimental blood and sexual stage recombinant vaccines have not lived up to their promise, but quest for better combinations and more efficacious formulations is being pursued with vigour. In India, scientist at the international Centre for Genetic Engineering and Biotechnology (ICGEB) have carried out, first of its kind, phase I clinical trial of a malaria vaccine based on two major blood stage proteins, produced by recombinant methods in India<sup>13</sup>. Similarly, another experimental vaccine against *Plasmodium vivax* (highly prevalent in India) is being developed for clinical trials in India. These completely indigenous

efforts have opened the door for development of vaccines against diseases for which there are no vaccines available yet including malaria.

The journey and story of RTS,S illustrate the scientific, logistic and financial hurdles, not to mention single minded doggedness of the team that developed the vaccine will be faced by researchers, industry and funders in developing vaccines that have not yet been developed, particularly against highly pathogenic parasites and bacteria. Long term continued support and appreciation of the complex nature of developing vaccines against human diseases will be required from the funding agencies and the pharma industry. With that, and new technological advances it is certain that novel vaccines will be developed which will be added as crucial weapons in the control, and elimination of infectious diseases.

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#### References

- Morrison C. Landmark green light for Mosquirix malaria vaccine. *Nat Biotechnol* 2015; 33 : 1015-6.
- Gordon DM, McGovern TW, Krzych U, Cohen JC, Schneider I, LaChance R, *et al.* Safety, immunogenicity and efficacy of a recombinantly produced *Plasmodium falciparum* circumsporozoite protein-hepatitis B surface antigen subunit vaccine. *J Infect Dis* 1995; 171 : 1576-85.
- Stoute JA, Slaoui M, Heppner DG, Momin P, Kester KE, Desmons P, *et al.* A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. RTS,S Malaria Vaccine Evaluation Group. *N Engl J Med* 1997; 336 : 86-91.
- Stoute JA, Kester KE, Krzych U, Welde BT, Hall T, White K, *et al.* Long-term efficacy and immune responses following immunization with the RTS,S malaria vaccine. *J Infect Dis* 1998; 178 : 1139-44.
- Bojang KA, Milligan PJ, Pinder M, Vigneron L, Alloueche A, Kester KE, *et al.*; RTS,S Malaria Vaccine Trial Team. Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet* 2001; 358 : 1927-34.
- Kester KE, Cummings JF, Ockenhouse CF, Nielsen R, Hall BT, Gordon DM, *et al.*; RTS,S Malaria Vaccine Evaluation Group. Phase 2a trial of 0, 1, and 3 month and 0, 7, and 28 day immunization schedules of malaria vaccine RTS,S/AS02 in malaria-naïve adults at the Walter Reed Army Institute of Research. *Vaccine* 2008; 26 : 2191-202.
- Ballou WR. The development of the RTS,S malaria vaccine candidate: challenges and lessons. *Parasite Immunol* 2009; 31 : 492-500.
- The RTS S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Med* 2014; 11 : e1001685.
- RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet* 2015; 386 : 31-45.
- Hoffman SL, Billingsley PF, James E, Richman A, Loyevsky M, Li T, *et al.* Development of a metabolically active, non-replicating sporozoite vaccine to prevent *Plasmodium falciparum* malaria. *Hum Vaccin* 2010; 6 : 97-106.
- Seder RA, Chang LJ, Enama ME, Zephir KL, Sarwar UN, Gordon IJ, *et al.* Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. *Science* 2013; 341 : 1359-65.
- Shekalaghe S, Rutaihwa M, Billingsley PF, Chemba M, Daubenberger CA, James ER, *et al.* Controlled human malaria infection of Tanzanians by intradermal injection of aseptic, purified, cryopreserved *Plasmodium falciparum* sporozoites. *Am J Trop Med Hyg* 2014; 91 : 471-80.
- Chitnis CE, Mukherjee P, Mehta S, Yazdani SS, Dhawan S, Shakri AR, *et al.* Phase I clinical trial of a recombinant blood stage vaccine candidate for *Plasmodium falciparum* malaria based on MSP1 and EBA175. *PLoS One* 2015; 10 : e0117820.