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Letter to the Editor

Combatting *Plasmodium falciparum* malaria in endemic settings: Vaccination should complement rather than devalue low-technology interventions

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To the Editor

According to the World Health Organization (WHO), in 2022, the most recent year for which figures are available, there were 249 million clinical cases reported across 85 malaria-endemic countries, of which 608,000 were fatal [1], mainly in early childhood. The confirmed case incidence of 58 per 1000 population at risk exceeded pre-COVID-19 pandemic levels in 2019, rising to over 50% higher than the expected numbers set out by the global technical strategy for malaria [2]. This trend contrasts with the sharp decline in malaria mortality in the first fifteen years of this century, so raises an alarm regarding the control and prevention of a disease that is an enduring global health threat. It is therefore of the highest priority to recover momentum towards achieving the aspirational goal of a world with 90% less malaria incidence and mortality six years from now that was set out in 2015 by the WHO's Global Malaria Program [2].

Vaccines are coming

It is against this backdrop that after many decades of painstaking research and development, followed by countless and often ultimately fruitless clinical trials, we are finally entering the era of the commercially available malaria vaccine. In fact, there are now not one but two regulatory authority-approved malaria vaccines, RTS,S/AS01 and R21/Matrix-M [3, 4]. Their initial phased roll-out is limited to some African countries, with Cameroon leading the way, which to date has been associated with a decrease in severe cases and a moderate reduction in early childhood deaths [5]. Both vaccines target *P. falciparum*, one of a handful of species of *Plasmodium* protozoan parasite that cause disease in humans, but that which is responsible for by far the most mortality.

Successful malaria vaccine production is a landmark achievement in vaccinology and tropical medicine, which should be a reason for celebration among the global community of healthcare professionals. The vaccine creators may be fast-tracked to a Nobel Prize before the legacy of their inventions, eradication of malaria, is realized. Indeed, the efficacy of current versions of each vaccine is modest [6], their safety not universally accepted by

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experts [7], their target groups at present limited to young children and pregnant women in highly endemic settings [8], their roll out to communities in most need in its very early stages [9], their immunization programs financially and logistically complicated [10], while hindered by vaccine hesitancy [11]. So, given these collective concerns, this milestone may be regarded as the end of the beginning, rather than the beginning of the end, of malaria control and prevention.

Current interventions

Meanwhile, taking personal protective measures, such as wearing long-sleeved, loose-fitting clothing and applying insect repellant to exposed body parts, and vector control interventions including sleeping under an insecticide-coated bed net, and performing indoor residual spraying (IRS), remain the best ways to avoid contracting this potentially deadly *Anopheles* mosquito-borne disease [12]. After all, it stands to reason that if a person does not get bitten by the transmission vector, they will not be infected by the pathogen. This speaks to a central tenet of infection control, that prevention is better than cure [13], which is especially valid given the constant challenge presented by antimalarial drug resistance to treatment regimens [14], in particular artemisinin-based combination therapies, notably emerging in, but not limited to, southeast Asia [15]. Vaccines will provide a valuable new weapon in this arsenal of interventions but by themselves currently do not offer the solution to the scourge of malaria.

Emerging and persistent challenges

A recent feature article by Bloomberg News [16], albeit with a provocatively misleading title, has highlighted to a wider audience what those in the public health community in sub-Saharan Africa and southeast Asia know all too well. Namely, poor distribution and inadequate quality of mosquito netting continue to pose significant challenges in the fight against malaria. This is particularly pertinent today in light of the increasing recognition that climate change is as an emerging factor in what is already an intractable problem, as the ranges of vector mosquito species are affected by fluxes in precipitation and temperature [17,18]. Thus, unpredicted extreme weather events such as flooding and heatwaves appear to lead to malaria outbreaks and increased local transmission [19]. Hence, despite the guarded optimism surrounding vaccination of target groups identified as most susceptible to clinical infection, to keep abreast of the constantly evolving malaria epidemiology landscape there remains a pressing need for innovation, implementation and impact of low-technology approaches [12, 20].

First and foremost among these integrated vector management tools are long-lasting insecticide-treated nets (LLINs) [21]. The distribution of free or subsidized mosquito nets has been a crucial strategy for combating malaria in low- and lower-middle-income countries [22]. However, despite efforts to increase the use of mosquito nets for malaria prevention, challenges such as insufficient studies, inadequate surveillance, incorrect net assembly, improper net use (typically, for fishing), and variations in malaria transmission dynamics persist, particularly in less developed countries, exemplified by Ethiopia [23]. The disparities in access to mosquito nets and their usage can be attributed to factors like socio-economic status and dwelling characteristics [24].

Net gains

Mosquito nets impregnated with insecticides have long been instrumental in reducing malaria transmission, especially in sub-Saharan Africa [25]. This is where the disease burden is highest, with more than half of all recent malaria-related deaths occurring in just four countries; Democratic Republic of the Congo, Niger, Nigeria, and Tanzania [1]. However, the effectiveness of LLINs may be limited due to behavioral adaptations of mosquito vectors, such as earlier biting times, and local negative perceptions towards using LLINs [26]. Additionally, the resistance of mosquitoes to insecticides, like pyrethroids used in LLINs, is an obstacle to malaria control efforts [27].

Furthermore, the knowledge and attitudes of communities play a crucial role in the effective use of mosquito nets for malaria prevention. Factors such as education level, age, occupation, and attitude significantly influence a person's choice to sleep under a mosquito net with the purpose to prevent parasite transmission [28]. Changing negative perceptions held by intended users of mosquito nets is required to increase their acceptance as a primary form of protection against blood-feeding, adult female *Anopheles*. Hence, targeted community engagement and education is essential for the success of such malaria control programs [29].

Seeking sustainable solutions

Although mosquito nets remain a cornerstone of malaria prevention efforts globally,

challenges such as inadequate distribution, improper use, insecticide resistance, and behavioral adaptations of mosquitoes continue to impede their effectiveness [20]. Addressing these concerns requires an orchestrated, multifaceted intervention program at local levels to ensure sustained progress in reducing symptomatic malaria prevalence among communities in high transmission zones [30]. Relevant approaches include improving LLIN supply chains, enhancing LLIN distribution strategies, intensifying community outreach activities with a focus on promoting correct LLIN usage, expanding mosquito surveillance, and developing alternative vector control methods [31].

While the last of these priorities relates to researching and funding innovations, progress in other focus areas will come through robust enforcement of current directives and better implementation of existing intervention technologies. Together, these incremental advances will have a measurable beneficial societal impact for relatively modest fiscal outlay, a critical counterpoint to high-technology vaccine design and distribution. The eagerly anticipated launch of national malaria vaccination programs is looming in the foreseeable future, the impact of which will be almost immediate according to at least one notable protagonist [32]. Given this powerful advocacy for vaccines, it may be tempting for some low-income countries to downscale or even discontinue various current interventions, notably LLINs and IRS.

Integrating old and new tools

A reallocation of limited resources might appear *prima facie* as an expedient economic measure. However, I contend this would be an act of public health folly that would lessen the likelihood of providing equitable protection. One only has to cast one's mind back to the COVID-19 pandemic to appreciate that when funding for malaria control and prevention is cut, the effect is both immediate and pronounced, as evidenced by the resurgence in malaria incidence [1, 2, 33]. The impact of localized preventive measures in continuing to mitigate the spread of malaria should therefore not be understated, literally, at all costs [34]. Hence, in order to accelerate progress towards elimination in malaria-endemic hot spots, notably to deliver maximum public health impact in areas of sub-Saharan Africa and southeast Asia, the advent of vaccines should enhance, not diminish, the sustained positive impact of affordable, low-technology interventions [15, 35].

Conclusions

The global health challenge posed by malaria continues to be significant. Despite a decline in malaria mortality in the early 2000s, recent trends show a concerning rise in confirmed incidence, surpassing pre-COVID-19 pandemic levels. The imminent widespread introduction of two commercially available vaccines against *P. falciparum* marks a pivotal advancement in prevention of this major human pathogen, albeit with moderate concerns over several issues. While first generation versions offer a remarkably promising new tool, they are not the panacea that is the holy grail of infectious disease vaccinology. Until such time, established interventions like insecticide-treated nets and indoor residual spraying remain crucial to malaria control.

Challenges persist, including poor distribution and quality of mosquito netting, exacerbated by climate change impacts on vector *Anopheles* species. In order to address these concerns, an integrated modus operandi is needed that combines traditional techniques with innovative strategies. This should emphasize improving net distribution, enhancing surveillance, and tackling mosquito behavioral adaptations. For concerted progress towards global elimination of *P. falciparum* malaria to be made, it is imperative that in the foreseeable future a multifaceted low-technology approach continues alongside vaccine implementation, rather than be replaced by it.

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