Chapter 1

Malaria Elimination: Challenges and Opportunities

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Additional information is available at the end of the chapter

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Abstract

In 2016, 91 countries reported a total of 216 million cases of malaria, an increase of 5 million cases over the previous year, and the estimated malaria deaths worldwide were 445,000 like in 2015. This suggests that despite a substantial reduction in the malaria burden observed since 2010, largely attributed to the scale-up of effective control measures (vector control interventions, efficacious antimalarial treatment), the rate of decline of both clinical cases and malaria deaths has stalled since 2014 and in some regions even reversed. Achieving universal access to standard control interventions, such as case management, implementation of vector control methods, seasonal malaria chemoprevention, and intermittent preventive treatment for pregnant women, remains a priority. It is essential to contain emerging drug resistance in malarial parasite and insecticide resistance in mosquito vector species. Additional new interventions to accelerate interruption of transmission are in crucial need for their rapid integration within the standard control activities. These integrated control approaches must be implemented at community level with the active involvement of the local populations to reach high coverage. Finally, political and financial supports should be maintained and even doubled to reach the 2030 targets of the WHO global technical strategy for malaria.

Keywords: malaria elimination, mass drug administration, drug resistance, insecticide resistance

1. Introduction

In 2016, 91 countries reported a total of 216 million cases of malaria, an increase of 5 million cases over the previous year. The estimated number of malaria deaths worldwide was 445,000, about the same number reported in 2015 [1]. This suggests that, despite a substantial reduction in the malaria burden observed since 2010, largely attributed to the scale-up of effective control measures, including vector control interventions and treatment with

efficacious antimalarial medicines, the rate of decline of both clinical cases and malaria deaths has stalled since 2014 and in some regions (the Americas mainly and marginally in the Southeast Asia, Western Pacific, and African regions) even reversed [1]. The World Health Organization (WHO) has estimated that to meet the 2030 targets of global malaria strategy, a minimum investment of US$ 6.5 billion per year by 2020 is required [2]. In 2016, such investment was US$ 2.7 billion, less than half of that required amount, and since 2014 in many high-burden countries, investments in malaria control have declined [1]. The call for malaria eradication launched at the Malaria Forum in October 2007 by the Bill & Melinda Gates Foundation and then supported by the WHO, Roll Back Malaria (RBM) Partnership, and many other organizations and institutions seems to be at crossroads [3].

2. Components of malaria elimination strategy

The WHO currently considers malaria elimination at the national level as a continuum rather than the achievement of milestones for specific phases [2]. It is structured in 4 components (A–D), each of them to be implemented according to the malaria transmission intensity. Component "A" consists of enhancing and optimizing vector control and case management, which includes universal access to malaria preventions, diagnosis, and treatment for at-risk populations, and once elimination has been achieved, "focalized" vector control programs rather than scaling back these activities; component "B" aims at increasing the sensitivity and specificity of surveillance to detect, characterize, and monitor all cases (individual and in foci), namely, to transform malaria surveillance into a core intervention; component "C" aims at accelerating transmission reduction in which new interventions such as mass drug administration (MDA) or new vaccines are included; and component "D" is implemented when transmission intensity is low to very low, which includes the search for the few remaining infections and any foci of ongoing transmission, clearing them with appropriate treatment and possibly additional vector control activities [2].

3. Resistance of *Plasmodium falciparum* to anti-malaria drugs

Resistance to first-line treatments for *Plasmodium falciparum* malaria and to the insecticides used for *Anopheles* vector control is threatening malaria elimination efforts [4]. Artemisinin and its derivatives provide the fastest parasite clearance among available antimalarial drugs and have been combined with an antimalarial drug of a different class in order to (i) enhance complete cure rates, (ii) shorten the duration of therapy for artemisinin monotherapies, and (iii) delay the selection and spread of resistant parasites [5, 6]. Artemisinin-based combination treatments (ACTs) are currently recommended for the management of uncomplicated malaria cases. In 2007, the first cases of delayed parasite clearance, suggesting artemisinin resistance, were observed at the Thailand-Cambodia border [7, 8]. Artemisinin resistance has now been reported in 5 countries of the Greater Mekong Subregion (GMS), which includes Cambodia, Myanmar, Laos, Thailand, and Vietnam, and delayed parasite clearance has been linked to

point mutations in the propeller region of a *P. falciparum* protein gene on chromosome 13 (K13) [9]. Artemisinin resistance may have spread to or emerged in Bangladesh [10] and has extended across much of Myanmar with a high prevalence of *P. falciparum* parasites carrying K13-propeller mutations reported next to the north-western border of India [11]. Resistance may have also emerged in South America, including Guyana, Suriname, French Guiana, and bordering areas of Brazil and Venezuela, [12, 13] that shares several characteristics with the GMS, increasing the risk of selecting resistant parasites. These include higher *P. falciparum* transmission than the rest of the Amazon Basin, highly mobile populations, availability and widespread use of several antimalarial drugs of questionable quality, including artemisinin monotherapies, and poor access and use of formal malaria diagnostic and treatment facilities [14]. Besides artemisinin resistance, the prevalence of molecular markers correlated to resistance to the partner drugs has increased. For example, changes in the prevalence of *pfcrt* and *pfmdr1* alleles have been observed in many areas where ACTs including amodiaquine or lumefantrine have been intensively used [4]. However, outside the GMS, recommended ACTs' efficacy remains acceptable (4). In Southeast Asia, the intensive use of dihydroartemisinin-piperaquine (DP) has resulted in selection of parasites with multiple resistance mechanisms, and in Cambodia high levels of treatment failure to DP are now observed [15]. Resistance to piperaquine (clinical and *in vitro*) may be associated to *plasmepsins* 2–3, but other markers could be involved [4].

4. Resistance of *Anopheles* mosquito vectors to insecticides

Resistance of malaria vectors to the 4 insecticide classes (pyrethroids, organochlorines, organophosphates, and carbamates) used for vector control interventions threatens malaria prevention and control efforts. Of the 76 malaria endemic countries that reported standard monitoring data from 2010 to 2016, resistance was detected in 61 countries to at least one insecticide in one malaria vector from one collection site, and 50 countries had resistance to 2 or more insecticides [1]. Resistance to pyrethroids, insecticides used in all long-lasting insecticidal nets (LLINs), is widespread though its impact on LLIN effectiveness is unclear [16]. There was no association between malaria disease burden and the level of resistance in a WHO-coordinated study implemented in 5 countries (Sudan, Kenya, India, Cameroon, and Benin) [1]. However, given the complexity in measuring the impact of insecticide resistance, it is not possible to equate lack of evidence of impact with evidence for no impact [16].

5. Asymptomatic malaria infections and mass drug administration (MDA)

One of the major problems to achieve malaria elimination is represented by the hidden parasite reservoir in the human host. Microscopy (and rapid diagnostic tests (RDTs)) underestimates by about half the prevalence of *Plasmodium* infection, and this difference is greatest in low-transmission settings—many asymptomatic infections can persist for significant periods of

time. The presence of *P. falciparum* gametocytes is positively associated with the absence of clinical symptoms and low asexual parasite densities; mosquitoes can become infected with gametocyte densities as low as 5 gametocytes/μl and theoretically as low as one gametocyte/μl—children with undetectable gametocytaemia by molecular methods were still observed to be infectious to mosquitoes [17]. To accelerate achieving malaria elimination, the human reservoir of infection needs to be tackled with new approaches. There is a growing interest in MDA of at-risk populations or in malaria hot-spot areas with an effective antimalarial to reduce the parasite reservoir in human host [18]. MDA aims to provide full post-treatment courses to the whole population to clear asymptomatic infections and provide posttreatment prophylaxis to prevent reinfection. The use of MDA is recommended in areas approaching interruption of transmission, with good access to treatment, effective vector control, and surveillance systems, ensuring a minimal risk of reintroduction of infection [19]. MDAs have been conducted using a variety of drug regimens at different dosages, timings, and frequency. There is evidence of substantial but short-lived reduction in *P. falciparum* parasite carriage [20]. In Zambia, a cluster-randomized control trial implemented in a population of 330,000 individuals, distributed in 56,000 households, compared MDA with DP (2 rounds), at the household level (DP to all members of household with at least a RDT-positive individual) and standard control measures (case management, LLIN, indoor residual spraying (IRS), and intermittent preventive treatment during pregnancy). MDA decreased significantly malaria prevalence and incidence in low (malaria prevalence <10%) but not in high (malaria prevalence ≥10%) transmission areas [21]. With the growing awareness of heterogeneity and clustering in transmission, MDA approaches have been modified by systematic (mass screening and treatment) or focused (focal screening and treatment) screening and treatment of populations in defined geographical areas. Reactive case detection, i.e., screening and treating positive contacts in response to a clinical event, has been tested and implemented in some countries [22–25]. However, its impact has been variable as it is affected by the sensitivity of the diagnostic tool and the radius of intervention around a clinical case [26–29].

The antimalarial treatment administered during MDA campaigns could be complemented by single low-dose of primaquine, an 8-aminoquinoline that is able to clear mature *P. falciparum* gametocytes [30], and/or ivermectin, a systemic endectocidal drug that can be administered safely to both humans and animals but proven toxic to *Anopheles* mosquitoes when they take a blood meal from a host that has recently received the drug [31, 32]. Primaquine may cause a dose-dependent hemolysis, mainly in individuals with deficiency of the enzyme glucose 6-phosphate dehydrogenase (G6PD) in red blood cells [33], and this has slowed down its implementation. Nevertheless, a single low-dose of primaquine can significantly reduce gametocyte carriage in both symptomatic [33] and asymptomatic [34] individuals and reduces onward transmission from man to vector [35]. Ivermectin can be safely administered with an ACT [36, 37] and has been used widely against parasitic diseases in humans, with record of more than 2 billion doses in MDA campaigns against onchocerciasis and lymphatic filariasis. In Burkina Faso, Liberia, and Senegal, one round of MDA with ivermectin at the standard dose of 150 μg/kg decreased substantially *An. gambiae* survival for 6 days and reduced the proportion of sporozoite-positive (infectious) mosquitoes for 2 weeks [38]. However, evidence of ivermectin as an additional tool to decrease malaria transmission is limited and needs to be further quantified, possibly by a cluster randomized

trial in a country with high coverage of standard control interventions and substantial residual malaria transmission.

6. Conclusions

In conclusion, achieving universal access to standard control interventions, namely, case management, LLIN, IRS, seasonal malaria chemoprevention, and intermittent preventive treatment for pregnant women, remains a priority. It is essential to contain emerging drug resistance in malarial parasite and insecticide resistance in mosquito vector species. There is a dire need of additional new interventions to accelerate interruption of transmission. These should be evaluated and rapidly integrated within the standard control activities. Most of these should be implemented at the community level, and it will be important to actively involve the local populations to reach high coverage. Finally, political and financial supports should be maintained and even increased; current financial support is less than half of that estimated to reach the 2030 targets of the WHO global technical strategy for malaria [1].

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