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Changes in Malaria Epidemiology in Africa and New Challenges for Elimination

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Abstract

Although the burden of *Plasmodium falciparum* malaria is gradually declining in many parts of Africa, it is characterized by spatial and temporal variability that presents new and evolving challenges for malaria control programs. Reductions in the malaria burden need to be sustained in the face of changing epidemiology whilst simultaneously tackling significant pockets of sustained or increasing transmission. Large-scale, robust surveillance mechanisms that *measure* rather than *estimate* the actual burden of malaria over time from large areas of the continent where such data are lacking need to be prioritized. We review these fascinating developments, caution against complacency, and make the case that improving the extent and quality of malaria surveillance is vital for Africa as she marches on towards elimination.

Malaria in a Moment

Malaria is caused by infection with protozoan parasites of the *Plasmodium* species. *Plasmodium falciparum* is widespread in Africa while *P. vivax, P. ovale*, and *P. malariae* infections are less common and geographically restricted [1,2]. The parasites are transmitted by *Anopheles* mosquitoes, with *An. gambiae sensu stricto*, *An. funestus*, and *An. arabiensis* being the most prevalent in Africa [3]. Patients present with nonspecific symptoms, including fever, rigors, and chills, and the majority will not require hospital admission. Severe malaria develops in a minority, and in children it may manifest as a fever, impaired consciousness, severe anaemia, respiratory distress, convulsions, and hypoglycemia, among other symptoms [4].

The epidemiology of malaria varies geographically depending on the local malaria transmission intensity or *endemicity class* (Box 1) [5]. While the exact numbers may be uncertain and underreporting is inevitable, 395 000 deaths were estimated in Africa in 2015 [6]. Infection with *P. falciparum* in the absence of overt clinical symptoms is also common [7]. It is often referred to as being asymptomatic, but may be better termed chronic and is probably not as benign as the former term might suggest [8]. Pregnant women often harbor

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chronic low-density infections with adverse outcomes for both mother and child [9]. The impact of malaria extends beyond health facilities to homes and everyday lives: children may develop long-term neurological sequelae following severe malaria attacks [10], more subtle developmental and cognitive impairments as a result of both severe and uncomplicated episodes [11], and families face substantial economic consequences [12].

Given the current momentum and enthusiasm for malaria elimination in Africa, we contrast recently published modeled trends of the burden against those from empirical studies and show that much more remains to be achieved. We review new challenges for elimination where control has been successful and consider challenges where it has been limited, highlighting research gaps.

Measuring Malaria: Metric Matters

Given the broad range of possible clinical presentations of malaria, it is not obvious what aspect (s) of the disease can and should be measured in order to accurately monitor changing epidemiology. On the face of it, making a diagnosis of malaria should be relatively simple based on readily defined clinical features and supported by positive identification of parasites in peripheral blood smears. In practice in endemic areas, this seemingly straightforward situation is problematic because of the high prevalence of chronic *P. falciparum* infections (Box 2), and the potential for many other conditions to cause fever and/or symptoms similar to severe malaria. Confirming that the parasitaemia one detects is the cause of the presenting symptoms in a patient remains challenging [13], even in well-resourced research centres. The malaria-positive fraction (MPF, Box 3) of hospital admissions or outpatient attendees [14,15] is used as an index of transmission intensity but may be confounded by variability in its denominator. It can be deceptively high when the denominator comprises cases selected based on a high index of suspicion, and is more accurate when all cases presenting to a facility are tested. Additionally, the utilization of formal health services is variable and can be low [16]. Community surveys of parasite prevalence give a broader picture of the overall parasite burden in the population by including asymptomatic individuals of all ages, but the relationship between parasite prevalence and disease incidence is complex and nonlinear [5]. Furthermore, parasite prevalence surveys are often opportunistic, prone to observer bias, nonstandardized, and affected by a multitude of factors including the age-structure of the sample, the timing of sampling in relation to local malaria transmission seasons, and the methodology and rigor applied to parasite detection [17,18] (Box 2). Serological markers show promise, particularly in low-transmission settings, but need further validation [19] and are not yet widely used. Furthermore, data are either lacking [20] or have questionable quality from many parts of the continent: thus the malaria burden may be underestimated in areas where it is greatest for a host of reasons, not least poverty and political instability [14,21].

Monitoring malaria is thus challenging in the clinic and community. The array of metrics utilized further compounds the situation (Box 3). There is no consensus on which is best, and whilst many of them are correlated, these relationships are not absolute and one metric may not accurately reflect another in different transmission settings. Importantly, estimates of the malaria burden ought to be interpreted with an appreciation of the variability that

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arises through methodological differences between studies, and the inevitable limitations of aggregating such data.

Declining Malaria but Lingering Uncertainty and Substantial Heterogeneity

The above challenges notwithstanding, independent research groups have applied different large-scale modeling techniques to estimate a range of malaria metrics and arrived at the unanimous conclusion that the burden of malaria in Africa is decreasing (Figure 1A). In the last 10 years the population at risk of infection has shrunk [22], malaria deaths have declined [23], as has the age-standardized prevalence of infection in children 2–10 years old [22,24]. However, the magnitude of both the absolute burden and the change vary considerably between reports. For example, estimates of cases in Africa differ by as much as 100–200 million episodes in a single year (Figure 1B and [25]). Careful scrutiny of the published estimates reveals that the magnitude of the decline in case numbers falls within the margins of error between yearly estimates, thus requiring judicious interpretation. Not surprisingly, the greatest uncertainty coincides with the areas of highest burden and the areas with highest predicted decline (Figure 2A), somewhat obscuring the picture.

We analyzed trends in the malaria burden from recently published empirical studies and found that, despite the overall decline, a sobering pattern marked by a limited number of studies and spatial as well as temporal heterogeneity was apparent. One in four countries (82%) from the WHO African region published trends in the malaria burden that were either inconsistent (rising in some parts of the country and declining in others) or showed evidence of a temporal increase or resurgence (Figure 2B). A sustained decline was reported from only four countries (and the island of Zanzibar), but in most of these there was only one study available (Figure 2B). Together, these studies represent just 22 of 45 countries that comprise the WHO African region, and the bulk of the research covered the years 2006–2011, presumably a reflection of the time lag between data collection and publication. We limited our analysis to studies showing trends over two consecutive years in the last decade. Nevertheless, the predominantly heterogeneous success of malaria control suggests that the situation is potentially fragile. A major challenge will be the ability to achieve and sustain gains in all areas until elimination becomes a reality because history is clear: malaria *can* and *does* come back [26].

Drivers of the Decline

Empirical studies showing a reduction in the malaria burden (Figure 2B) attributed it to a scale-up of combinations of control strategies. In the main, these were long-lasting insecticide-treated nets (LLINs) or insecticide treated nets (ITNs), indoor residual spraying (IRS) and **intermittent preventive therapy** (see Glossary) for pregnant women (IPTp) for prevention, better diagnostics for case ascertainment, and effective treatments using artemisinin-based combination therapies (ACTs).

The majority of directly observed studies did not generally single out ITNs as the sole or major driver of the decline as recently suggested [24]. In sub-Saharan Africa the proportion of children under 5 years of age and sleeping under ITNs has increased from <2% in the

year 2000 to an estimated 68% (95% confidence interval 61–72%) in 2015, although the estimates vary widely between countries [6]. Despite these gains, recent studies highlighted the fact that the distribution, ownership, and actual use of ITNs is still inefficient and potentially undermines its effectiveness [27].

Larval control, environmental management, and improved access to healthcare are important but underappreciated partners in the observed success [6]. Investments in health systems and improved availability of ACTs and rapid diagnostic tests (RDTs) through global subsidies have also played a role [6]. Other approaches are under investigation, and some have shown promise but not yet been widely deployed, including **seasonal malaria chemoprevention** (SMC) [28] and **mass drug administration** (MDA) [29].

Potential explanations for a sustained or increased burden of malaria reported from empirical studies (Figure 2B) are centered around insufficient coverage of interventions for a multitude of reasons and failing interventions mainly due to drug resistance. Challenges to coverage include the timely availability of funding which, in turn, depends on transparency, accountability, and robust procurement and supply chains. Insufficient uptake interventions and utilization of hospitals, as well as hard to reach populations, were also reported.

Of note, the effectiveness of different interventions has not been similar across all settings [30], and understanding which intervention will work best, under which conditions and for how long, will be critically important for further reductions in the malaria burden. Additionally, a significant proportion of the apparent decline cannot be directly attributed to any intervention [14,31]. Where long-term data are available, in some areas it is evident that a reduction in the malaria burden preceded the implementation of major control activities [14,32,33]. Additional factors that have not been measured, or are difficult to quantify, may be important in this regard. These may include improved economic status, the use of hospital facilities, and an increased availability of diagnostics (Figure 3, Box 2).

Changing Clinical Epidemiology

Increase in the Median Age at Admission to Hospital

Modeling studies predict that, although the burden of malaria cases will shift to older children as transmission declines, the most severe consequences will continue to primarily affect the youngest children (<5 years) [34,35]. These predictions were borne out in a recent 25-year analysis in Kenya where the highest MPF was observed to rise slightly to children older than 5 years, while the median age at admission doubled significantly from approximately 2 to 4 years [36]. Similar patterns were observed in West Africa [15,37].

Less Anaemia but More Cerebral Malaria

Declining transmission has been shown to shift the balance of the clinical presentation in children less than 5 years old from a predominance of severe anaemia in the early years to one of more cerebral malaria in the later years [38]. Likewise, the mean haemoglobin at admission in children with positive malaria slides [15] and in the community [32] increased with decreasing transmission, though the latter study included subjects of all ages. Malaria control efforts should therefore continue to focus on children under the age of 5 years, even

as other emerging populations at risk gain prominence. Data on other clinical presentations of malaria that might be expected to change with declining transmission, such as the proportion of children with seizures and frequency of repeated seizures, the mean parasite density at admission, and the proportion of children presenting with impaired consciousness [39], have yet to be published.

Emerging Populations at Risk

School-Age Children and Teenagers

Children between the ages of 5 years and teen-age are coming to the fore as having an elevated risk of uncomplicated malaria. They had more episodes with progressively declining transmission [32,40], higher than their younger counterparts aged below 5 years [40,41]. Peak parasite prevalence in asymptomatic infections has also risen to older children and suggests a slowing of the rate at which the ability to control parasites is acquired [32,42,43]. Control strategies that previously focused on under-fives therefore need to extend to older-age categories.

Adults

Recent studies support the view that adults are also emerging as a population that warrants monitoring. Adults are themselves reported to be at increased risk of clinical episodes of malaria presumably due to the waning antimalarial immunity that follows decreased exposure to parasites [44]. For example, the prevalence of microscopically detected parasitaemia in febrile adults presenting to hospital more than doubled from 19 to 42% in Gabon in the context of declining transmission over a 20-year period [45]. These proportions may be higher with more sensitive diagnostic tools [46] (Box 2). Additionally, adults may put those surrounding them at risk by continuing to harbor low-density chronic infections even as transmission declines [32,47]. Importantly, household surveys for parasitaemia that contribute substantially to estimates of the malaria burden are often only comprised of children [48]. As such, the true extent of the malaria burden in older children and adults is infrequently measured, and how this is changing over time, as transmission declines, is largely unknown.

Geographical Risk Areas

As transmission declines, and the proportions of individuals harboring asymptomatic or clinical infections decreases, the geographic clustering of infections becomes more apparent. Such clusters, often called **malaria hotspots**, have been detected using many different malaria indices, including incidence, prevalence, serological markers of exposure, and mosquito density. The scale of a hotspot can vary from a few households to subnational regions depending on the granularity of the analysis [49] but generally they become more pronounced as transmission declines. Identification or prediction of hotspots could theoretically help target resources more effectively to reduce residual transmission. The detection of hotspots is not standardized [49,50], and longitudinal studies show that they can be spatially and temporally dynamic, which complicates identification and targeting [49,51]. Although the idea of targeted malaria control within hotspots is logically attractive, its effectiveness has yet to be proven [52].

Silent Sustainers

As the burden of malaria decreases there has been a renewed focus on low-density chronic infections [53]. Recent studies indicate a significant burden in infants [54], children of schoolgoing age [55–57], pregnant women [58,59], and nonpregnant adults [60]. Chronic infections may be microscopic or submicroscopic, and whilst many studies show that the former are transmissible to mosquitoes, and may serve as a neglected reservoir for continued transmission, the evidence is debatable for the latter [61,62]. However, more research using sensitive molecular tools is needed to better understand the relative importance of this reservoir to the elimination agenda in different transmission settings [63]. Whilst it is clear that,without active surveillance, chronic infections remain unnoticed and can persist for months to years, potentially sustaining transmission, the resources required to ‘identify and treat’ all infections are not insignificant [64]. In this regard, some have advocated for **active case detection** (ACD) [65] and blanket strategies such as MDA [29]. Undoubtedly, the choice of method would vary by setting, and implementation should be guided by a careful cost-benefit analysis.

Changing Parasite Populations

The threat posed by the development of parasite resistance to drugs is not specific just to declining transmission, but is highly relevant for elimination. ACTs are first-line treatments for uncomplicated malaria in most of sub-Saharan Africa [66]. They act fast, are highly effective, and are also believed to play a role in reducing population-level transmission by quickly clearing gametocytes [67]. Fortunately, resistance to ACTs has not yet been detected in Africa [66], though it goes without saying that continued monitoring is a high priority. It is predicted that the emergence of a slow-clearance phenotype in Africa,as has been observed in South East Asia, could increase morbidity by 10 million episodes over 5 years [68].

Other parasite adaptations that relate more directly to the declining malaria transmission intensity have been reported in some settings, but the potential challenge that this poses to elimination over and above what might be expected in lower versus higher transmission environments is unclear. These include a decrease in the multiplicity of infection, increased inbreeding rates leading to a lower genetic diversity, and a decrease in effective population size [69]. An interesting recent observation that has implications for case detection and diagnosis is the fact that some parasites lack the gene encoding histidine-rich protein 2 (HRP-2), which may give them a selective advantage in areas where HRP-2-based malaria diagnostics are widely deployed [70].

Changing Vector Populations

Resistance in mosquitoes is acquired through several pathways, either specifically related to the target of the insecticide (**target-site mutations**) or related to detoxification and sequestration of the insecticide (**metabolic resistance**). In Africa, ITNs are exclusively impregnated with **pyrethroids**. Phenotypic resistance and genetic markers of target-site resistance to pyrethroid in *An. gambiae sensu lato*, consisting of single-nucleotide substitutions in the *kdr* gene, have been reported concurrent with the role out of ITNs (for

example [71–73]). The use of pyrethroids as agricultural pesticides in Africa has also been associated with increasing levels of resistance in local mosquito populations [74,75]. Similarly, reports of **metabolic resistance** [76] and **cross-resistance** are increasing and can affect multiple classes of insecticides, which is particularly problematic for planning vector-control operations [77]. Despite increasing vector resistance, evidence for an epidemiological impact is sparse, and the strongest evidence implicates resistance in reduced efficacy of IRS rather than ITNs [78,79]. Several studies have shown continued protection from ITNs in the context of high levels of vector resistance to pyrethroids [77]. Randriamaherijaona *et al.* demonstrated that mosquito resistance did not compromise the personal protection of treated nets *per se*, but that resistant mosquitoes were more likely to survive following successful ingestion of a blood meal [80] potentially contributing to reduced community protection from ITNs. More recently, Ferguson *et al.* showed that, although resistant mosquitoes may not be killed by insecticides, their average life span is reduced by about 50% upon exposure, providing a convincing explanation for the continued effectiveness of ITNs [81].

Behavioral Resistance

There is some evidence that vector populations are exhibiting altered feeding and resting patterns in the face of increasing ITN use, so called ‘behavioral resistance’. ITNs work because the vector has historically been active at night when people are usually asleep. IRS is effective because most malaria vectors are **endophagic** and **endophilic**; they seek blood meals indoors and rest indoors before leaving the house where they fed. Reports of malaria vectors adapting their behavior by feeding earlier, feeding outdoors, and resting outdoors after feeding indoors, are accumulating (for example [82–85]; for an excellent review see [86]). There is debate as to whether these changes reflect shifting vector composition within complexes, pre-existing outdoor-feeding subpopulations that come to the fore as mosquito populations decline, inheritable genetic traits, or the innate flexibility of vectors when their preferred feeding opportunity is not available [86]. Each of these scenarios has different implications for the future efficacy of ITNs. If behavioral resistance is an inheritable trait, it will continue to expand in a manner similar to physiological resistance at a rate determined by the number of genetic loci involved. If a small, pre-existing subpopulation of outdoor feeding vectors is revealed as indoor feeding populations decline, that subpopulation is likely to maintain its ecological niche without compromising ITN efficacy but will create a minimum threshold below which transmission becomes resistant to current control strategies. Malaria vectors are also becoming more flexible in their host selection; even *An. gambaie sensu stricto*, previously thought to be highly **anthropophilic**, has been shown to take nearly half of blood meals from other hosts [87]. Although it may not reduce the individual efficacy of ITNs, this host plasticity reduces the mass mortality effect of ITN coverage, leading to larger and older mosquito populations. It is predicted that behavioral changes can have as large, or larger, impact than physiological resistance on efficacy of vector-control measures [86].

Challenges for National Governments

One lesson that stands out from a historical view of malaria control is that efforts must be sustained, not only for gains to be maintained but to prevent resurgence of malaria [26]. For resource-constrained settings, sustainability is always a concern. In Africa, ~89% percent of malaria-control activities and commodities are funded by global programs and only 11% percent by local governments [21]. If attention and emphasis on malaria wanes globally, there will be major consequences for Africa. There are also operational challenges such as identifying optimum mechanisms to maintain high ITN coverage between mass-distribution campaigns [27,88,89], improving infrastructure for case management (availability of diagnostic tools, stock-outs of drugs, motivation of health workers), and overcoming behavioral challenges to encourage correct and consistent use of ITNs and reduce presumptive use of artemisinin-combination therapies, both by health workers and community members.

Arguably, the single biggest challenge for national governments is monitoring malaria consistently and reliably through time. Remarkable amounts of scientific time and expertise have been spent estimating the burden of malaria in Africa. This is due in large part to the paucity of reliable health system surveillance data from the entire continent. Surveillance also has important implications for measuring the effectiveness of control interventions, resource allocation, planning, and tailoring national programs to suit the local epidemiology and specific needs of the population.

Concluding Remarks

Although the burden of malaria is declining in Africa, significant uncertainty on its absolute magnitude persists, and pockets remain where urgent action is still needed (see Outstanding Questions). Where significant gains have been realized, it will be vital not to give complacency a foothold and continue to support national governments with constrained budgets to keep up malaria surveillance, even as it declines. Keeping pace with changes in the environment, the parasite, the vector, and human activities will be essential for success. Saving lives is the ultimate goal of malaria control, and in our view, continued quality surveillance at all levels of this complex interplay will be the greatest challenge as Africa aims for elimination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Howes RE, et al. *Plasmodium vivax* transmission in Africa. PLoS Negl Trop Dis. 2015; 9:e0004222. [PubMed: 26587988]
2. Roucher C, et al. A 20-year longitudinal study of *Plasmodium ovale and Plasmodium malariae* prevalence and morbidity in a West African population. PLoS One. 2014; 9:e87169. [PubMed: 24520325]
3. Sinka ME, et al. The dominant *Anopheles* vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic précis. Parasites Vectors. 2010; 3:1–34. [PubMed: 20051120]
4. Marsh K, et al. Indicators of life-threatening malaria in African children. N Engl J Med. 1995; 332:1399–1404. [PubMed: 7723795]
5. Snow RW, Marsh K. The consequences of reducing transmission of *Plasmodium falciparum* in Africa. Adv Parasitol. 2002; 52:235–264. [PubMed: 12521262]
6. WHO. World Malaria Report. World Health Organization; 2015.
7. Lindblade KA, et al. The silent threat: asymptomatic parasitemia and malaria transmission. Expert Rev Anti Infect Ther. 2013; 11:623–639. [PubMed: 23750733]
8. Chen I, et al. 'Asymptomatic' malaria: a chronic and debilitating infection that should be treated. PLoS Med. 2016; 13:e1001942. [PubMed: 26783752]
9. Steketee RW, et al. The burden of malaria in pregnancy in malaria-endemic areas. Am J Trop Med Hyg. 2001; 64(1–2 Suppl):28–35.
10. Mishra SK, Newton CR. Diagnosis and management of the neurological complications of *falciparum* malaria. Nat Rev Neurol. 2009; 5:189–198. [PubMed: 19347024]
11. Holding PA, Kitsao-Wekulo PK. Describing the burden of malaria on child development: what should we be measuring and how should we be measuring it? Am J Trop Med Hyg. 2004; 71(Suppl. 2):71–79.
12. Sicuri E, et al. The economic costs of malaria in children in three sub-Saharan countries: Ghana, Tanzania and Kenya. Malaria J. 2013; 12:307.
13. Koram KA, Molyneux ME. When is 'malaria' malaria? The different burdens of malaria infection, malaria disease, and malaria-like illnesses. Am J Trop Med Hyg. 2007; 77(Suppl. 6):1–5.
14. O'Meara WP, et al. Changes in the burden of malaria in sub-Saharan Africa. Lancet Infect Dis. 2010; 10:545–555. [PubMed: 20637696]
15. Ceesay SJ, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet. 2008; 372:1545–1554. [PubMed: 18984187]
16. Geldsetzer P, et al. The recognition of and care seeking behaviour for childhood illness in developing countries: a systematic review. PLoS One. 2014; 9:e93427. [PubMed: 24718483]
17. Tusting LS, et al. Measuring changes in *Plasmodium falciparum* transmission: precision, accuracy and costs of metrics. Adv Parasitol. 2014; 84:151–208. [PubMed: 24480314]
18. Mappin B, et al. Standardizing *Plasmodium falciparum* infection prevalence measured via microscopy versus rapid diagnostic test. Malaria J. 2015; 14:460.
19. Helb DA, et al. Novel serologic biomarkers provide accurate estimates of recent *Plasmodium falciparum* exposure for individuals and communities. Proc Natl Acad Sci U S A. 2015; 112:E4438–E4447. [PubMed: 26216993]
20. Gething PW, et al. Declining malaria in Africa: improving the measurement of progress. Malaria J. 2014; 13:39.
21. WHO. The World Malaria Report. World Health Organization; 2014.
22. Noor AM, et al. The changing risk of *Plasmodium falciparum* malaria infection in Africa: 2000-10: a spatial and temporal analysis of transmission intensity. Lancet. 2014; 383:1739–1747. [PubMed: 24559537]
23. Murray CJ, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384:1005–1070. [PubMed: 25059949]

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24. Bhatt S, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015; 526:207–211. [PubMed: 26375008]
25. Cibulskis RE, et al. Worldwide incidence of malaria in 2009: estimates, time trends, and a critique of methods. PLoS Med. 2011; 8:e1001142. [PubMed: 22205883]
26. Cohen JM, et al. Malaria resurgence: a systematic review and assessment of its causes. Malaria J. 2012; 11:122.
27. Bhatt S, et al. Coverage and system efficiencies of insecticide-treated nets in Africa from 2000 to 2017. Elife. 2015; 4:e0967.
28. Meremikwu MM, et al. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. Cochrane Database Syst Rev. 2012; 2
29. Poirot E, et al. Mass drug administration for malaria. Cochrane Database Syst Rev. 2013; 12
30. Kamuliwo M, et al. The changing burden of malaria and association with vector control interventions in Zambia using district-level surveillance data, 2006-2011. Malaria J. 2013; 12:437.
31. Marsh K. Africa in transition: the case of malaria. Int Health. 2016; 8:155–156. [PubMed: 27178672]
32. Farnert A, et al. Epidemiology of malaria in a village in the Rufiji River Delta, Tanzania: declining transmission over 25 years revealed by different parasitological metrics. Malaria J. 2014; 13:459.
33. Snow RW, et al. Changing malaria prevalence on the Kenyan coast since 1974: climate, drugs and vector control. PLoS One. 2015; 10:e0128792. [PubMed: 26107772]
34. Carneiro I, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS One. 2010; 5:e8988. [PubMed: 20126547]
35. Roca-Feltrer A, et al. The age patterns of severe malaria syndromes in sub-Saharan Africa across a range of transmission intensities and seasonality settings. Malaria J. 2010; 9:282.
36. Mogeni P, et al. Age, spatial, and temporal variations in hospital admissions with malaria in Kilifi County, Kenya: a 25-year longitudinal observational study. PLoS Med. 2016; 13:e1002047. [PubMed: 27352303]
37. Bouyou-Akotet MK, et al. Evidence of decline of malaria in the general hospital of Libreville, Gabon from 2000 to 2008. Malaria J. 2009; 8:300.
38. O'Meara WP, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet. 2008; 372:1555–1562. [PubMed: 18984188]
39. Idro R, et al. Severe malaria in children in areas with low, moderate and high transmission intensity in Uganda. Trop Med Int Health. 2006; 11:115–124. [PubMed: 16398762]
40. Mawili-Mboumba DP, et al. Increase in malaria prevalence and age of at risk population in different areas of Gabon. Malaria J. 2013; 12:3.
41. Ursing J, et al. Malaria transmission in Bissau, Guinea-Bissau between 1995 and 2012: malaria resurgence did not negatively affect mortality. PLoS One. 2014; 9:e101167. [PubMed: 24984039]
42. Espie E, et al. Spatio-temporal variations in malaria incidence in children less than 10 years old, Health District of Sokone, Senegal, 2010-2013. PLoS One. 2015; 10:e0137737. [PubMed: 26381623]
43. Ishengoma DS, et al. Declining burden of malaria over two decades in a rural community of Muheza district, north-eastern Tanzania. Malaria J. 2013; 12:338.
44. Murungi LM, et al. A threshold concentration of antimerozoite antibodies is required for protection from clinical episodes of malaria. Vaccine. 2013; 31:3936–3942. [PubMed: 23800539]
45. Bouyou-Akotet MK, et al. Falciparum malaria as an emerging cause of fever in adults living in Gabon, Central Africa. Biomed Res Int. 2014; 2014
46. Kipanga PN, et al. High-resolution melting analysis reveals low Plasmodium parasitaemia infections among microscopically negative febrile patients in western Kenya. Malaria J. 2014; 13:429.
47. Trape JF, et al. The rise and fall of malaria in a West African rural community, Dielmo, Senegal, from 1990 to 2012: a 22 year longitudinal study. Lancet Infect Dis. 2014; 14:476–488. [PubMed: 24813159]
48. WHO. World Malaria Report. World Health Organization; 2013.

49. Bousema T, et al. Hitting hotspots: spatial targeting of malaria for control and elimination. PLoS Med. 2012; 9:e1001165. [PubMed: 22303287]
50. Kangoye DT, et al. Malaria hotspots defined by clinical malaria, asymptomatic carriage, PCR and vector numbers in a low transmission area on the Kenyan coast. Malaria J. 2016; 15:213.
51. Bejon P, et al. A micro-epidemiological analysis of febrile malaria in coastal Kenya showing hotspots within hotspots. Elife. 2014; 3:e02130. [PubMed: 24843017]
52. Bousema T, et al. The impact of hotspot-targeted interventions on malaria transmission in Rachuonyo South District in the Western Kenyan Highlands: a cluster-randomized controlled trial. PLoS Med. 2016; 13:e1001993. [PubMed: 27071072]
53. Galatas B, et al. Malaria parasites in the asymptomatic: looking for the hay in the haystack. Trends Parasitol. 2016; 32:296–308. [PubMed: 26708404]
54. Ceesay SJ, et al. Malaria prevalence among young infants in different transmission settings, Africa. Emerg Infect Dis. 2015; 21:1114–1121. [PubMed: 26079062]
55. Pinchoff J, et al. Individual and household level risk factors associated with malaria in Nchelenge District, a region with perennial transmission: a serial cross-sectional study from 2012 to 2015. PLoS One. 2016; 11:e0156717. [PubMed: 27281028]
56. Nankabirwa J, et al. Malaria in school-age children in Africa: an increasingly important challenge. Trop Med Int Health. 2014; 19:1294–1309. [PubMed: 25145389]
57. Mathanga DP, et al. The high burden of malaria in primary school children in Southern Malawi. Am J Trop Med Hyg. 2015; 93:779–789. [PubMed: 26283750]
58. Boudova S, et al. Pregnant women are a reservoir of malaria transmission in Blantyre, Malawi. Malaria J. 2014; 13:506.
59. Chaponda EB, et al. High burden of malaria infection in pregnant women in a rural district of Zambia: a cross-sectional study. Malaria J. 2015; 14:380.
60. Jenkins R, et al. Prevalence of malaria parasites in adults and its determinants in malaria endemic area of Kisumu County, Kenya. Malaria J. 2015; 14:263.
61. Goncalves BP, et al. Infectivity of microscopic and submicroscopic malaria parasite infections in areas of low malaria endemicity. J Infect Dis. 2016; 213:1516–1517. [PubMed: 26908734]
62. Lin JT, et al. The role of submicroscopic parasitemia in malaria transmission: what is the evidence? Trends Parasitol. 2014; 30:183–190. [PubMed: 24642035]
63. Bousema T, et al. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. Nat Rev Microbiol. 2014; 12:833–840. [PubMed: 25329408]
64. Tiono AB, et al. Dynamics of malaria transmission and susceptibility to clinical malaria episodes following treatment of *Plasmodium falciparum* asymptomatic carriers: results of a cluster-randomized study of community-wide screening and treatment, and a parallel entomology study. BMC Infect Dis. 2013; 13:535. [PubMed: 24215306]
65. Sturrock HJ, et al. Targeting asymptomatic malaria infections: active surveillance in control and elimination. PLoS Med. 2013; 10:e1001467. [PubMed: 23853551]
66. Menard D, et al. A worldwide map of *Plasmodium falciparum* K13-propeller polymorphisms. N Engl J Med. 2016; 374:2453–2464. [PubMed: 27332904]
67. Group WGS. Gametocyte carriage in uncomplicated *Plasmodium falciparum* malaria following treatment with artemisinin combination therapy: a systematic review and meta-analysis of individual patient data. BMC Med. 2016; 14:79. [PubMed: 27221542]
68. Slater HC, et al. Assessing the potential impact of artemisinin and partner drug resistance in sub-Saharan Africa. Malaria J. 2016; 15:10.
69. Escalante AA, et al. Malaria molecular epidemiology: lessons from the international centers of excellence for malaria research network. Am J Trop Med Hyg. 2015; 93(Suppl 3):79–86. [PubMed: 26259945]
70. Cheng Q, et al. *Plasmodium falciparum* parasites lacking histidine-rich protein 2 and 3: a review and recommendations for accurate reporting. Malaria J. 2014; 13:283.
71. Edi CA, et al. Long-term trends in *Anopheles gambiae* insecticide resistance in Cote d'Ivoire. Parasit Vectors. 2014; 7:500. [PubMed: 25429888]

72. Hemingway J. The role of vector control in stopping the transmission of malaria: threats and opportunities. Philos Trans R Soc Lond B Biol Sci. 2014; 369
73. Trape JF, et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. Lancet Infect Dis. 2011; 11:925–932. [PubMed: 21856232]
74. Yadouleton A, et al. Cotton pest management practices and the selection of pyrethroid resistance in Anopheles gambiae population in northern Benin. Parasit Vectors. 2011; 4:60. [PubMed: 21489266]
75. Nkya TE, et al. Impact of environment on mosquito response to pyrethroid insecticides: facts, evidences and prospects. Insect Biochem Mol Biol. 2013; 43:407–416. [PubMed: 23123179]
76. Riveron JM, et al. Directionally selected cytochrome P450 alleles are driving the spread of pyrethroid resistance in the major malaria vector *Anopheles funestus*. Proc Natl Acad Sci USA. 2013; 110:252–257. [PubMed: 23248325]
77. Ranson H, et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol. 2011; 27:91–98. [PubMed: 20843745]
78. Sharp BL, et al. Malaria vector control by indoor residual insecticide spraying on the tropical island of Bioko, Equatorial Guinea. Malaria J. 2007; 6:52.
79. Maharaj R, et al. Impact of DDT re-introduction on malaria transmission in KwaZulu-Natal. S Afr Med J. 2005; 95:871–874. [PubMed: 16344885]
80. Randriamaherijaona S, et al. Do holes in long-lasting insecticidal nets compromise their efficacy against pyrethroid resistant *Anopheles gambiae* and *Culex quinquefasciatus*? Results from a release-recapture study in experimental huts. Malaria J. 2015; 14:332.
81. Viana M, et al. Delayed mortality effects cut the malaria transmission potential of insecticide-resistant mosquitoes. Proc Natl Acad Sci USA. 2016; 113:8975–8980. [PubMed: 27402740]
82. Russell TL, et al. Increased proportions of outdoor feeding among residual malaria vector populations following increased use of insecticide-treated nets in rural Tanzania. Malaria J. 2011; 10:80.
83. Govella NJ, et al. Entomological surveillance of behavioural resilience and resistance in residual malaria vector populations. Malaria J. 2013; 12:124.
84. Cooke MK, et al. 'A bite before bed': exposure to malaria vectors outside the times of net use in the highlands of western Kenya. Malaria J. 2015; 14:259.
85. Sougoufara S, et al. Biting by *Anopheles funestus* in broad daylight after use of long-lasting insecticidal nets: a new challenge to malaria elimination. Malaria J. 2014; 13:125.
86. Gatton ML, et al. The importance of mosquito behavioural adaptations to malaria control in Africa. Evolution. 2013; 67:1218–1230. [PubMed: 23550770]
87. Ndenga BA, et al. Malaria vectors and their blood-meal sources in an area of high bed net ownership in the western Kenya highlands. Malaria J. 2016; 15:76.
88. Theiss-Nyland K, et al. Operational challenges to continuous LLIN distribution: a qualitative rapid assessment in four countries. Malaria J. 2016; 15:131.
89. Clark S, et al. A longitudinal analysis of mosquito net ownership and use in an indigenous Batwa population after a targeted distribution. PLoS One. 2016; 11:e0154808. [PubMed: 27145034]
90. Malaria Conference in Equatorial Africa (1950: Kampala, Uganda), World Health Organization, Commission for Technical Co-operation in Africa South of the Sahara. Report on the Malaria Conference in Equatorial Africa, held under the joint auspices of the World Health Organization and the Commission for Technical Co-operation in Africa South of the Sahara, Kampala, Uganda, 27 November-9 December 1950. Wld Hlth Organ Tech Rep Ser. 1951; 38:1–72.
91. Snow RW, et al. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature. 2005; 434:214–217. [PubMed: 15759000]
92. Hay SI, et al. A world malaria map: *Plasmodium falciparum* endemicity in 2007. PLoS Med. 2009; 6:e1000048. [PubMed: 19323591]

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Box 1

Malaria Endemicity Classes

These give an indication of the burden of malaria in a given locale; areas are classified as holo-, hyper-, meso-, and hypoendemic.

Classification as Proposed in the WHO 1951 Report on the Malaria Conference in Equatorial Africa [90]

- Hypoendemic malaria: spleen-rate in children 2–10 years of age, 0–10%
- Mesoendemic malaria: spleen-rate in children 2–10 years of age, 11–50%
- Hyperendemic malaria: spleen-rate in children 2–10 years of age, constantly over 50%; spleen-rate in adults, high
- Holoendemic malaria: spleen-rate in children 2–10 years of age, constantly over 50%; spleen-rate in adults, low; it is in this type of endemicity that the strongest adult tolerance is found.

Classification Based on Parasite Prevalence

- Hypoendemic malaria: parasite rate in children 2–10 years of age, 0–10%
- Mesoendemic malaria: parasite rate in children 2–10 years of age, 10–50%
- Hyperendemic malaria: parasite rate in children 2–10 years of age, 50–75%
- Holoendemic malaria: parasite rate in children 2–10 years of age, >75%

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Box 2

Diagnosing Malaria

Infection with *Plasmodium* parasites may or may not lead to symptoms recognizable as an acute infection prompting care. On the other hand, those presenting with fever and malaria-like symptoms may or may not be infected with *Plasmodium*, and even when they are infected the parasites may not always be the cause of the acute symptoms.

Presumptive or Clinical Diagnosis

For decades, presentation with a fever, particularly in children, was assumed to be malaria and treated with antimalarials. This practice continues when diagnostic tools are not available (e.g., underresourced clinics, retail outlets). Although the presence of fever is highly sensitive for malaria, it lacks specificity which leads to overdiagnosis. These cases are counted as malaria cases although they may be designated ‘unconfirmed’ or ‘clinical’ malaria.

Diagnosis by Light Microscopy

Examination of stained blood smears by light microscopy has been used to detect parasites in the peripheral blood since the late 1800s. Microscopy is inexpensive and, when done well, can be very sensitive and specific. The quality of microscopic diagnosis is often compromised by poor equipment, underqualified staff, high workload, and limited availability of electricity and reagents.

Diagnosis by Rapid Diagnostic Test (RDT)

Immunochromatographic antigen-based single-use tests detect circulating antigen in an active infection. Tests can have excellent sensitivity and specificity compared to light microscopy, with some loss of sensitivity at very low parasite densities. Tests based on the HRP2 antigen do exhibit reduced specificity since HRP2 can circulate in the bloodstream for a week after treatment. RDTs are simple, do not require electricity, and their availability has greatly expanded the reach of diagnosis.

New technologies, including urine and saliva tests, are under development. Highly sensitive PCR methods are used primarily for research. However, the recently developed loop-mediated isothermal amplification (LAMP), a nucleic acid-based diagnostic tool that is cheaper, faster, and easier than PCR but with equal sensitivity, has potential for application in targeting the malaria infectious reservoir through mass screening and treatment (MSAT).

In Africa, case numbers obtained through routine health information systems are confounded by two main problems: (i) incomplete reporting (low reporting from the public sector, and lack of engagement of private sector in government reporting), and (ii) inclusion of both unconfirmed cases and diagnostically confirmed cases in the totals. Because clinical diagnosis has very low specificity, when diagnosis is scaled up the total malaria case numbers may be observed to decline (Figure 3).

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Box 3

Malaria Metrics

The epidemiology of malaria is closely linked to its transmission intensity. Malaria metrics often either focus on the clinical disease burden, for example case numbers, or may be more generalized to detect how many people in a given locale are infected with parasites regardless of whether or not they have overt clinical symptoms, for example parasite prevalence. The entomological inoculation rate (EIR) is a more direct measure of transmission intensity. Malaria control is guided both by estimates of the clinical burden and transmission intensity.

- Spleen rate: the incidence of splenic enlargement in children between 2 and 10 years of age, and thought to reflect intensity of malaria transmission. This metric is not commonly used at the present time.
- Parasite prevalence/parasite rate: the proportion of the population in a given locale with detectable parasites in blood, and thought to reflect the intensity of malaria transmission.
- Entomological inoculation rate: the number of infectious mosquito bites per person per unit time and the traditional gold standard for measuring the intensity of transmission.
- Seroconversion rate: the frequency by which seronegative individuals become seropositive upon malaria exposure per unit of time. It is thought to be a good indicator of exposure to infectious mosquitoes and reflect the intensity of transmission. This measure has particular promise as a surveillance tool in low-transmission settings, and there are efforts to identify serological biomarkers that can better discriminate between cumulative malaria exposure and recent infection.
- Malaria-positive fraction: the proportion of children admitted to hospital or seen at outpatient health facilities who are positive for malaria parasites. Its denominator could be all patients or those selected based on a high index of suspicion. It is thought to be an indicator of malaria transmission intensity.
- Incidence rate: the proportion of new cases of malaria diagnosed within a given period of time in a defined population.
- Case numbers: the total number of clinical cases of malaria reported over a given time frame in a given area.
- Deaths: the numbers of deaths attributable to malaria is often estimated from verbal autopsies.
- Slide positivity rate: the number of laboratory-confirmed malaria cases per 100 suspected cases examined and thought to reflect changes in clinical disease incidence. Its denominator is usually suspected malaria cases rather than all patients as in the MPF.

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Trends

Malaria is declining in Africa overall but there is considerable uncertainty around reported estimates.

In some areas, the burden of malaria has remained unchanged or increased.

More time is spent *estimating* rather than *measuring* the malaria burden.

Changes in malaria transmission intensity have brought to the fore emerging populations at risk.

Sustaining the gains in malaria control is a major challenge for elimination.

More extensive and high-quality data on the actual malaria burden is vital to guide control on the path to elimination.

Glossary

Active case detection (ACD): definitions vary with context, but in general this refers to the active testing for malaria infections in individuals who may or may not complain of symptoms.

Anthropophilic: refers to mosquitoes that preferentially bite humans for their blood meal as opposed to other animals.

Cross-resistance: when resistance to one drug renders mosquitoes resistant to an insecticide with a similar mechanism of action.

Endophagic: refers to mosquitoes feeding indoors.

Endophilic: refers to mosquitoes resting indoors after a blood meal.

Intermittent preventive therapy (IPT): the administration of a full course of an antimalarial treatment to a population at risk at specified time points regardless of whether or not they are known to be infected. Examples include IPTi, IPTc, and IPTp for infants, children, and pregnant women respectively.

Malaria hotspots: defined variably between studies but in general refers to a defined locale within which some individuals experience significantly more malaria than others.

Mass drug administration (MDA): the administration of a therapeutic antimalarial regimen to an entire population at the same time whether or not they are infected as a strategy for malaria control and elimination.

Metabolic resistance: mosquitoes get better at degrading or sequestering insecticides by altering specific enzymes which serve to decrease the availability of the drug at the target site.

Pyrethroids: one of the four main classes of insecticide used for malaria control and includes drugs such as Permethrin and Deltamethrin. The three other main classes are the organophosphates, for example, Malathion, organochlorines such as dichlorodiphenyltrichloroethane (DDT), and carbamates such as Carbofuran.

Seasonal malaria chemoprevention: previously referred to as IPTc (‘c’ for children), the treatment of all children for malaria at regular intervals during the malaria transmission season.

Target-site mutations: a common mechanism of insecticide resistance where mosquitoes undergo point mutations at the target site of an insecticide thereby reducing the effectiveness of the insecticide.

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Outstanding Questions

What is the true magnitude of the burden of malaria in Africa, and how much has this really declined?

Which data sources are the most reliable for monitoring malaria, and how can they be improved or better supported?

How much do adults contribute to the burden of malaria in Africa, and is this shifting over time as transmission declines? How big an infectious reservoir is this?

Why has the burden of malaria not decreased in certain areas despite the implementation of multiple control measures?

Which interventions for malaria control work best, where and for how long?

Under which circumstances is targeted control effective?

In areas where there is a clear decline, which strategies need to be put in place to prevent resurgence?

Can these gains in reducing the burden of malaria be sustained?

Which strategies will be most effective at eliminating the silent infectious reservoir of chronic low-density infections, and when should these be introduced?

Will elimination of the silent infectious reservoir accelerate elimination and is it worth the extra effort?

How will climate change impact transmission?

How will changing land use and human activities impact malaria transmission?

What is the impact of the increased mobility of populations on strategies for malaria elimination?

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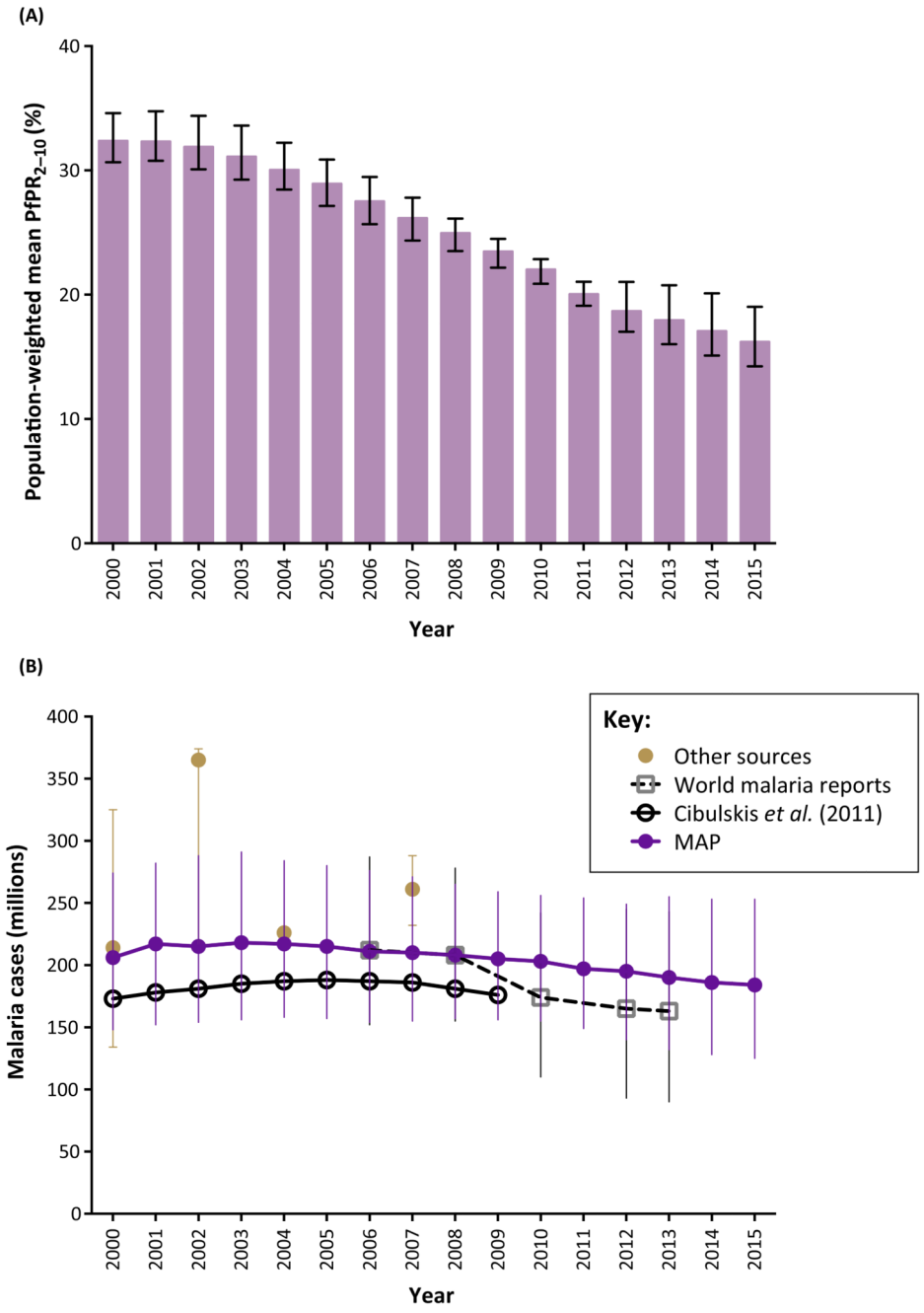

Figure 1. Declining Burden of Malaria in Africa.

(A) The modeled *Plasmodium falciparum* parasite prevalence in children aged between 2 and 10 (*Pf*$PR_{2–10}$) years shows a clear decline in Africa. In this figure, Africa includes all African countries and is different from the WHO designated AFRO region. Data from Malaria Atlas Project (MAP) (www.map.ox.ac.uk). (B) The trend is less clear with other malaria metrics and is obscured by huge uncertainty. The estimated total number of *Plasmodium falciparum* cases (in millions) in Africa in each year between 2000 and 2015. Point estimates and 95% confidence or credible intervals are presented from: (i) Malaria

Atlas Project (MAP) (www.map.ox.ac.uk); (ii) Cibulskis *et al.* [25]; (iii) other sources (for 2000: http://archives.who.int/prioritymeds/report/append/610snow_wp11.pdf; for 2002: Snow *et al.* [91]; for 2004: http://archives.who.int/prioritymeds/report/append/610snow_wp11.pdf; for 2004: http://www.who. int/malaria/publications/atoz/incidence_estimations2.pdf; for 2007: Hay *et al.* [92]); (iv) World Malaria Reports (each data point is from the report in the following year). All estimates are from the WHO AFRO Region. World Malaria Reports do not specifically exclude other malaria species, but these cases are very rare in sub-Saharan Africa and therefore not likely to affect the comparison between sources. Single point estimates from other sources were offset slightly on the x-axis for clarity.

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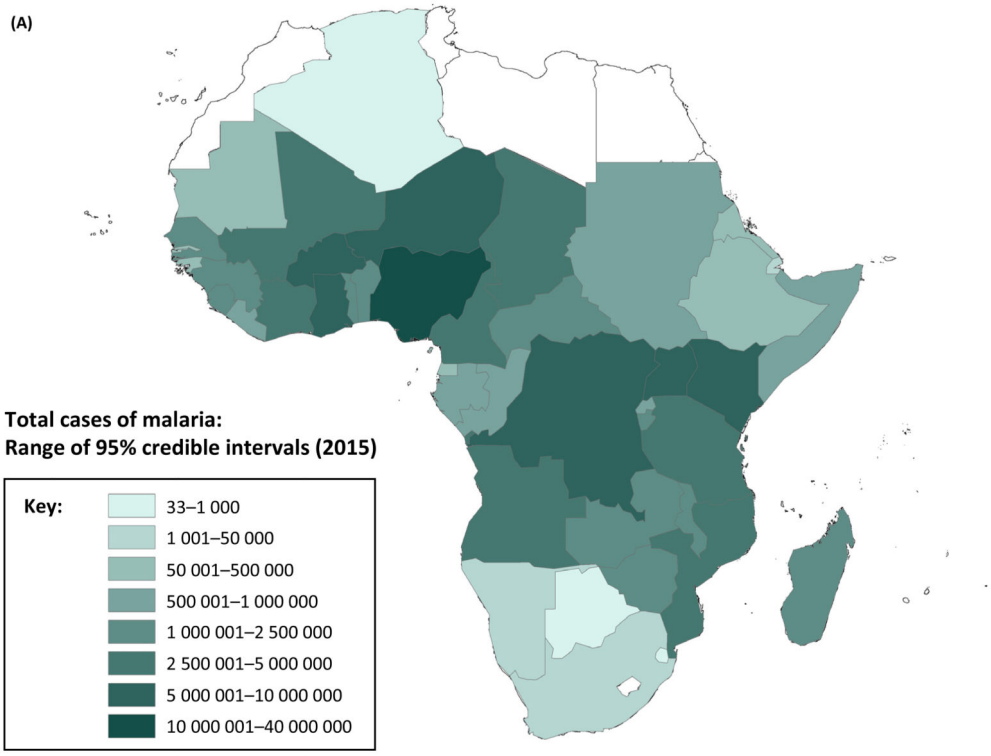

(B)

WHO region	Study area	Number of studies	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Central Africa	Angola	1										
	Equatorial Guinea	1										
	Gabon	2										
	Sao Tome & Principe	1										
East Africa	Ethiopia	2										
	Kenya	9										
	Malawi	3										
	Rwanda	2										
	Tanzania	4										
	Uganda	2										
	Comoros	1										
	Zanzibar	1										
Southern Africa	Botswana	1										
	South Africa	3										
	Zambia	5										
	Zimbabwe	3										
West Africa	Burkina Faso	2										
	Cameroon	1										
	Gambia	2										
	Guinea Bissau	1										
	Mali	2										
	Senegal	3										
	Togo	1										

Figure 2. Uncertainty in the Estimates of Total Malaria Case Burden in Africa.

(A) The difference between the upper and lower 95% credible intervals for total estimated malaria cases per country in 2015. Malaria Atlas Project (MAP) (www.map.ox.ac.uk). Briefly, estimates are derived from inputting prevalence values extrapolated from survey data into functions describing the modeled relationship between prevalence and incidence. Case counts are generated by multiplying incidence and population data. (B) Trends in malaria burden in WHO African region from 2006 to 2015. Studies on malaria burden in Africa with data for more than two consecutive years were obtained from Pubmed (https://

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www.ncbi.nlm.nih.gov/pubmed). Studies with data from before 2006 and those designed specifically to test an intervention were excluded. A total of 51 longitudinal studies from 22 countries were included (see Table S1 in the supplemental information online for a complete list of studies). The trend in malaria cases, admissions, and/or parasite prevalence in each country was summarized year-by-year and indicated as: decline (green), increase (red), or as differing between studies (yellow). The island of Zanzibar is part of Tanzania but was shown separately as it has experienced a sustained decline in transmission.

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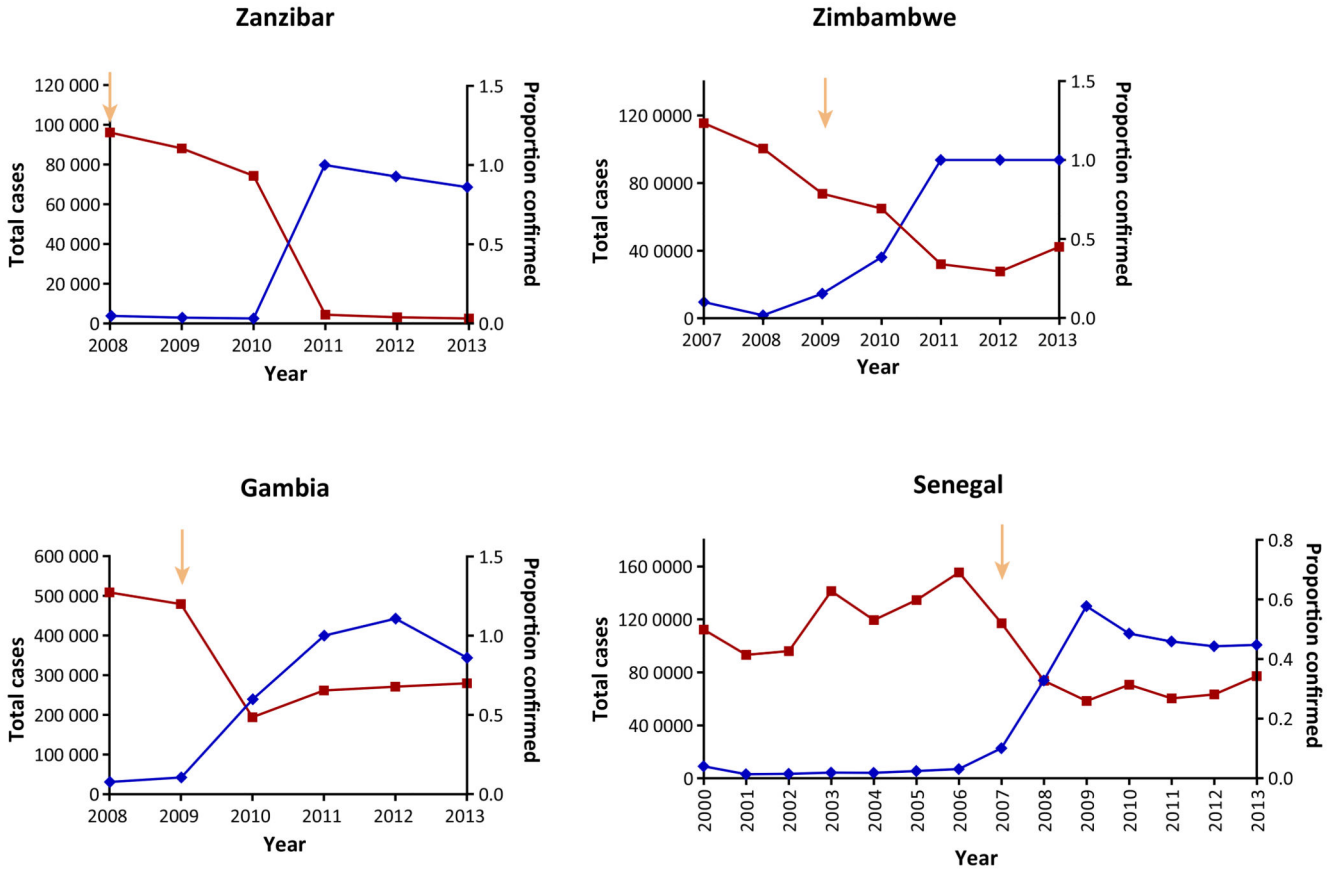

Figure 3. Temporal Trends in Malaria Cases before and after Introduction of Rapid Diagnostic Tests.

Total annual malaria cases (confirmed and unconfirmed, red lines) reported from routine government surveillance in five countries are plotted before and after introduction of rapid diagnostic tests (RDTs). The proportions of total cases that were confirmed with microscopy or RDT are plotted for the same time period. The year RDTs were rolled out in each country is indicated by the yellow arrows. The blue lines show the proportion of confirmed cases. Select countries that showed a decline in total cases and had at least 5 years of diagnosis data were included to illustrate the temporal trends in cases and testing rates. Of interest, The Gambia reported more confirmed cases than total cases in 2012, which illustrates the question of data quality when quantifying the burden of malaria through routine reporting. All data are from World Malaria Report 2014 [21].