Malaria: Control, Elimination, and Eradication

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ABSTRACT: Control, elimination, and eradication of malaria is one of the world's greatest public health challenges, especially in Sub-Saharan Africa. While there has been an impressive gain in malaria control with decreased mortality rate over the years, eradication and elimination seem to be elusive in Sub-Saharan Africa. Control and elimination of malarial parasites was previously achieved in Europe and America using insecticides and manipulation of environmental and ecological characteristics. The emergence of drug-resistant parasites coupled with environments that support the breeding of mosquito vector and the need for caution with insecticides, such as dichlorodiphenyltrichloroethane, has slowed down control efforts, making elimination and eradication an uphill task in Sub-Saharan Africa. The expectation of producing an effective vaccine has been on for >40 years, but the recent breakthrough announcement of a malaria vaccine showing some level of protection among infants and children 3–4 years post vaccination seems like an excellent starting point. The globally accepted strategy for the control of malaria rely on chemotherapy, but unfortunately the overreliance on chemotherapy without proper control of drug usage and diagnosis has encouraged the selection of drug-resistant parasites, significantly contributing to the problem. Therefore, the prospects of malaria eradication rest heavily on integrated approaches that would include chemotherapy, vector control, manipulation of environmental and ecological characteristics, and vaccination. This article reviews the current state of malaria control and elimination and the need for an multistrategic integrated approach in order to achieve malaria eradication if the challenges faced by elimination are addressed.

KEYWORDS: malaria, control, elimination, eradication, challenges, approach

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Introduction

Malaria is an ancient disease, still prevalent in many tropical countries of the world, accounting for ~250 million clinical cases and ~1 million deaths each year, the majority of which occur in children younger than 5 years and in pregnant women.[1,2] Alongside the significant morbidity and mortality are socio-economic burdens, health inequities, and drain on human resources and productivity, interrupting educational training and causing persistent economic disadvantages thereby.[2,3]

Plasmodium falciparum and *Plasmodium vivax* account for the vast majority (>90%) of human malarial infections worldwide, in addition *Plasmodium ovale*, *Plasmodium malariae* and the recently included *Plasmodium knowlesi*[4] are also implicated. It can be transmitted from one human to another by infected female anopheline mosquitoes during a blood meal and simultaneous injection with sporozoites, the infective stage for the parasite. The uniqueness of malaria as a disease is derived from the complexity of its life cycle, involving humans and mosquitoes, and the structural and genetic changes between hepatocytes, red blood cells, and stages within the mosquitoes.[5,6] The duration of the *Plasmodium* developmental stage in the mosquito can vary substantially, depending on the parasite species and environmental conditions.[7]

The complexity of the life cycle is a major challenge to malaria control efforts. In the last 10 years, there has been renewed efforts to increase funding in order to achieve global malaria eradication.[2] The increased funding coupled with strong political will has led to an increased coverage of malaria control programs and a reduction in disease and deaths in several Sub-Saharan African and tropical countries. The introduction of the Roll Back Malaria (RBM) partnership and the launching of its Global Malaria Action Plan have brought about reduced morbidity and mortality of malaria by reaching universal coverage and strengthening health systems. In a departure from the previous efforts at malaria eradication, current strategies demand an integrated approach and multistage interventions. In this review, we will examine the current status of malaria control strategies, propose strategies for future eradication and elimination, and point out gaps in the current methods that would need revamping for ultimate progress and total eradication.

Current Status of Malaria Control, Eradication, and Elimination

The World Health Organization (WHO) in the 1950s under the auspices Global Malaria Eradication Program attempted

malaria eradication in endemic areas, with Africa surprisingly excluded, in spite of the huge disease burden within the continent.[8] In the past few years, African countries, such as Tanzania, Sao Tome and Principe, Eritrea, and Rwanda, where malaria is endemic, have provided high-risk populations with effective mosquito control intervention and access to artemisinin-based combination therapies (ACTs).[9–11] Additionally, small elimination campaigns utilizing frequent insecticide spraying in houses and rounds of mass treatment were undertaken in Nigeria, under the auspices of the Garki project[12] and on the Kenyan/Tanzanian border, termed the Pare-Taveta project.[8,13] These projects entailed the combination of frequent insecticide spraying in houses to reduce vector populations and mass treatment to reduce the human infectious reservoir. The report from these projects showed a significant decline in the incidence of infection and disease, but long-term result shows that control measures were not sufficient to eliminate the parasite. Failure to sustain these programs inevitably led to infection rebound in later years.[8] These projects revealed the possibility of technically reducing the transmission of malaria and moving on to elimination, but the operational and financial resources needed for sustainability are not available in Sub-Saharan Africa, where the biggest challenge to malaria currently occurs.

The efforts at controlling malaria in the past 15 years have yielded some positive results with mortality rates decreasing by an impressive 47% between 2000 and 2013 globally and by 54% in the WHO African Region.[14] Malaria was successfully eliminated in Tunisia in 1979, in Maldives in 1984,[15] and in seven other malaria-endemic countries; the United Arab Emirates (1998), Mauritius (1998), Egypt (1998), Morocco (2005), Syria (2005), Algeria (2006), and Turkmenistan (2006) recorded zero locally acquired cases about this period.[16] The WHO Eastern Mediterranean and European region countries also approached malaria elimination in the 1990s,[15] starting with individual countries and later extending to neighboring countries. Five African countries launched a subregional malaria elimination program in 1997, and by the year 2006, just a single case of locally acquired malarial infection was recorded in Algeria.[15] Not too long afterward in the Arabian Peninsula, the United Arab Emirates was certified malaria free by the WHO in 2007.[17] In Oman, only four cases of malaria were reported in 2007, while in Iraq, only two cases of local transmission were reported in 2007. Other endemic areas in this region, such as Sudan, Afghanistan, and Yemen, also recorded ~40% reduction in the reported cases of malaria with estimated cases declining from 15 to 10.5 million between the years 2000 and 2006.[15]

The WHO European region recorded a sharp drop in the reported malaria cases, from 90,000 to <1000 cases between 1992 and 2007, and in 2005, the region adopted a joint strategy of malaria elimination.[15,18] In Central and South America, the past years have witnessed a decline in the incidence and mortality of malaria in 15 of the 21 malaria-endemic countries in the region, including a reduction in the absolute number of cases in all countries except Peru and Colombia.[19] In the WHO Western Pacific and Southeast Asia regions, reported malaria cases and mortality have declined steadily over the past decade with the exception of Myanmar, Papua New Guinea, and Solomon Islands.[20]

Sub-Saharan Africa poses the biggest challenge to global eradication initiative of malaria, given the high prevalence and intensity of *P. falciparum* transmission across most of the continent. This transmission pattern is further complicated by local variation in the major *Anopheles* vector populations that sustain transmission (principally *Anopheles gambiae* s.l. and *Anopheles funestus*), although ~70 relevant species have been identified worldwide.[21] Additionally, biological and socioeconomic features in many tropical countries have contributed, in no small measure, to frustrate control and elimination programs, preventing implementation of disease control over broad spatial and temporal scales.[22] Most of the Sub-Saharan African countries are currently in the control stage based on WHO/RBM classification and, therefore, need to scale-up intervention to sustain the control efforts and reduce the disease burden.[23] Infection prevalence in children aged 2–10 years has been reduced by about half since the year 2000, with about a third of this decline occurring after the year 2005.[24] This decline was largely attributed to the patterns of increasing coverage of insecticide-treated nets (ITNs), which were viewed as the most important intervention followed by ACTs and indoor residual spraying (IRS) in that order across Africa.[24]

Strategies for Malaria Control, Eradication, and Elimination

The discussion on the control and possible eradication of malaria is always an important agenda in international health forum.[25,26] Malaria eradication is a worthwhile goal that has been vigorously pursued, and the malaria community is currently more equipped to make an appreciable progress toward the actualization of this goal. With increasing research capabilities, the global malaria research community seemed well positioned to innovatively think about the tools, strategies, and implementation of programs that would be required to achieve effective control and eradication.

Research activities for malaria control have focused on the development of new drugs and vaccines with decreasing emphasis on vector control and creating a cleaner environment that would disrupt the breeding of the mosquito vector. Unfortunately, parasite resistance to available antimalarials is spreading and has rendered treatment increasingly difficult in endemic areas.[27–30] Chloroquine was referred to as a wonder drug when it was introduced >50 years ago, and it was the cornerstone of antimalarial treatment for many years in Africa.[31] It was cheap, with very low toxicity, effective against all forms of malaria, relatively easy to manufacture, chemically stable, and readily stored and transported, even under extreme climatic conditions,[27] attributes, which none of the currently

available antimalarials possess.[28,32] The emergence and spread of chloroquine-resistant *P. falciparum* in Sub-Saharan Africa led to one of the greatest public health challenges,[27,28] prompting the use of sulfadoxine–pyrimethamine (SP) and many other alternative antimalarials. However, resistance to SP and the other antimalarials developed rapidly a few years after their introduction,[33] with SP currently recommended only for intermittent preventive therapy in pregnancy (IPTp).[34] IPTp-SP is effective at preventing maternal anemia and low birth weight in areas where *P. falciparum* is susceptible to SP,[35,36] but the success of the intervention is threatened in many communities in Africa where resistance of *P. falciparum* to SP has been reported.[37,38] Following the WHO guideline for the treatment of uncomplicated malaria, ACTs were adopted in all malaria-endemic areas where resistance has been reported to chloroquine and other antimalarials. Adoption of ACTs reportedly led to a large reduction in confirmed malaria cases and contributed to the reduction in all mortality among children younger than 5 years of age.[39,40] Concerted effort is needed to protect ACTs so that it can enjoy a longer use as an effective antimalarial. Proper education of clinicians and the general populace in malaria-endemic areas on the need not to use ACTs for presumptive treatment of malaria is imperative and urgently needed. Exposure of malarial parasites to subtherapeutic levels of antimalarial drugs will only kill sensitive parasites but allow those with resistant mutations to survive and reproduce.[41] Diagnostic confirmation, using any of the WHO-approved rapid kits and microscopy where possible, before commencement of ACT treatment should be urgently pursued.[42]

Along with drug development, huge resources have been spent toward producing a malaria vaccine. The complexity of a parasite's life cycle have severely hampered vaccine development strategies since an immune response targeting one stage may not offer protection against a later stage.[43,44] Significant progress has been made in the last few years and this is yielding the first generation of GlaxoSmithKline (GSK) malaria candidate vaccines, RTS,S/AS01 (Mosquirix™), which got the approval of the Committee for Medicinal Products for Human Use of the European Medicines Agency in July 2015. Phase 3 trial data showed that the vaccine only reduced episodes of malaria in babies aged 6–12 weeks by 27% and by ~36% among children aged 5–17 months.[45] This observation has left some researchers uncomfortable considering the complexities and potential effects of using this vaccine when it only provides partial protection, making it less attractive and more risky.[46,47] Nonetheless, the WHO has thrown its weight behind the vaccine, and is currently reviewing when and where it could be used or deployed.

Vector control is another essential tool that has been shown to reduce malaria transmission,[48] which unfortunately has not received as much attention and funding as drug discovery and vaccine production, until recently. Vector control strategies include the following preventive interventions: IRS, ITNs, and outdoor spraying with dichlorodiphenyltrichloroethane.[49] In response to the Millennium Development Goals of infectious disease eradication, there has been a rapid scale-up of ITNs, including long-lasting insecticide-treated nets (LLINs). IRS has had a long and distinguished history in malaria control, and continues to be used in many parts of the world.[49] It uses wettable powders recommended by the WHO, including malathion, fenitrothion, pirimiphos-methyl, bendiocarb, propoxur, alpha-cypermethrin, cyfluthrin, deltamethrin, etofenprox, and lambda-cyhalothrin.[50,51] These insecticides are normally sprayed between once and thrice a year, and the timing of spraying depends on the type of insecticide and transmission season. IRS works by repelling mosquitoes from entering houses and by killing female mosquitoes that are resting inside houses, after a blood meal. The introduction of IRS has reportedly led to the spectacular reduction of malaria in South Africa, Swaziland, Namibia, Zimbabwe, and Mozambique, and it continues to protect >13 million people.[52,53]

Changes in disease prevalence largely followed patterns of increasing ITN and LLIN coverage, and this appears to be the most important intervention across Africa, accounting for an estimated 68% (range 62%–72%) decline in *P. falciparum* rate recorded in 2015.[24] Malaria deaths are declining with the massive scaling up of control measures, of which ITNs are a major component reducing deaths in children and providing personal protection to the user.[54] The LLINs have increased killing effects on the vectors compared with traditional ITNs and are more durable and effective for at least 3 years, even after repeated washing.[49] Both ITNs and LLIN are simple to use, easy to deliver to rural communities, and cost-effective when used in highly endemic malarious areas.[55] Pyrethroids are the only class of insecticide currently used for ITNs and it has a repellent effect, by preventing entry of mosquitoes into houses as well as disrupting blood feeding and premature exit of mosquitoes from the home.[49] The emergence and spread of insecticide resistance threatens the effectiveness of ITNs and indoor residual house spraying. Currently, pyrethroid resistance in *Anopheles* vectors has been reported in 27 countries in Sub-Saharan Africa.[56] Unlike IRS with many classes of insecticides, ITNs are especially vulnerable to insecticide resistance, because there are no readily available approved alternative insecticides to pyrethroids.[49,50]

It is clear that the control, elimination, and eradication of malaria cannot be achieved with a single approach or strategy. However, chemotherapy and vaccine development efforts receiving more funding and attention at the expense of vector control strategies is an indication that the expected control and elimination scenario may not be achieved soon. The fact that vector control has been successfully used to eliminate malaria in Europe, Asia, and some African countries in the past renders this an important strategy worthy of renewed attention and funding than what has been presently obtained. This goal of malaria eradication cannot be achieved without

a sustained commitment that would include integrated multilayer strategies.

Conclusion

The success of malaria elimination in some countries is an indication that eradication is possible. The current potential barrier to malaria elimination lies within uncertainties concerning the durability of funding, the reported cases of resistance to artemisinin, and the detection of pyrethroid resistance in a number of populations of malaria vectors. Malaria still remains an enormous burden of global proportions, and its eradication or elimination at the present resembles an ambitious goal. Although the tools needed for malaria control are much improved, alongside the excitement of the possibility of first licensed malaria vaccine, there is an imperative to maintain continued progress, which demands more commitment from government and nationals of endemic countries, global partners, and donors. Research into new medications, insecticides, and vaccines would still be required to achieve the eventual goal of eradication and elimination. The malaria research community and organizations saddled with the goal of malaria eradication and elimination should be satisfied with the achievements recorded till date. While there is a need to manage these achievements cautiously, we move forward with confidence supported by renewed political will, improved scientific tools for control, elimination, and eradication, and the assurance that a new day is on the horizon.

Author Contributions

Developed the structure and arguments and contributed to the writing of the manuscript: OO. Wrote the first draft of the manuscript: AAA and SAA. Made critical revisions and approved final version: OO and BNT. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Phillips RS. Current status of malaria and potential for control. *Clin Microbiol Rev*. 2001;14(1):208–226.
2. Hall BF, Fauci AS. Malaria control, elimination, and eradication: the role of the evolving biomedical research agenda. *J Infect Dis*. 2009;200(11):1639–1643.
3. WHO. *World Malaria Report 2011*. WHO; 2011. Available at: http://www.who.int/malaria/world_malaria_report_2011/en/. Accessed September 26, 2015.
4. Ramasamy R. Zoonotic malaria—global overview and research and policy needs. *Front Public Health*. 2014;2:123.
5. Prudêncio M, Rodriguez A, Mota MM. The silent path to thousands of merozoites: the *Plasmodium* liver stage. *Nat Rev Microbiol*. 2006;4(11):849–856.
6. Rennenberg A, Lehmann C, Heitmann A, et al. Exoerythrocytic *Plasmodium* parasites secrete a cysteine protease inhibitor involved in sporozoite invasion and capable of blocking cell death of host hepatocytes. *PLoS Pathog*. 2010;6(3):e1000825.
7. Aly ASI, Vaughan AM, Kappe SHI. Malaria parasite development in the mosquito and infection of the mammalian host. *Annu Rev Microbiol*. 2009;63:195–221.
8. Griffin JT, Hollingsworth TD, Okell LC, et al. Reducing *Plasmodium falciparum* malaria transmission in Africa: a model-based evaluation of intervention strategies. *PLoS Med*. 2010;7(8):e1000324.
9. Bhattarai A, Ali AS, Kachur SP, et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Med*. 2007;4(11):e309.
10. Tambo E, Adedeji AA, Huang F, Chen J-H, Zhou S-S, Tang L-H. Scaling up impact of malaria control programmes: a tale of events in Sub-Saharan Africa and People's Republic of China. *Infect Dis Poverty*. 2012;1(1):7.
11. Eisele TP, Larsen DA, Walker N, et al. Estimates of child deaths prevented from malaria prevention scale-up in Africa 2001–2010. *Malar J*. 2012;11:93.
12. Molineaux L, Storey J, Cohen JE, Thomas A. A longitudinal study of human malaria in the West African Savanna in the absence of control measures: relationships between different *Plasmodium* species, in particular *P. falciparum* and *P. malariae*. *Am J Trop Med Hyg*. 1980;29(5):725–737.
13. Draper CC, Smith A. Malaria in the pare area of Tanganyika. Part II. Effects of three years' spraying of huts with dieldrin. *Trans R Soc Trop Med Hyg*. 1960;54:342–357.
14. WHO. *Who Global Malaria Programme: World Malaria Report*. 2014. Available at: http://www.who.int/malaria/publications/world_malaria_report_2014/wmr-2014-no-profiles.pdf. Accessed September 26, 2015.
15. Mendis K, Rietveld A, Warsame M, Bosman A, Greenwood B, Wernsdorfer WH. From malaria control to eradication: the WHO perspective. *Trop Med Int Health*. 2009;14(7):802–809.
16. WHO. *World Malaria Report*. WHO; 2009. Available at: http://www.who.int/malaria/world_malaria_report_2009/en/. Accessed September 26, 2015.
17. Meleigy M. The quest to be free of malaria. *Bull World Health Organ*. 2007;85(7):507–508.
18. WHO/EURO. *Tashkent Declaration: The Move from Malaria Control to Elimination in the WHO European Region*. 2006. Available at: http://www.euro.who.int/__data/assets/pdf_file/0005/98753/E89355.pdf.
19. Behrens RH, Carroll B, Beran J, et al; TropNetEurop. The low and declining risk of malaria in travellers to Latin America: is there still an indication for chemoprophylaxis? *Malar J*. 2007;6(1):114.
20. WHO, WPRO. *World Malaria Day: WHO Stresses Need to Fight Malaria Now More Than Ever*. WPRO; 2014. Available at: http://www.wpro.who.int/mediacentre/releases/2014/20140425/en/. Accessed September 26, 2015.
21. Hay SI, Sinka ME, Okara RM, et al. Developing global maps of the dominant anopheles vectors of human malaria. *PLoS Med*. 2010;7(2):e1000209.
22. Roche B, Broutin H, Choisy M, et al. The niche reduction approach: an opportunity for optimal control of infectious diseases in low-income countries? *BMC Public Health*. 2014;14(1):753.
23. WHO. *Roll Back Malaria Partnership. The Global Malaria Action Plan*. Geneva: WHO; 2008.
24. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*. 2015;526(7572):207–211.
25. WHO Malaria Policy Advisory Committee and Secretariat. Malaria policy advisory committee to the WHO: conclusions and recommendations of seventh biannual meeting (March 2015). *Malar J*. 2015;14:295.
26. WHO. Meeting of the International Task Force for Disease Eradication—November 2012. *Wkly Epidemiol Rec*. 2013;88(7):75–80.
27. Ogungbamigbe TO, Ojurongbe O, Ogunro PS, Okanlawon BM, Kolawole SO. Chloroquine resistant *Plasmodium falciparum* malaria in Osogbo Nigeria: efficacy of amodiaquine + sulfadoxine-pyrimethamine and chloroquine + chlorpheniramine for treatment. *Mem Inst Oswaldo Cruz*. 2008;103(1):79–84.
28. Ojurongbe O, Ogungbamigbe TO, Fagbenro-Beyioku AF, Fendel R, Kremsner PG, Kun JF. Rapid detection of Pfcrt and Pfmdr1 mutations in *Plasmodium falciparum* isolates by FRET and in vivo response to chloroquine among children from Osogbo, Nigeria. *Malar J*. 2007;6(1):41.
29. Braun V, Rempis E, Schnack A, et al. Lack of effect of intermittent preventive treatment for malaria in pregnancy and intense drug resistance in western Uganda. *Malar J*. 2015;14(1):372.
30. Barik TK. Antimalarial drug: from its development to deface. *Curr Drug Discov Technol*. 2015;1875–6220.
31. Anvikar AR, Arora U, Sonal GS, et al. Antimalarial drug policy in India: past, present & future. *Indian J Med Res*. 2014;139(2):205–215.
32. Talisuna AO, Bloland P, D'Alessandro U. History, dynamics, and public health importance of malaria parasite resistance. *Clin Microbiol Rev*. 2004;17(1):235–254.
33. Ojurongbe O, Oyedeji SI, Oyibo WA, Fagbenro-Beyioku AF, Kun JF. Molecular surveillance of drug-resistant *Plasmodium falciparum* in two distinct geographical areas of Nigeria. *Wien Klin Wochenschr*. 2010;122(23–24):681–685.
34. WHO. *Updated WHO Policy Recommendation: Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)*. WHO; 2012. Available at: http://www.who.int/malaria/publications/atoz/who_iptp_sp_policy_recommendation/en/. Accessed October 1, 2015.
35. Eisele TP, Larsen DA, Anglewicz PA, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis*. 2012;12(12):942–949.
36. Ter Kuile FO, van Eijk AM, Filler SJ. Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: a systematic review. *JAMA*. 2007;297(23):2603–2616.
37. Nosten F, McGready R. Intermittent presumptive treatment in pregnancy with sulfadoxine–pyrimethamine: a counter perspective. *Malar J*. 2015;14(1):248.
38. Ojurongbe O, Tijani BD, Fawole AA, Adeyeba OA, Kun JF. Prevalence of dihydrofolate reductase gene mutations in *Plasmodium falciparum* isolate from pregnant women in Nigeria. *Infect Dis Rep*. 2011;3(2):e16.

39. Ojurongbe O, Lawal OA, Abiodun OO, Okeniyi JA, Oyeniyi AJ, Oyelami OA. Efficacy of artemisinin combination therapy for the treatment of uncomplicated falciparum malaria in Nigerian children. *J Infect Dev Ctries*. 2013;7(12):975–982.
40. Visser BJ, Wieten RW, Kroon D, et al. Efficacy and safety of artemisinin combination therapy (ACT) for non-falciparum malaria: a systematic review. *Malar J*. 2014;13:463.
41. Yeung S, Pongtavornpinyo W, Hastings IM, Mills AJ, White NJ. Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices. *Am J Trop Med Hyg*. 2004;71(suppl 2): 179–186.
42. Ojurongbe O, Adegbosin OO, Taiwo SS, et al. Assessment of clinical diagnosis, microscopy, rapid diagnostic tests, and polymerase chain reaction in the diagnosis of *Plasmodium falciparum* in Nigeria. *Malar Res Treat*. 2013;2013:308069.
43. Karunamoorthi K. Malaria vaccine: a future hope to curtail the global malaria burden. *Int J Prev Med*. 2014;5(5):529–538.
44. Hoffman SL, Vekemans J, Richie TL, Duffy PE. The march toward malaria vaccines. *Vaccine*. 2015;49(6 suppl 4):S319–S333.
45. RTS, S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Med*. 2014; 11(7):e1001685.
46. Penny MA, Galactionova K, Tarantino M, Tanner M, Smith TA. The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up phase III data and simulation models. *BMC Med*. 2015;13(1):170.
47. Crompton PD, Pierce SK, Miller LH. Advances and challenges in malaria vaccine development. *J Clin Invest*. 2010;120(12):4168–4178.
48. Churcher TS, Cohen JM, Novotny J, Ntshalintshali N, Kunene S, Cauchemez S. Public health. Measuring the path toward malaria elimination. *Science*. 2014; 344(6189):1230–1232.
49. Strode C, Donegan S, Garner P, Enayati AA, Hemingway J. The impact of pyrethroid resistance on the efficacy of insecticide-treated bed nets against African anopheline mosquitoes: systematic review and meta-analysis. *PLoS Med*. 2014; 11(3):e1001619.
50. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2010. Available at: http://onlinelibrary.wiley.com/
51. WHOPES. *WHO Pesticide Evaluation Scheme: "WHOPES."*. WHO; 2015. Available at: http://www.who.int/whopes/en/. Accessed September 24, 2015.
52. Mabaso MLH, Sharp B, Lengeler C. Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying. *Trop Med Int Health*. 2004;9(8):846–856.
53. Kim D, Fedak K, Kramer R. Reduction of malaria prevalence by indoor residual spraying: a meta-regression analysis. *Am J Trop Med Hyg*. 2012;87(1):117–124.
54. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database Syst Rev*. 2004;(2):CD000363.
55. Okumu FO, Chipwaza B, Madumla EP, et al. Implications of bio-efficacy and persistence of insecticides when indoor residual spraying and long-lasting insecticide nets are combined for malaria prevention. *Malar J*. 2012;11(1):378.
56. Ranson H, N'guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? *Trends Parasitol*. 2011;27(2):91–98.