Commodifying Vaccines to Curtail Antibiotic Resistance Impact in Malaria Endemic Countries

Maria Khan

Department of Microbiology, Peshawar Institute of Cardiology-MTI, Peshawar, Pakistan

ABSTRACT

Rampant and prevalent deployment of an efficient malaria vaccine in Pakistan, together with basic control and preventive measures, could significantly decrease the economic and healthcare burden caused by drug-resistant malaria. Moreover, RTS, S/AS01 vaccine has attained a much-needed breakthrough after decades of growth, as an innovative vaccine for malaria in Phase III clinical trials, and presently undergoing implementation studies. So far Gavi, WHO, and other stakeholders are contemplating on the practical issues, risk-benefit, and cost-effectiveness in resource-limited settings of vaccine implementation capacity. Imminent advances, like using a delayed as well as enhanced protection, divided schedule for dosing, and alternate adjuvants are likely to attain the vital goal of eradication of malaria. Vaccination is a potentially critical component of efforts to arrest the development and dissemination of antimicrobial resistance; though little is known about the impact vaccination may have within low-and-middle-income countries.

Key Words: *Antimicrobial resistance, Malaria, Vaccine.*

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Antimicrobial resistance (AMR) is a leading global health threat,[1] with 1.27 million deaths attributed to AMR in 2019 alone.[2] AMR development is thought to be primarily driven by antimicrobial use,[3] but with resistant genes and their host bacteria capable of passing between people, animals, and the environment, multi-faceted approaches are needed to curb AMR development and dissemination.[4] In 2016, a global review on AMR set out ten recommendations for tackling this global pandemic,[5] one of which was vaccination.[6]

Vaccines may directly and indirectly impact on AMR, however, vaccines that target viruses and parasites may also deliver an indirect effect on AMR.[7] Conversely, vaccines may also exert a resistance selection pressure on target and/or bystander pathogens.[8] Thus, to understand these complex interactions more fully, it is crucial that the putative impact of vaccines on AMR is evaluated in a systematic manner.

Varying responses to vaccination have been perceived among low-income (LIC), low- and-middle-income countries (LMICs) and high-income countries (HIC), with vaccines frequently under-performing expectations in LMICs despite high vaccine coverage rates.[9]

Correspondence to: Dr. Maria Khan, Department of Microbiology, Peshawar Institute of Cardiology-MTI, Peshawar, Pakistan
E-mail: kmaria22@hotmail.com

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However, many LMICs also have severely limited access to diagnostics and appropriate antibiotics,[10] with empirical and potentially unnecessary antibiotic prescriptions being a common reality of clinical practice.[11] Hence, whilst there is an intrinsic need to conduct vaccine impact evaluations in both HICs and LMICs, there is also a need to evaluate whether vaccination can play a cost-effective role in assisting equitable provision of antibiotics to those at greatest need.[12]

In accordance with World Health Organization (WHO), approximately 219 million malaria cases worldwide were reported in 2017, which were slightly lower than that in 2010, i.e. 239 million but higher than in 2016 which were 217 million.[13] Pakistan is ranked as one of the highest burden regions in combating malaria, with an expected one million cases per annum.[14] Conferring to statistics of WHO, presently, 84% of malaria is due to *Plasmodium vivax* (*P. vivax*) whereas *Plasmodium falciparum* (*P. falciparum*) accounts to 14.9% and mixed infection due to *P. falciparum* and *P. vivax* is 1.1% cases.[13] Especially, extremely underdeveloped and impoverished areas of Khyber Pakhtunkhwa and adjoining Tribal districts of Pakistan have the highest burden of malaria cases attributing to influx of internally displaced persons and previously settled Afghan refugees.[15] Moreover, the emergence of drug resistance in *Plasmodium* contribute to pose an enormous risk to efficient malaria control and management in Pakistan. Mostly, *P. falciparum* chloroquine resistance transporter (PfCRT) gene mutations lead to chloroquine resistance, initially emerged in 1960s in Latin America and South-East Asia and in 1970s in East Africa.[16]

Malaria vaccine is an effective mode to fight the colossal socioeconomic encumbrance as a result of this infection.[17] Therefore, an effective vaccine can both prevent sensitive and resistant infections, overall decreasing selection pressure for resistance and pathogen-associated antimicrobial use.[18] In contrast, developing an antimalarial vaccine is challenging, mostly due to an intricate life cycle of the parasite and inadequate knowledge regarding immune system's response.[19] In 2021, RTS,S/AS01 became the first malaria vaccine to be recommended by WHO for general use in the paediatric population.[20] Finally, pilot studies were underway in Malawi, Kenya, and Ghana for RTS, S/AS01 vaccine to answer the unresolved concerns related to vaccine and its implication on public health use.[17] As it is a subunit lyophilised injection delivered intramuscularly targeting *P. falciparum*, therefore, it is delivered *via* three doses at five, six, and seven months of age followed by a fourth dose at 18-21 months of age.[21]

Phase III trials indicated that the RTS, S/AS01 vaccine was effective at reducing clinical malaria.[22] However, although rare, increases in febrile convulsions, meningitis, cerebral malaria, and mortality rates in RTS, S/AS01 vaccinated individuals led to a recommendation for further safety profiling and impact assessment.[21] The unique nature of RTS, S/AS01 vaccine portrays a pioneer for vaccine development against malaria. None of the vaccines for malaria has progressed to Phase III trials, specifically aiming *P. falciparum* has received positive opinion from the Medicines Agency of Europe, or suggested by the WHO advisory committees for execution among moderate--to-high malaria transmission areas of African settings.[17] Additional candidate vaccines for *Plasmodium* i.e. PfSPZ and R21 are in progressive development. These vaccines are on trial for efficacy and safety in malaria non-infected and infected individuals. Both vaccines and other potential products are scheduled in the Rainbow Tables of WHO[23] and have been lately appraised.[2]

Many challenges are required to be flagged immediately and effectively to devise an ideal prophylactic malaria vaccine. For the current implementation studies, manufacturers are making continuous efforts, but there is still uncertainty regarding their long-term supply. It should be emphasised that companies manufacturing vaccines should plot well in advance about vaccine assembling to meet demands. If implementation studies are in support of vaccine usage, then unprecedented delays can be overcome by careful planning. Challenges facing transportation and storage of vaccines, training of healthcare personnel as well as advocacy and partnerships need likewise consideration at the local, regional, and national levels.

COMPETING INTEREST:

The author declared no competing interest.

AUTHOR'S CONTRIBUTION:

MK: Substantial contributions to the conception or design of the work and drafting the work.

The author approved the final work for publication.

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