Malaria Elimination: Challenges and Opportunities

Umberto D’Alessandro

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].

Author details

Umberto D’Alessandro
Address all correspondence to: udalessandro@mrc.gm
Medical Research Council Unit, The Gambia and London School of Hygiene and Tropical Medicine, Fajara, The Gambia

References

[1] WHO. World malaria report. Geneva: World health organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. http://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf?jsessionid=DBAA4A8F412049581DEC3652C2EE8E5?sequence=1; 12 December 2017

[2] WHO. Global Malaria Programme. A framework for malaria elimination. Geneva: World Health Organization; 2017. http://apps.who.int/iris/bitstream/handle/10665/254761/9789241511988-eng.pdf?sequence=1; 12 December 2017

[3] Alonso PL, Brown G, Arevalo-Herrera M, Binka F, Chitnis C, et al. A research agenda to underpin malaria eradication. PLoS Medicine. 2011;8:e1000406. DOI: 10.1371/journal.pmed.1000406

[4] The malERA Refresh Consultative Panel on Insecticide and Drug Resistance. An updated research agenda for insecticide and drug resistance in malaria elimination and eradication. PLoS Medicine. 2017;14:e1002450. DOI: 10.1371/journal.pmed.1002450
[5] White NJ, Olliaro PL. Strategies for the prevention of antimalarial drug resistance: Rationale for combination chemotherapy for malaria. Parasitology Today. 1996;12:399-401

[6] White NJ. Preventing antimalarial drug resistance through combinations. Drug Resistance Updates. 1998;1:3-9

[7] Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Artemisinin resistance in Cambodia 1 (ARC1) study consortium. Evidence of artemisinin-resistant malaria in Western Cambodia. The New England Journal of Medicine. 2008;359:2619-2620

[8] Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F, Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegardh N, Socheat D, White NJ. Artemisinin resistance in Plasmodium falciparum malaria. The New England Journal of Medicine. 2009;361:455-467

[9] Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois AC, Khim N, Kim S, Duru V, Bouchier C, Ma L, Lim P, Leang R, Duong S, Sreng S, Suon S, Chuar CM, Bout DM, Ménard S, Rogers WO, Genton B, Fandeur T, Miotto O, Ringwald P, Le Bras J, Berry A, Barale JC, Fairhurst RM, Benoit-Vical F, Mercereau-Puijalon O, Ménard D. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature. 2014;505:50-55

[10] Takala-Harrison S, Laufer MK. Antimalarial drug resistance in Africa: Key lessons for the future. Annals of the New York Academy of Sciences. 2015;1342:62-67

[11] Tun KM, Imwong M, Lwin KM, Win AA, Hlaing TM, Hlaing T, Lin K, Kyaw MP, Plewes K, Faiz MA, Dhorda M, Cheah PY, Pukrittayakamee S, Ashley EA, Anderson TJ, Nair S, McDew-White M, Flegg JA, Grist EP, Guerin P, Maude RJ, Smithuis F, Dondorp AM, Day NP, Nosten F, White NJ, Woodrow CJ. Spread of artemisinin-resistant Plasmodium falciparum in Myanmar: A cross-sectional survey of the K13 molecular marker. The Lancet Infectious Diseases. 2015;15:415-421

[12] Vreden SG, Jitan JK, Bansie RD, Adhin MR. Evidence of an increased incidence of day 3 parasitaemia in Suriname: An indicator of the emerging resistance of Plasmodium falciparum to artemether. Memórias do Instituto Oswaldo Cruz. 2013;108:968-973

[13] Chenet SM, Akinyi Okoth S, Huber CS, Chandrabose J, Lucchi NW, Talundzic E, Krishnalall K, Ceron N, Musset L, Macedo de Oliveira A, Venkatesan M, Rahman R, Barnwell JW, Udhayakumar V. Independent emergence of the Plasmodium falciparum Kelch propeller domain mutant allele C580Yin Guyana. The Journal of Infectious Diseases. 2016;213:1472-1475

[14] Achan J, Mwesigwa J, Edwin CP, D’Alessandro U. Malaria medicines to address drug resistance and support malaria elimination efforts. Expert Review of Clinical Pharmacology. 2017;11:61-70. DOI: 10.1080/17512433.2018.1387773

[15] Amaratunga C, Lim P, Suon S, Sreng S, Mao S, Sopha C, Sam B, Dek D, Try V, Amato R, Blessborn D, Song L, Tullo GS, Fay MP, Anderson JM, Tarning J, Fairhurst RM. Dihydroartemisinin-piperaquine resistance in Plasmodium falciparum malaria in Cambodia: A multisite prospective cohort study. The Lancet Infectious Diseases. 2016;16:357-365. DOI: 10.1016/S1473-3099(15)00487-9. PMID: 26774243
[16] Ranson H, Lissenden N. Insecticide resistance in African Anopheles mosquitoes: A worsening situation that needs urgent action to maintain malaria control. Trends Parasitol. 2015;32:187-196. DOI: 10.1016/j.pt.2015.11.010. PMID: 26826784

[17] Lindblade KA, Steinhardt L, Samuels A, Kachur SP, Slutsker L. The silent threat: Asymptomatic parasitemia and malaria transmission. Expert Review of Anti-Infective Therapy. 2013;11:623-639

[18] Bousema T, Drakeley C. Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination. Clinical Microbiology Reviews. 2011;24:377-410

[19] WHO. Global Malaria Programme: The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria. Geneva: World Health Organization; 2015. http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf?ua=1; 12 December 2017

[20] Poiriot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database of Systematic Reviews. 2013;12:CD008846

[21] Eisele TP, Bennett A, Silumbe K, Finn TP, Chalwe V, Kamuliwo M, Hamainza B, Moonga H, Kooma E, Chizema Kawesha E, Yukich J, J1 K, Porter T, Conner RO, Earle D, Steketee RW, Miller JM. Short-term impact of mass drug administration with dihydroartemisinin plus piperaquine on malaria in Southern Province Zambia: A cluster-randomized controlled trial. The Journal of Infectious Diseases. 2016;214:1831-1839

[22] Kern SE, Tiono AB, Makanga M, Gbadoé AD, Premji Z, Gaye O, Sagaral, Ubben D, Cousin M, Oladiran F, Sander O, Ogutu B. Community screening and treatment of asymptomatic carriers of Plasmodium falciparum with artemether-lumefantrine to reduce malaria disease burden: A modelling and simulation analysis. Malaria Journal. 2011;10:210

[23] Stresman GH, Kamanga A, Moono P, Hamapumbu H, Mharakurwa S, Kobayashi T, Moss WJ, Shiff C. A method of active case detection to target reservoirs of asymptomatic malaria and gametocyte carriers in a rural area in Southern Province, Zambia. Malaria Journal. 2010;9:265

[24] Sturrock HJ, Novotny JM, Kunene S, Dlamini S, Zulu Z, Cohen JM, Hsiang MS, Greenhouse B, Gosling RD. Reactive case detection for malaria elimination: Real-life experience from an ongoing program in Swaziland. PLoS One. 2013;8:e63830

[25] Littrell M, Sow GD, Ngom A, Ba M, Mboup BM, Dieye Y, Mutombo B, Earle D, Steketee RW. Case investigation and reactive case detection for malaria elimination in northern Senegal. Malaria Journal. 2013;12:331

[26] Hustedt J, Canavati SE, Rang C, Ashton RA, Khim N, Berne L, Kim S, Sovannarothe S, Ly P, Ménard D, Cox J, Meek S, Roca-Felttrer A. Reactive case-detection of malaria in Pailin Province, Western Cambodia: Lessons from a year-long evaluation in a pre-elimination setting. Malaria Journal. 2016;15:132
[27] Searle KM, Hamapumbu H, Lubinda J, Shields TM, Pinchoff J, Kobayashi T, Stevenson JC, Bridges DJ, Larsen DA, Thuma PE, Moss WJ. Evaluation of the operational challenges in implementing reactive screen-and-treat and implications of reactive case detection strategies for malaria elimination in a region of low transmission in Southern Zambia. Malaria Journal. 2016;15:412

[28] Smith Gueye C, Sanders KC, Galappaththy GN, Rundi C, Tobgay T, Sovannaroth S, Gao Q, Surya A, Thakur GD, Bobogare A, Deniyage SL, Satimai W, Taleo G, Hung NM, Cotter C, Hsiang MS, Vestergaard LS, Gosling RD. Active case detection for malaria elimination: A survey among Asia Pacific countries. Malaria Journal. 2013;12:358

[29] Tiono AB, Ouedraogo A, Ogutu B, Diarra A, Coulibaly S, Gansane A, Sirima SB, O'Neil G, Mukhopadhyay A, Hamed K. A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of *Plasmodium falciparum* in Burkina Faso. Malaria Journal. 2013;12:79

[30] WHO Policy Brief on Single-Dose Primaquine as Gametocytocide in *Plasmodium falciparum* malaria; 2015. http://www.who.int/malaria/publications/atoz/who_htm_gmp_2015.1.pdf?ua=1; 12 December 2017

[31] Foy BD, Kobylinski KC, da Silva IM, Rasgon JL, Sylla M. Endectocides for malaria control. Trends in Parasitology. 2011;27:423-428

[32] Reddy MR, Overgaard HJ, Abaga S, Reddy VP, Caccone A, Kiszewski AE, Slotman MA. Outdoor host seeking behaviour of *Anopheles gambiae* mosquitoes following initiation of malaria vector control on Bioko Island, Equatorial Guinea. Malaria Journal. 2011;10:184. DOI: 10.1186/1475-2875-10-184

[33] Eziefula AC, Pett H, Grignard L, Opus S, Kiggundu M, Kamya MR, Yeung S, Staedke SG, Bousema T, Drakeley C. Glucose-6-phosphate dehydrogenase status and risk of hemolysis in *Plasmodium falciparum*-infected African children receiving single-dose primaquine. Antimicrobial Agents and Chemotherapy. 2014;58:4971-4973

[34] Okebe J, Bousema T, Affara M, Di Tanna GL, Dabira E, Gaye A, Sanya-Isijola F, Badji H, Correa S, Nwanakma D, Van Geertruyden JP, Drakeley C, D'Alessandro U. The gametocytocidal efficacy of different single doses of primaquine with dihydroartemisinin-piperaquine in asymptomatic parasite carriers in the Gambia: A randomized controlled trial. eBioMedicine. 2016;13:348-355

[35] Dicko A, Brown JM, Diiawara H, Baber I, Mahamar A, Soumare HM, Sanogo K, Koita F, Keita S, Traore SF, Chen I, Poirot E, Hwang J, McCulloch C, Lanke K, Pett H, Niemi M, Nosten F, Bousema T, Gosling R. Primaquine to reduce transmission of *Plasmodium falciparum* malaria in Mali: A single-blind, dose-ranging, adaptive randomised phase 2 trial. The Lancet Infectious Diseases. 2016;16:674-684. DOI: 10.1016/S1473-3099(15)00479-X

[36] Smit MR, Ochomo E, Aljayyoussi G, Kwambai T, Abong’o B, Bayoh N, Gimnig J, Samuels A, Desai M, Phillips-Howard PA, Kariuki S, Wang D, Ward S, Ter Kuile FO. Efficacy and safety of high-dose ivermectin for reducing malaria transmission: Protocol for a double-blind, randomized, placebo-controlled, dose-finding trial in Western Kenya. JMIR Research Protocols. 2016;5:e213
[37] Ouédraogo AL, Bastiaens GJ, Tiono AB, Guelbéogo WM, Kobylinski KC, Ouédraogo A, Barry A, Bougouma EC, Nebie I, Ouattara MS, Lanke KH, Fleckenstein L, Sauerwein RW, Slater HC, Churcher TS, Sirima SB, Drakeley C, Bousema T. Efficacy and safety of the mosquitocidal drug ivermectin to prevent malaria transmission after treatment: A double-blind, randomized, clinical trial. Clinical Infectious Diseases. 2015;60:357-365

[38] Alout H, Krajacich BJ, Meyers JI, Grubaugh ND, Brackney DE, Kobylinski KC, Diclaro JW 2nd, Bolay FK, Fakoli LS, Diabaté A, Dabiré RK, Bougma RW, Foy BD. Evaluation of ivermectin mass drug administration for malaria transmission control across different West African environments. Malaria Journal. 2014;13:417
