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Malaria: Key challenges and potential solutions

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About the author:

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1. The current malaria burden:

Great progress has been made in reducing the global burden of malaria since the turn of the century, with approximately 700 million cases averted and malaria mortality in Africa decreasing by 37% since 2000. This decrease in malaria transmission has been largely achieved by the scale up of insecticide-based measures targeting the Anopheles mosquitoes that transmit the disease. Harder to measure, but likely a major contributory factor to the decline in cases, are factors related to improvements in health systems, housing, and household income that have occurred across large areas afflicted by malaria.

Persistence of malaria

Malaria remains a disease of poverty, and hence, progress has been slowest in countries with the weakest health infrastructure and regions that are plagued by civil unrest. In addition, growing resistance to drugs and insecticides threatens some of the recent gains.

Indeed, continent wide trends extrapolated from modelling studies of the past and current burden of malaria do not always represent the picture on the ground. In some countries, such as Burkina Faso, Uganda, and Mali, malaria has remained stubbornly persistent despite high coverage of the WHO recommended strategy of universal coverage with vector control and prompt access to diagnosis and treatment.

Furthermore, the dramatic reductions in malaria transmission since 2000 have precipitated a renewed call to eliminate malaria as a public health problem. This has significantly altered the dialogue, and as a consequence, the investment in resources and research towards measures aimed at ‘shrinking the malaria map’ have increased. Today, just 15 countries account for 80% of the malaria burden; all but one of these are in sub-Saharan Africa, but they are not the focus of the elimination efforts. Indeed modelling studies have predicted that, even with 90% coverage with all currently recommended interventions, plus the addition of multiple rounds of mass drug administration to clear the parasite reservoir, elimination is unlikely to be achieved across much of Africa.

Resistance to malaria drugs

The spread of resistance also threatens progress against malaria and, unless the pace at which new tools are evaluated and implemented is accelerated, risks derailing control efforts and curtailing any ambitions of elimination.

Below, four of the key challenges currently facing malaria are briefly outlined, together with some measures that could help address these challenges.

2. Key Challenge 1: Increasing access to proven interventions

There are five key pillars to WHO's strategy to prevent malaria:

- Universal coverage with measures that target the adult mosquito vector: long lasting insecticidal nets (LLINs) or indoor residual spraying (IRS);
- Rapid diagnosis and treatment with artemisinin combination therapy;
- Intermittent preventative treatment of malaria in pregnancy;
- Seasonal malaria chemoprevention (in some settings only);
- Surveillance to target malaria interventions more effectively.

These interventions have been massively scaled up in the past five years with impressive results. But important coverage gaps and inequities in access to these proven tools remain. An estimated £2.6bn was spent on malaria prevention in 2017 but WHO estimates that this is only about half the amount required. With competing demands on over-stretched budgets, **demonstration of value for money** is critical. Vector control is already recognised to be one of the most cost effective public health interventions in existence but the impact of interventions across multiple vector borne diseases is rarely accounted for. For example LLINs are estimated to cost $1.27 per malaria case averted. But these are frequently deployed in areas where vector borne diseases are co-endemic; if the impact on lymphatic filariasis[1], leishmaniasis[2], etc. were also accounted for the case for investing in vector control would be even stronger. This is a missed opportunity to leverage more funding.

In addition to funding, the **capacity gap needs to be addressed**. There is a chronic lack of capacity in many malaria endemic countries which impinges on all aspects of malaria prevention from implementation to evaluation. Furthermore, although universal coverage with a handful of proven interventions is the current gold standard for malaria prevention, this will undoubtedly change as bespoke packages of locally appropriate interventions are required to drive malaria cases down; this will require personnel at country (and global) level with the necessary expertise to select and evaluate the most appropriate package of interventions.

3. Key challenge 2: Residual transmission

The gains in malaria control have been largely driven by scale up of current interventions. However it is clear that, even if implementation of these tools achieves very high levels, malaria transmission will persist. This was demonstrated in a modelling study led by Imperial College (Walker Griffin, Ferguson & Ghani, 2016) and is illustrated below in maps that show the package of available tools needed to reach pre-elimination settings (<1 case/1000 people/year) assuming

[1] Commonly known as elephantiasis, lymphatic filariasis is caused by filarial parasites which are transmitted to humans through mosquitoes and black flies. The disease causes painful and debilitating swelling due to impairment of the lymphatic system (WHO, 2017c).

[2] Leishmaniasis is a disease caused protozoan *Leishmania* parasites which are transmitted by the bite of infected female phlebotomine sandflies (WHO, 2018).

90% coverage with each tool. The panel on the left (Fig. 1) shows that this target is impossible across much of Africa with existing tools of LLINs, IRS and Seasonal Malaria Chemoprophylaxis (SMC). If SMC is substituted for three rounds of mass drug administration (MDA), the picture (Fig. 2) improves but thresholds would not be reached in all regions.

Figure 1

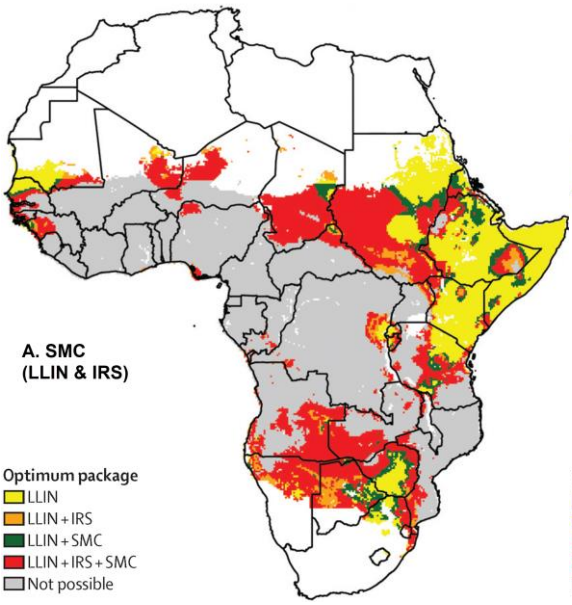
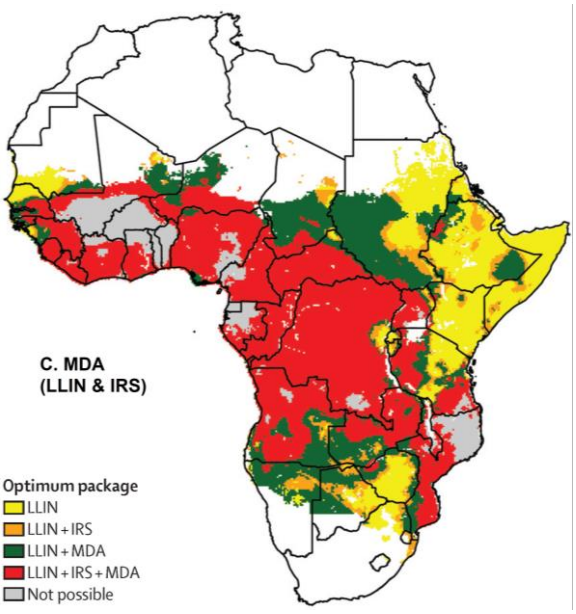


Figure 2



Source: Walker et al., (2016)

Outdoor biting mosquitoes

Part of the problem is that current vector control interventions largely target mosquitoes that rest and blood feed indoors. Although this is the predominant behaviour pattern exhibited by the major malaria vectors in Africa, substantial amounts of transmission occurs outside the home, either by mosquitoes feeding before people retire to bed, or by mosquitoes feeding on individuals working or resting outdoors during the peak periods of malaria biting activity.

Hence to reduce malaria transmission further, additional measures that target outdoor biting mosquitoes need to be layered on top of the current indoor based interventions. Although there has been some encouraging data in recent years on pilot studies targeting outdoor transmission, much more remains to be done and it will be many years before these tools are ready to be implemented at scale.

Mass drug administration

Mass drug administration approaches are also being piloted in several settings with SMC now a recommended intervention for children living in areas in the Sahel with highly seasonal

transmission (Bâ et al., 2018). The idea of these population scale drug administration programmes is to reduce the level of malaria parasites by targeting both symptomatic and asymptomatic infections. These interventions are often very effective in the short term but are expensive and challenging to sustain and risk exacerbating the levels of drug resistance.

4. Key Challenge 3: Resistance to insecticides and drugs

All WHO-approved LLINs contain pyrethroid insecticides; all drugs recommended for malaria treatment contain artemisinins. Hence the emergence of impactful levels of resistance to these chemistries in the mosquitoes and parasites could unravel the current gains unless off the shelf alternatives are ready to replace these.

The Medicines for Malaria Venture (MMV), launched in 1999, and the Innovative Vector Control Consortium, founded in 2005, are both **product development partnerships** aimed at ensuring a steady pipeline of new drugs and insecticides, accessible to the communities where they are needed. Both of these ventures have had success. For example, as a direct result of these PDPs, longer lasting formulations of insecticides are increasing the impact of IRS and new drugs to treat severe malaria in children are widely used. But the pathway from discovery to delivery is long, and, in particular for new insecticides, there is a high risk that our current tool box will be depleted by resistance before new alternatives are readily available.

Resistance management approaches

In addition to new chemistries, **resistance management approaches** urgently need to be implemented to reduce the selection and spread of resistance. The first reports of artemisinin resistance resulted in a rapid mobilisation of resources to contain or eliminate artemisinin resistance where it already exists and prevent its spread to new regions. This has largely been successful with artemisinin parasites to date confined to South East Asia.

The response to insecticide resistance has been slower. No non-pyrethroid LLINs are currently available. New LLINs containing pyrethroids plus a synergist, PBO, which increases the potency of the insecticide against pyrethroid resistant mosquito populations are in production, but it has taken 10 years from the first of these receiving WHO approval as a standard LLIN to any large-scale deployment of these nets. Reducing the selection pressure in mosquitoes is complicated by the widespread use of existing insecticides in agriculture and in other public health products such as aerosols.

There are exciting opportunities to **exploit the behaviour of mosquitoes** to simultaneously reduce the amount of insecticide used whilst increasing the impact on disease vectors which warrant much further study. Promising results from trials of eaves baffles, partial IRS, and barrier nets with vertical panels on the roof of the net treated with an alternative insecticide class, to name just a few, give rise to encouragement that, with sufficient investment and robust trial design, we may be able to maintain the efficacy of vector control using existing chemistries whilst we await the promise of new insecticides from the PDP initiative.

5. Key Challenge 4: Accelerating access to new tools

In many malaria endemic countries, national malaria control strategy deviates very little from global recommendations issued by WHO. For countries with high burdens of malaria the key priority has been reducing malaria transmission by increasing coverage with proven tools, and hence the WHO policy of universal coverage with these interventions is entirely appropriate.

However, as transmission declines, or existing tools fail, more locally appropriate strategies are needed. Two of the major challenges in adapting and adopting national or regionally appropriate strategies are capacity gaps and the slow speed at which some new tools received WHO recommendation.

Addressing the **capacity gaps** in disease endemic countries in order to accelerate the generation and uptake of evidence at the local level must be an urgent priority.

Major challenges include:

- Poor surveillance to identify hotspots of transmission;
- Inadequate knowledge on the distribution, behaviour and resistance profiles of local vectors;
- Weak links between research institutes and control programmes in country;
- Existence of multiple donors (many with their own agendas);
- Reporting requirements that put further pressure on over stretched control programmes.

The list of challenges is seemingly endless and it is only by improving capacity in country that these can begin to be addressed. The lack of capacity clearly constrains the ability of countries to set their own agendas for reducing disease burden. In addition, critical data gaps can lead to inefficiencies and missed opportunities. **Investment in institutes and individuals in malaria endemic countries** must be a higher priority for national governments and donors.

Improvements to the speed at which new tools are evaluated and policy recommendations issued are also needed at the global level, particularly in the field of vector control. Whilst clearly rigorous and transparent processes for evaluating the safety and efficacy of any new drugs or tools are essential, there are cases where a pragmatic approach to ensuring that new tools ‘do no harm’ and evaluating their efficacy during a **phased roll out and evaluation** may be needed. Current WHO guidelines put a very strong emphasis on randomised control trials. These are widely accepted as the gold standard for drugs, vaccines, and other medical interventions but are not so readily adapted to evaluating all vector control tools that act at the community—rather than individual—level, and alternative approaches may be needed in parallel. There is an urgency to addressing this issue. While the debate on the evidence base needed for new tools rolls on, millions currently remain dependent on tools whose efficacy is being eroded by resistance.

6. Questions to guide readings

1. Has the focus on malaria elimination put some countries at higher risk of malaria?
2. How do countries make decisions on the most appropriate national strategy for malaria control when they are frequently bound by global policies?
3. What role can donors and implementers play in helping generate the evidence needed to evaluate new vector control tools?
4. What are the key factors that need to be addressed to support the retention of staff in malaria control programmes and local research institutes?
5. Malaria is a vector borne disease. What are the opportunities for delivering and demonstrating better value for money by greater integration with other vector borne disease programmes?

7. Readings

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