ELIMINATION OF MALARIA – HALF-WAY THERE

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Twenty years ago, malaria was reputed to cause a million deaths a year, a figure that was cited widely, although this was no more than an informed guess. However, when improved methods for measuring malaria mortality were developed, it seemed that this figure was probably approximately correct. WHO now estimates that in 2015 there were 429,000 (uncertainty interval 235-639,000) deaths from malaria, and 212 (uncertainty interval 148-394) million cases of malaria, declines of approximately 62% and 41% respectively during the past 15 years.[1] The key to this success has been a remarkable increase in funding for malaria control, both from the international donor community and from malaria affected countries, from a few hundred million dollars in 2000 to $2.9 billion in 2015.[1] This increase in funding has allowed a massive scaling up of control tools that were already available a decade ago, namely insecticide treated bednets (ITNs), rapid diagnostic tests (RDTs) and artemisinin combination therapy (ACT). A recent study suggests that scaling up of ITNs has accounted for 68% % of the reduction in cases of malaria seen during the period 2000 to 2015, with RDTs and ACT accounting for 22 % and Indoor Residual Spraying (IRS) for a further 10%.[2] Use of currently available tools has led to elimination of malaria, defined as interruption of local transmission of malaria, in 17 countries, including Sri Lanka, during the past 15 years.[1]

Reduction in the burden of malaria by around a half during a 15-year period is a remarkable global health success. However, addressing the remaining half faces a number of major challenges. Firstly, there is the challenge of sustaining national and international funding for malaria control at a time of political uncertainty and declining malaria incidence. Secondly, there is political instability in some of the areas where malaria transmission remains high, making effective control difficult or impossible to achieve. Finally, there is the threat posed

by the potential emergence and spread of artemisinin-resistant *Plasmodium falciparum* parasites in sub-Saharan Africa and by the rapidly increasing resistance of malaria vectors to the pyrethroid insecticides employed in ITNs. There is strong evidence that the emergence and spread of chloroquine-resistant *P. falciparum* towards the end of the last century led to a marked increase in deaths from malaria, an increase that the global health community was slow to recognise.[3] Consequently, there are legitimate concerns that the spread of parasites resistant to artemisinins from Asia to Africa,[4] or local emergence of resistant parasites in Africa, will have an impact on malaria mortality similar to the one seen following the emergence of chloroquine resistance. However, although the emergence of artemsinin-resistant parasites in Africa would be a setback, this would probably be less damaging than was the emergence and spread of chloroquine resistance for several reasons. Firstly, there is now wider recognition of the importance of on-going surveillance for drug resistance, and secondly development of molecular methods for measuring resistance has made this easier to follow than was the case in the past.[5] Finally, there has been wise investment in the development of new anti-malarial drugs before, rather than after, they are needed to deal with resistant parasites. Through the work of organisations such as the Medicines for Malaria Venture, a promising range of antimalarial drugs with novel modes of action, including those that have transmission blocking activities, has been developed and several of these drugs are in clinical trials. There is a good chance that one or more of these drugs would be available for clinical use should artemisinins-resistant parasites appear and spread in Africa in the next few years. The emergence and spread of anopheline mosquitoes resistant to the pyrethroid group of insecticides used in ITNs is probably a greater threat to malaria control than drug resistance.[6] Development and evaluation of novel insecticides for use in IRS and in ITNs is difficult and expensive and perhaps more challenging than

development of new antimalarial drugs. Although progress is being made in this field through organisations such as the Innovative Vector Control consortium, there is a risk that there will be a gap between the failure of pyrethroid-impregnated nets, currently the most important of current malaria control tools, and an effective replacement.

Although further, intensified efforts at scaling up current malaria control interventions may provide some further gains, it is unlikely that elimination of malaria will be achieved in high transmission areas without the employment of additional tools. The two interventions most likely to fill this gap are a malaria vaccine and/or some form of genetically modified mosquitoes, although there may be a role for other vector control interventions, such as larviciding, in some limited situations. Developing a malaria vaccine has been challenging but one partially effective malaria vaccine (RTS,S/AS01) has achieved a positive opinion from a regulatory authority[7] and will now be deployed in three large-scale pilot projects. The development of vaccines based on irradiated or genetically modified sporozoites is also making good progress.[8] Genetic modification of anopheline mosquitoes making them unable to reproduce or genetically resistant to malaria, and driving these modified mosquitoes through the population, has for many years seemed an impossible dream but recent development in molecular biology, including development of the CRISP/cas9 gene editing technique, have the potential to transform this dream into a reality. Although there are many safety and ethical challenges to be met, this approach to malaria control is becoming a realistic option.[9]

An advantage of ITNs as a malaria control tool has been the fact that in sub-Saharan Africa nearly all malaria is transmitted by night-biting mosquitoes. Thus, it was possible to recommend and deploy this intervention across the continent. This universality of approach

is not likely to apply to many of the new interventions under development or recently deployed. For example deployment of Seasonal Malaria Chemoprevention (SMC) is restricted to the areas of the Sahel and sub-Sahel of Africa where malaria transmission is limited to a few months each year.[10] It is important that deployment of the new tools emerging in the coming years is also based on a careful match between the properties of the intervention and knowledge of the local epidemiology of malaria. Ensuring that this happens will need an expansion in the number of well-trained scientists from endemic countries in the many disciplines that will be needed to achieve malaria elimination in high transmission areas.

Words: 1051

I declare that I have no conflict of interest.

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