

Should India be considering deployment of the first malaria vaccine RTS,S/AS01?

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INTRODUCTION

Vaccines have proven to be a potent public health tool in humankind's fight against infectious diseases, as has also been seen in the COVID-19 pandemic. Malaria vaccines have been in development since the 1960s with substantial progress in the last decade. 6 October 2021 marks a historic day in the deployment of malaria vaccines when the RTS,S/AS01 (RTS,S) vaccine was recommended by WHO for use among children living in moderate-to-high *Plasmodium falciparum* malaria transmission regions such as those found in sub-Saharan Africa.¹

RTS,S/AS01 ON THE HORIZON

Currently, several *P. falciparum* vaccine candidates are in development and these target various stages of the parasite life cycle. The WHO approved RTS,S/AS01E (RTS,S) is a vaccine made by using recombinant fragments from the circumsporozoite protein (from the sporozoite stage) that is in fusion with hepatitis B surface antigen.² It is the first malaria vaccine shown to provide partial protection against malaria in phase III trials. Encouraging results from pilot implementation programmes in three African countries namely Ghana, Kenya and Malawi wherein >800 000 children have been vaccinated since 2019 led to WHO recommendation of its use in sub-Saharan African countries.¹ The pilot programme was preceded by a phase III trial at 11 sites spanning seven sub-Saharan African countries from 2009 to 2014.³ The pilots have demonstrated ~40% reduction in malaria episodes, substantial reduction in severe malaria cases and one death averted for every 200 vaccinees. The pilot studies also successfully proved that it is feasible to deliver vaccine equitably in routine use without any negative impact on insecticide treated bed net use, and in fact 90% of children benefited from at

Summary box

- ▶ Vaccines are highly successful public health tools in controlling infectious diseases. Malaria continues to be a major cause of mortality especially among children in developing countries of Africa and Asia. Malaria vaccine has been in development since past few decades and on completion of phase III, RTS,S/AS01 entered into pilot implementation studies in three sub-Saharan African countries.
- ▶ The pilot implementation in three African countries demonstrated ~40% reduction in malaria episodes and one death averted for every 200 vaccinees. Based on these results, WHO on 6 October 2021 recommended the use of malaria vaccine RTS,S in children in sub-Saharan Africa and in moderate-to-high transmission regions as defined by WHO.
- ▶ We assessed the implications of the newly recommended RTS,S/AS01 malaria vaccine for India, a major contributor of malaria in the South East Asian region. The current epidemiological scenario may not require immediate deployment of malaria vaccine in India as it is a low-transmission setting. However, there are several gaps in our understanding of the true picture of malaria burden and these require inputs from research.

least one preventive intervention (Insecticide-Treated Nets (ITN) or vaccine). The vaccine is now recommended for 5–17 months children living in areas having moderate-to-high intensity of malaria transmission. Also, malaria endemic countries need to take an individual decision whether to adopt the vaccine as part of national malaria control strategies.¹

IMPLICATIONS FOR INDIA

According to WHO, India experienced ~5.6 million cases and ~7,920 estimated deaths in 2019.⁴ India is 1 of the 11 countries (the only non-African nation) being supported in the High Burden to High Impact initiative, for countries which accounted for ~70% of the global estimated cases and



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deaths from malaria.⁴ As per the national malaria control programme of the country, there were 0.33 million reported cases and 77 deaths in 2019.⁵ India harbours substantial burden of malaria due to *Plasmodium vivax* (47% of all malaria cases in 2019) and the epidemiological situation in India is further complicated by the overlapping distributions of *P. falciparum* and *P. vivax* malaria. There is disparity in number of cases and deaths reported by the national programme and those estimated by WHO. India's national programme data are based on malaria cases diagnosed in public health sector and do not include the possibly substantial caseload being managed by the private sector. WHO estimates are based on mathematical methods which take into consideration cases being treated in private sector and presumptive treatments in addition to other parameters. There has been a decline of 83.34% in malaria cases and 92% in malaria deaths in two decades between 2000 and 2019 as per national malaria control programme. Since 2012, India consistently has annual parasite incidence (API) less than one.⁵

While recommending the first malaria vaccine, WHO has advised the countries to take an individual decision whether to adopt the vaccine as part of national malaria control strategies. As India is targeted for malaria elimination by 2030, it is important that India assesses the need of the vaccine given the current epidemiological scenario and other factors.

India is a 'low-transmission setting'

As per WHO, intensity of transmission can be gauged by prevalence rate of *P. falciparum* in 2–10 year old children ($PfPR_{2-10}$) or by number of cases per 1000 population at risk (API). High-transmission settings typically have $PfPR \geq 35\%$ or API of 450; moderate transmission is at $PfPR$ of 10%–35% or API of 250–450, low-transmission settings are at $PfPR$ of 1%–10% or 100–250 API and very low-transmission settings are marked by 0%–1% of $PfPR$ or API < 100.⁶ Therefore, India as a country is categorised in very low-transmission settings by WHO estimates as well as those reported by the national malaria control programme. If more granular data are examined, that is, at district level (which is the administrative unit of national malaria programme), none of the 720 odd districts had API of more than 44 in 2019 thus bringing the districts in the bracket of very low-transmission settings. However, India has a weak surveillance system and its malaria numbers arise from public health sector only and thus is possibly undermining the real burden.⁷ There is an urgent need to assess the malaria burden in private sector and also the hidden burden in community in form of asymptomatic and subpatent infections especially in case of forest malaria.⁸

Few deaths

The reported mortality caused by malaria is negligible at 77 deaths in 2019 and the malaria vaccine's clear benefit is in preventing severity and deaths. In the national data capture system, data on severe cases

is not accounted for. Also, owing to the weak health-care infrastructure in India, especially in rural areas, severe cases of malaria may not have access to the suitable health facilities. To fill in the above gap, systematic studies are needed to estimate the severe cases of malaria in the community.^{7,9}

Significant *P. vivax* burden of India

Approximately half of malaria burden in India is due to *P. vivax*, which has its own challenges and cannot be resolved with this *P. falciparum* vaccine. Epidemiologically, India does not have exclusive *P. falciparum* or *P. vivax* areas in the country but rather has a mix of multiple species including *Plasmodium ovale* and *Plasmodium malariae*.¹⁰ Therefore, a vaccine combating *P. falciparum* only may create a false sense of security and failure of which (in case vaccinee contracts *P. vivax* malaria) can give rise to lack of trust and faith.

Cost-effectiveness

In a WHO coordinated mathematical model study, significant public health impact of RTS,S/AS01 was predicted in scenario with $PfPR_{2-10}$ of 10% to 65% corresponding to API of more than 250, that is, moderate and high transmissions. However, at $PfPR_{2-10}$ of 3% the vaccine was deduced not to be cost-effective.¹¹ Hence, India at its current low endemicity level may better divert its financial resources in providing the communities with interventions such as insecticide treated bednets, indoor residual spray and improvement of its healthcare infrastructure.

CONCLUSION

The malaria vaccine RTS,S holds promise for high-transmission settings, such as African countries, but whether a similar situation exists in some endemic pockets of India remains unaddressed. Thus, there are crucial epidemiological gaps in the Indian settings that highlight the need for research. This will enable evidence-based strategies that may pave the way for RTS,S use in India and elsewhere.

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