International Scholars Journals

African Journal of Malaria and Tropical Diseases ISSN 4123-0981 Vol. 7 (2), pp. 001-002, February, 2019.
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Editorial

The Malaria and the vaccine candidates

The news of the trial of the new malaria vaccine produced by GlaxoSmithKline (GSK) in cooperation with the Malaria Vaccine Initiative (sponsored partly by Melinda and Bill Gates Foundation) has provoked this editorial.

Malaria remains one of the oldest afflictions of man. Malaria probably is as old as humanity. It was one of the earliest fevers to have an academic description in Medicine. Hippocrates (460–370 BC) described the periodicity of malaria at a time when the disease was endemic in the South of Europe – Greece and Italy. Galen also wrote several treatises in Rome about malaria. The eradication of malaria from Greece, Italy and the rest of the South of Europe was not by the use of vaccine but by improved environmental health - mainly drainage. Without water stagnation, the vector of the malaria parasite, the anopheles mosquito will not breed. The geographical spread of malaria includes Africa, Asia, Middle-east, South America and parts of Australasia. With frequent Air travels, distance is no longer a barrier to infection by a tropical disease agent. Imported malaria does occur in London and in other commercial capitals in Europe and America. The anopheles mosquito which boards a free flight from the Tropics will bite a few more people in London or elsewhere before dying. Once in a while, clusters of 4 to 5 cases of malaria without travel history are identified in cities in Europe and United States. Around the world, malaria causes about 500 million clinical diseases yearly with about 1 million deaths per year. The Sub-Saharan Africa carries the brunt with most deaths among children below 5 years of age.

Malaria has defied several eradication efforts. The parasite has developed resistance to several drugs, the recent being the front line drug – Artemisinin (In the June 2009 Editorial, I extensively dealt with Artemisinin resistance). The manpower cost of Malaria in Africa in terms of office and labor absenteeism has not been properly quantified by any research to my knowledge but estimates go in terms of billions of dollars. The school absenteeism with consequent loss of educational hours is a problem. Because of the yearly mortality of almost one million, there is great interest in the new vaccine. Unfortunately, Malaria has defeated many researches worth billions of dollars. There have been several malaria candidate vaccines but hardly have they gone beyond the stage of research in the laboratory animals. Therefore, the new vaccine going to phase III clinical trial is a triumph. Readers should note that contrary to the publication by GlaxoSmithKline (GSK), the new vaccine candidate is not the first worldwide malaria vaccine trial that has gone through an advanced stage. Before this particular vaccine candidate, there was Dr. Patarayo's Spf66 malaria vaccine candidate. The Spf66 candidate vaccine was produced using synthetic plasmodium falciparum peptides and targeted against merozoites. The lofty idea was to destroy the merozoites emerging from the hepatocytes before they enter the erythrocytes. The initial trial showed great success demonstrating about 70 % protection. As the trials continued, the fortunes of the candidate vaccine, Spf66 dwindled and dwindled until the protection it could afford was estimated to be only 31 % (Alonza et al. 1995, Médecine tropicale: revue du Corps de santé colonial, 1995; 55, 4 supp). By the time the vaccine was tried in Gambia during the rainy season, the efficacy of the vaccine disappeared and was nothing more than a placebo and the vaccine was abandoned (Cochrane Review; the full text of the review is available in *The Cochrane Library* (ISSN 1464-780X). Thus, Gambia was the Waterloo for Spf66 vaccine candidate. The rainy season remains the utmost trial for a malaria vaccine because it provides the water stagnation in which breed the insect vector – anopheles. Nigeria and Gambia are the holoendemic areas for malaria; the perennial malaria in these two West African countries makes them the ideal environments for testing the validity of any malaria vaccine.

We now have to watch with caution the new GSK vaccine trial. The vaccine is designed to target the sporozoites – the earliest form of the malaria parasite injected by the mosquitoes into the human being. The vaccine candidate is designated as RTS, S/AS02A. (R= repeated region, T= T-Cell epitope, S = Hepatitis B surface antigen, AS02A = proprietary oil in water emulsion owned by GSK. This is a re-combinant vaccine in which circumsporozoite protein of plasmodium falciparum is fused with Hepatitis B surface antigen (HBsAg). The vaccine is now called Mosquirix [or RTS, S]. The phase III trial has just started in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania. The trial is expected to involve up to 16,000 children. If successful, the vaccine will protect against malaria and against

hepatitis B. Unfortunately, Nigeria and Gambia were not included as the countries for phase III trial. In my own opinion, Gambia should have been included as one of the phase III trial countries at least to shed more light as to why the last malaria vaccine candidate, Spf66 which succeeded elsewhere failed in Gambia.

Why has malaria vaccine failed for so long? This is a serious scientific query. The answer is not easy. One of the problems is poor understanding of the biology of malaria. The life cycle of malaria parasite in both man and the anopheles vector is probably more complex than we know. The immunology of malaria is poorly understood. The changing immune characteristics of the different stages of the malaria parasite constitute a puzzle; the sporozoite, the pre-erythrocytic schizont, the merozoite emerging from the hepatocyte, the erythrocytic trophozoite, the erythrocytic schizont, the blood merozoite, the gametocyte and the gamete – are all different forms of the same parasite as the parasite keeps changing forms at different stages of infection. This is not just an ordinary biological polymorphism. All the forms possess different antigens and behave as different organisms, yet it is one and same organism. The antigen variations give the parasite an opportunity for immune masquerading and final evasion. Malaria has evaded the scientists for centuries. It took GlaxoSmithKline (GSK) about 22 years to come so far. If malaria escapes this time (by Immune masquerading and Evasion), then it may be another 22 years or never. If the new vaccine fails, then humanity should go and ask the Greeks and the Romans how they wiped out malaria from the South of Europe. The answer will be: Environmental Health – improved drainage; let no water stagnate in the tropics and the anopheles mosquitoes will disappear and there will be little or no malaria.

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International Journal of Medicine and Medical Sciences