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Malaria elimination: how far can we go without a vaccine?

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Global investment in malaria control has increased substantially during the past 10 years and has made it possible to scale up effective interventions such as longlasting insecticide-treated nets, indoor residual spraying, better diagnostic procedures and artemisinin-based combination therapy (ACT). During this period, there has been a dramatic fall in the incidence of clinical malaria in some countries in large part, though not entirely, as a consequence of these improved strategies. However, globally, and especially in sub-Saharan Africa, the burden of disease and death remains unacceptably high; the interventions may have proven effectiveness, and ACTs may have been adopted for first line treatment, but they are still not reaching many of the people who need them.[1]

Malaria control aims to reduce morbidity and malaria-associated mortality to levels where they no longer constitute a major public health problem. That is not to say that the investments can then be scaled down. Malaria is a complex disease caused by five species of *Plasmodium*, and the dynamics of transmission are characterised by considerable heterogeneity due to differences within and between the parasite species, the many mosquito vectors, and environmental, human and social factors. Relaxing at the point when good control has been achieved has, in the past, been the prelude to epidemics and resurgence of infections. Nevertheless, the successes from scaling up malaria control have heightened the prospect of progressing further to elimination country by country, or regionally, with the ultimate goal of eradication.[2] Elimination is a state where endemic transmission has been interrupted and the risk of onward transmission from imported cases is very low. There is a strong precedent; since 1945, 79 countries have eliminated malaria, and there are now up to 32 more considering elimination (Fig 1). The concept of progressively shrinking the malaria map recognises where elimination is possible[3] but, equally, where it is not. It would be misguided for many high burden countries in Africa to contemplate elimination when the strategy that will save most lives, and is more likely to be achieved, is sustained low endemic control.[1]

Where elimination is being considered, there are important decisions about changes in strategy that a country must take, preferably in collaboration with regional neighbours. It should not do this until malaria transmission is already at a low level. The fundamental change is that, while control focuses on preventing and treating clinical malaria, elimination requires identification of all infections, both symptomatic and asymptomatic. In some areas, there is an important reservoir of asymptomatic infections where parasite densities are very low but still capable of transmitting infection to vector mosquitoes.[4] Surveillance thus becomes an essential intervention capable of detecting infections remote from the established health facilities. When malaria transmission has reached a low level, it will commonly have become focal. There will be areas of high receptivity (hot spots) and these should be targeted with appropriate vector control measures, and proactive and reactive case detection based on parasite diagnosis. An alternative would be presumptive treatment employing mass drug administration. A further major challenge is to prevent importation of infections. Proactive case detection and/or screening of high risk migrants are demanding to implement, and this is where cross-border initiatives will help.[5]

For both elimination and prolonged low-level control strategies, the operational, technical and financial challenges have to be assessed in detail,[6] not least how the necessary long-term funding can be obtained to both achieve and sustain elimination.[7] The country commitment must include appropriate strengthening of the health systems, ideally as part of integrated capacity development that also enhances surveillance and management of other infections of public health importance.

Technically, there is much that can be achieved with the tools available. However, there is a need for a short-term operational research agenda focused on elimination particularly around the development of an effective surveillance system, active case detection, radical treatment and targeted vector control. The drug situation is also fragile. There is no good alternative to ACTs and there are reports of prolonged parasite clearance times that indicate a lower susceptibility to artemisinin.[8] Alternative drug combinations for treatment, for mass drug administration, and targeting the transmission stage of *Plasmodium falciparum* are now a priority. *P. vivax* is the dominant malaria in most of the countries pursuing or contemplating elimination but the one drug currently available for radical cure of this infection has a poor safety profile.

Current efforts to develop malaria vaccines are directed towards reducing morbidity and mortality. Despite an active research agenda, there is only one vaccine, the RTS, S vaccine based on the circum-sporozoite protein of *P. falciparum* and currently undergoing phase 3 trials, likely to be licensed soon.[9]

An alternative approach is now being advocated, namely the development of vaccines that interrupt transmission. Success in eliminating malaria is dependent on transmission being stopped. The proof of concept of a transmission-blocking vaccine directed against the sexual (infectious) stages of the parasite was shown years ago[10] and phase 1 clinical trials have begun. Vaccines against other stages of the lifecycle such as the pre-erythrocytic stages, if highly efficacious, would also impact on

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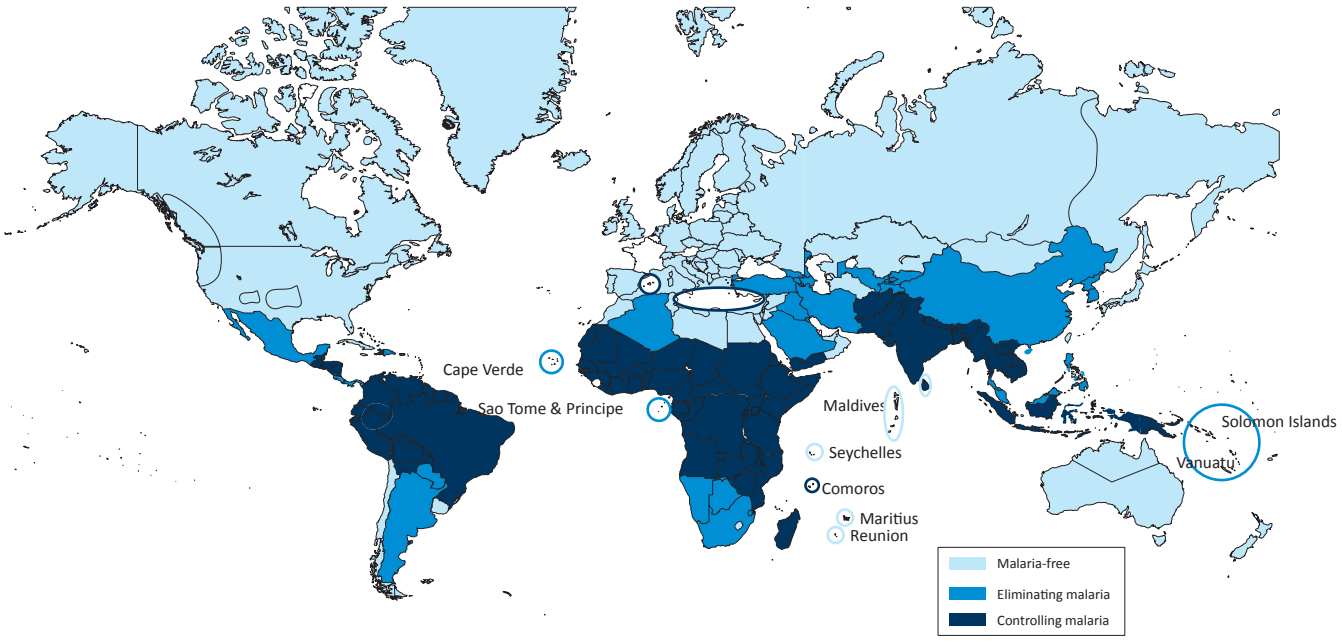

Fig 1. Categorising countries as malaria free, eliminating malaria or controlling malaria. Reproduced from the *Lancet* with permission from Elsevier.[3]

transmission as they would prevent or greatly reduce production of the gametocytes that infect mosquitoes. The target profile of a transmission-blocking vaccine requires immunisation of all age groups and a vaccine of high efficacy.[11] A combination vaccine may ultimately be what is required for elimination in some high burden areas where the need will be to achieve low endemic control, interrupt transmission, but then protect a population that would probably have lost its acquired immunity from any infections being reintroduced. Progress will be in stages, using new vaccines as part of integrated measures, before vaccination alone will be sufficient.

A great deal can be achieved with the available tools but, with a 10- to 20-year horizon, the currently used drugs and insecticides will need to be replaced; vaccines would add a new and probably necessary dimension to effectiveness. A recent malaria eradication research agenda (malERA) initiative set out the full extent of the challenges to be met.[12]

References

1 Snow RW, Marsh K. Malaria in Africa: progress and prospects in the decade since the Abuja Declaration. *Lancet* 2010;376:137–9.
2 Roll Back Malaria. *Global malaria action plan: for a malaria free world.* Geneva: World Health Organization, 2008.
3 Feachem RG, Phillips AA, Hwang J *et al.* Shrinking the malaria map: progress and prospects. *Lancet* 2010;376:1566–78.
4 Shekalaghe SA, Bousema JT, Kunei KK *et al.* Submicroscopic *Plasmodium falciparum* gametocyte carriage is common in an area of low and seasonal transmission in Tanzania. *Trop Med Int Health* 2007;12:547–53.
5 Moonen B, Cohen JM, Snow RW *et al.* Operational strategies to achieve and maintain malaria elimination. *Lancet* 2010;376:1592–603.
6 Zanzibar Malaria Control Programme. *Malaria elimination in Zanzibar: a feasibility assessment.* www.malariaeliminationgrouporg/sites/default/files/MalariaEliminationZanzibarpdf
7 Sabot O, Cohen JM, Hsiang MS *et al.* Costs and financial feasibility of malaria elimination. *Lancet* 2010;376:1604–15.
8 Dondorp AM, Yeung S, White L *et al.* Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010;8:272–80.
9 Casares S, Brumeanu TD, Richie TL. The RTS, S malaria vaccine. *Vaccine* 2010;28:4880–94.
10 malERA. A research agenda for malaria eradication: vaccines. *PLoS Med* 2011;8:e1000398.
11 Greenwood B, Targett G. Do we still need a malaria vaccine? *Parasite Immunol* 2009;31:582–6.
12 Alonso PL, Brown G, Arevalo-Herrera M *et al.* A research agenda to underpin malaria eradication. *PLoS Med* 2011;8:e1000406.

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