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## Introduction

Malaria is one of the major reasons for world’s morbidity and mortality. Especially, Malaria is a burden to societies in Africa, causing estimated deaths of around 5, 40, 000 during the year 2010 (World Health Organization, 2012). The majority of estimated cases accounting to 80% and deaths accounting to 91% occur in Africa and the huge proportion of deaths accounting to 86% occurs in African children under 5 years of age (World Health Organization, 2012). The human toll is unfortunate and the economic expense is immense. There is a serious need for novel & effective public health intervention. Vaccines are considered to be among the potential new interventions, which when combined with existing malaria control strategies can reduce the burden of malaria in prevalent areas. In the case of infectious diseases like malaria, even a moderately effective vaccine could possibly save thousands of lives. Even though existing malaria control strategies like long lasting insecticide nets, indoor residual spraying and artemisinin based combination therapy are mainly involved in reducing the burden of malaria globally,  a first generation malaria vaccine would be a complementary strategy to help in eradication of malaria (Genton, 2008). Presently, there are no licensed malaria vaccines, but a number of candidate vaccines which target different stages of the parasite life cycle are under research and development (Tediosi et al., 2009). The candidate vaccines which target the pre-erythrocytic stage of the parasite plasmodium falciparum are at the advanced stages in clinical development. Evaluation of a malaria vaccine should not be solely based on its efficacy and effectiveness. The cost effectiveness analyses also must be taken into consideration in the evaluation process. This enables the policy makers to take a wise decision, wherein introduction of a new vaccine into immunization programmes will not only impact the health of a society but also positively influence the social and economic benefits of a country (Ozawa et al., 2012). Cost effectiveness of a vaccine is a very important factor which needs to be measured by the developing countries because these countries are facing increasing pressures on how to allocate the limited resources and decide appropriately among various competing priorities. Also cost effectiveness analysis suggests to the governments if the preferred vaccine is an efficient investment or not (Ozawa et al., 2012). In 2011, World Health Organization proposed that cost effectiveness analysis of deploying a new vaccine into a national immunization programme should be considered prior to the implementation of a particular strategy (Hutubessy et al., 2011).

## RTS, S malaria candidate vaccine

RTS, S vaccine also known as RTS, S/AS is presently the most clinically advanced malaria candidate vaccine. This is the first paediatric vaccine to show that it can protect infants and young children living in malaria-endemic regions against the infection and clinical disease caused by the deadly malaria parasiteplasmodium falciparum. The RTS, S vaccine is a recombinant protein particle in which a component of the plasmodium falciparum circumsporozoite protein is fused to the hepatitis B virus surface antigen. This recombinant protein in combination with a GlaxoSmithKline multicomponent adjuvant system stimulates the production of high levels of antibodies and a modest T cell immunogenicity which affects the parasite’s capability to infect, grow and survive in the liver cells (Hill, 2011). The RTS, S vaccine was made by scientists at GlaxoSmithKline Biological laboratories in 1987. The initial development of this malaria vaccine was carried out by GlaxoSmithKline and Walter Reed Army Institute of Research. Later, the clinical development stages of this malaria candidate vaccine has been undertaken by GlaxoSmithKline in collaboration with the PATH Malaria Vaccine Initiative, Bill and Melinda Gates Foundation, 11 research centres in 7 African countries and many other educational institutions all over the world (Hill, 2011). The Clinical assessment of RTS, S malaria vaccine in adults started in the United States in 1992, and in Africa in the year 1998. RTS, S vaccine has progressed through the phase I and Phase II clinical trials in a number of African countries. In 2003, the Phase II trial carried out with more than 2000 children in Mozambique showed the possibility of administering RTS, S vaccine in children. Long term results from this trial demonstrated that the vaccine has clinical benefit which lasted for 45 months after the initial vaccination. When the RTS, S vaccine was administered to 6 – 10 week old infants, the RTS, S malaria vaccine showed a satisfactory safety and tolerability profile which is comparable to the profiles of standard vaccines given to infants under the national immunization programmes of Africa. The Phase III clinical trials commenced in May 2009 in sub Saharan African countries. The results from the two different studies conducted in young children and infants in Africa showed that the candidate vaccine provided considerable protection against the clinical disease and infection. At the time of the first vaccination, the clinical trial included 15, 460 people, in two different age groups: 6 – 12 weeks old and 5 – 17 months of age. The results from the first 12 months of follow up indicated that the RTS, S malaria vaccine reduced the incidence of clinical and severe malaria by 31% and 37% respectively in infants aged 6 – 12 weeks and in children aged 5 – 17 months, RTS, S vaccine decreased the incidence of clinical and severe malaria by 56% and 47% respectively (Wilby et al., 2012). Further results from the Phase III trial will be available in 2014 and these will help in understanding the complicated relationship between the immune response, vaccine efficacy and intensity of exposure.

## Cost Effectiveness Analysis

The RTS, S malaria vaccine is now close to licensing, but still it is uncertain how cost effective it would be, or who would it help most from its use (Maire et al2011). Based on the analysis of various models, assumptions, various parameters and uncertainties that exist in cost effectiveness models of malaria vaccine, the key factors predicting the cost effectiveness were found to be price per dose, vaccine efficacy, duration of protection and malaria transmission intensity (Moorthy et al., 2012). In order to get a better idea of the cost effectiveness of the RTS, S malaria vaccine, we need to have more details about the vaccine which would be available in 2014 from the completion of Phase III trial. Positive results from the clinical trials of RTS, S vaccine which gives protection against plasmodium falciparum malaria have indicated that there are high chances for this malaria vaccine to be granted  a license. This has brought in the pressing need to recognize the health, economic and social consequences that endemic countries face by approving and deploying this malaria vaccine. To analyse the cost-effectiveness of RTS, S vaccine, stochastic and computational simulation models of malaria epidemiology and vaccination have been developed. For the simulation, these models considered different vaccination approaches, transmission settings, other health interventions and time horizon of ten years (Maire et al., 2011). These models were simulated in stable populations of 100, 000 people.

Tediosi et al (2006) conducted a study to estimate the costs incurred for deploying a malaria vaccine via the Expanded Programme on Immunization.  In this study, they also predicted the cost per dose and cost per fully immunized child. These factors were vital in the cost- effectiveness analysis. Estimating cost of a health intervention is critical as this is important parameter in calculating the cost effectiveness ratio. This ratio gives information on allocative efficiency in terms of the cost per health gain of a given health intervention (Drummond et al., 1997). In this modelling, the estimated delivery cost of the malaria vaccine was based on the information that is available on DTP-HBV vaccine with likely characteristics, which was delivered through EPI in the study setting Tanzania. Also, the analysis assumed varying vaccine cost hypothesis ranging from US$1 per dose to US$10 per dose (Hutton et al, 2006). To predict the cost per dose delivered and cost per fully immunized child, the study took into account the expenses incurred in purchasing the vaccines, storing and distributing the vaccines, managing the Expanded Programme on Immunization, the delivery costs which included syringes, personnel, safety boxes, and management of waste; and also the money spent on training the workers involved in the vaccination programme. From the cost analysis, it was found that the average cost per fully immunized child increased from " US$4. 2 per FIC at a vaccine price of US$1 per dose to US$31. 2 at vaccine price of US$10 per dose" (Hutton et al., 2006). From this analysis, it is very clear that taking into account cost of delivering the vaccine is not enough . Other relevant costs should also be included before introducing the vaccine into the Expanded Programme on Immunization because all of these various cost parameters influence the decision making in estimating the annual budget for the vaccination programme. According to the model published by Maire et al (2011), it is evident that vaccine price of US$1 or US$2 per dose is highly cost- effective in most of the African settings. In addition to vaccine cost, the verdict to use RTS, S malaria vaccine depends partly on its effect. For most of the vaccines which prevent diseases, theirsignificant impact is attained by decreasing the transmission levels. Therefore it is important to consider the delivery strategies and various transmission levels. Analyzing the impact of the RTS, S malaria vaccine in changing malaria transmission settings is important in making cost- effectiveness predictions. Brooks et al (2012) conducted this analysis using computer simulation models wherein the vaccine profile of the RTS, S vaccine from the phase II trials was considered. Transmission settings were assumed to be fixed or the annual entomological inoculation rate (EIR) was varied between 2 to 20 (ibpa) over a period of 10 years. The vaccine was delivered using four different strategies which are: Expanded Programme on Immunization (EPI), Expanded Programme on Immunization along with catch up, EPI along with school-based campaigns, and EPI along with mass campaigns. This stochastic model also analysed the impact of the vaccine based on the delivering strategy (Brooks et al., 2012). Here the RTS, S vaccine was set to show efficacy of 60% " against the force of infection from the time of completion of the three dose vaccination regime" ( Brooks et al., 2012). Vaccine efficacy after one dose was taken as 40% and efficacy after two doses was taken as 50%. It is assumed that a three dose vaccination regime will enhance the immune responses and prolong the period of protection. Efficacy of the RTS, S vaccine against the infection was assumed to decay exponentially with a half life of 10 years. From the analysis of the model, it was found that the Expanded Programme on immunization, EPI together with catch-up and school based campaigns prevented 3 – 4 deaths per 1000 doses in surroundings where transmission was increasing or decreasing. In a transmission setting with annual entomological inoculation rate of 2 (ibpa), EPI, EPI along with catch-up and EPI with school based campaigns prevented 2 – 3 deaths per 1000 doses. When the vaccine was delivered through mass campaigns with EIR = 2 ibpa, it prevented 5 – 7 deaths per 1000 doses (Brooks et al., 2012). But mass campaign was not effective in higher transmission surroundings. EPI strategy showed relatively high efficiency per 1000 doses across all settings and this strategy is also proven to be compatible with present clinical trials . Therefore, it is cost-effective to introduce the RTS, S vaccine via this strategy. EPI with catch up vaccination given to children below 18 months was found to be an attractive option in locations with decreasing transmission. But to implement this strategy, additional investment will be needed. School based campaigns did not enhance the efficiency in any of the settings. Mass campaigns when compared to EPI were less efficient in transmission settings with EIR above 2 ibpa (Brooks et al., 2012).

## Travellers

## Risk of malaria in travellers

The possibility of malaria acquisition by travellers varies broadly with livelihood, activities and geographical regions (Leder et al., 2004). In the 1980s, the occurrence of malaria in European travellers who did not use chemoprophylaxis was 15. 2 per 1000 travellers per month in East Africa and 24. 2 per 1000 travellers per month in West Africa (Steffan et al., 1990). When the use of chemoprophylaxis by European travellers was taken into consideration, the occurrence of malaria was only 1. 7 per 1000 travellers in East Africa and 3. 8 per 1000 travellers in West Africa (Steffan et al., 1990). The study of traveller databases have revealed that the chances of acquiring malaria is highest in Africa and Oceania, the risks are moderate in South Asia and chances of acquiring malaria is low in South America, Central America and South-East Asia (Leder et al., 2004). In particular, the occupational travellers who stay in malaria – endemic regions are at higher risk of acquiring malaria (Chen et al., 2006).

## RTS, S malaria vaccine – a traveller’s vaccine?

The results that were demonstrated by the RTS, S malaria vaccine in clinical trials have led the people to believe that it’s possible to introduce public health intervention that could decrease the problems of malaria in malaria endemic regions but it is impractical, in the near future, for a malaria vaccine to act as a substitute for preventive measures against exposure and chemoprophylaxis in travellers (Genton, 2008). The main purpose of a malaria vaccine for travellers is to provide them with good protection against the infection or clinical disease. The other requirements which are needed to be considered for a traveller’s vaccine are short initial vaccination schedule, rapid onset of protection which is expected preferably 2 weeks after the last dose and the vaccine should not interfere with other travel vaccines administered (Genton, 2008). Also for a vaccine to be used as a supplementary protective measure by travellers, the vaccine should show an efficacy of about 60%. The efficacy which is mentioned is higher than the vaccine efficacy of about 50% which is needed to prevent clinical malaria in African children. This partially effective malaria vaccine will benefit the long – term travellers and soldiers positioned in malaria-endemic areas. The RTS, S vaccine if proven to show the above requirements  will also be applicable to short – term travellers like business travellers who repeatedly travel to low endemic areas. In this case the vaccine should show protection against infection at least for a year. In the initial clinical trials the RTS, S malaria vaccine has been confirmed to be a potential malaria vaccine presenting moderate efficacy in both malaria-naive and experienced adults as well as children (Regules et al., 2011). Prior to determining the cost effectiveness of the RTS, S malaria vaccine for use in travellers, it is important to further verify its efficacy and usefulness in non-immune populations. Therefore for the RTS, S vaccine to be a traveller’s vaccine, Phase III trials in these populations is desired (Wilby et al,. 2012). Even if this first generation vaccine (RTS, S vaccine) is launched, it is necessary to use other protective measures like long lasting insecticide treated nets, repellents and strict use of chemoprophylaxis when travelling to high malaria-endemic areas.

## Cost effectiveness of the RTS, S vaccine for African children

From the above analysis using cost effectiveness tools, we have observed that RTS, S malaria candidate vaccine will be highly cost effective at low transmission areas, however , it is not likely that this would lower the transmission levels except when the transmission is already at moderate levels. The RTS, S vaccine will be very effective if it’s deployed in combination with mosquito control methods which affect capacity of the vector (Maire et al., 2011)Analysis in Tanzania revealed that cost effectiveness of RTS, S vaccine at a low vaccine price is similar to that of the existing preventing measures against malaria and also RTS, S vaccine with modest efficacy and nominal effectiveness could be used as a cost effective public health intervention to reduce the incidence of malaria in sub- Saharan African countries particularly for children under the age of 2 years (Tediosi et al., 2006). Simulations performed by Tediosi et al (2009) showed that pre-erythrocytic vaccines are more cost effective in transmission settings with low EIR, when compared to other vaccine types. It is also predicted that pre erythrocytic vaccine demonstrating initial efficacy of 52% will be cost effective when it’s delivered through the Expanded Programme on Immunization.

Simulations show that administering RTS, S vaccine to infants in African countries through the Expanded programme on Immunization is most cost effective vaccination delivery strategy. But in low transmission scenarios the mass vaccination strategy was comparably more efficient. Another model suggested that mass vaccination is needed to stimulate herd immunity (Smith and Tediosi, 2012). Based on the various cost effectiveness evaluations conducted and clinical results of RTS, S vaccine so far, there is a probable chance of considering this malaria vaccine for use in African children from 6 weeks to 17 months old. But for making a final decision on RTS, S malaria vaccine adoption and deployment in Africa , there is a need for good quality information on local transmission intensities, incidence of malaria infections, duration of protection (Smith and Tediosi, 2012). Until the results from Phase IV trials become available, it is not practical to deploy the malaria vaccine for use in African children.