

Malaria eradication revisited

Nicholas M Douglas,^{1,2,3} * Thomas R Burkot⁴ and Ric N Price^{2,5,6}

1. Department of Medicine, University of Otago, Christchurch, New Zealand

2. Division of Global and Tropical Health, Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia

3. Department of Infectious Diseases, Christchurch Hospital, Christchurch, New Zealand

4. Australian Institute of Tropical Health and Medicine, James Cook University, Cairns, QLD, Australia

5. Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand

6. Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom

* Corresponding author: Dr Nicholas Douglas, Department of Medicine, University of Otago, Christchurch Hospital, Christchurch, New Zealand. E: Nicholas.Douglas@cdhb.health.nz

Manuscript word count: 3511

Keywords: malaria, Plasmodium, malaria control, vector control, malaria epidemiology, malaria eradication

Malaria is a mosquito-borne disease that has shaped human populations and their economies since antiquity. It is caused by single-celled parasites belonging to the genus *Plasmodium*, of which *P. falciparum* is the most pathogenic. Following a latent period of replication within the liver, *Plasmodium* parasites are released into the bloodstream where they invade erythrocytes, causing acute haemolysis

and varying degrees of microvascular obstruction and organ dysfunction. In the absence of pre-existing immunity, early diagnosis and treatment of malaria is required to prevent severe morbidity or death.

Following the discovery of the *Anopheles* mosquito vector in 1897, malaria control activities focused on reducing mosquito numbers through environmental modification. During the 1930s, residual insecticide spraying was adopted, initially using pyrethrum and later DDT (dichlorodiphenyltrichloroethane). Buoyed by notable successes, such as the elimination of malaria from Sardinia,¹ the newly formed World Health Organization (WHO) formalised a commitment to global eradication of malaria at the 1955 World Health Assembly; a target requiring extermination of every human malaria parasite on earth.² Regional and national action plans were organised into four phases: preparation, attack, consolidation and maintenance. Programmes relied heavily on vector control. Active case finding and antimalarial treatment, primarily with chloroquine, was intended to expand as the incidence of malaria decreased. On the eve of this audacious commitment to eradication, 182 countries or territories had ongoing endemic malaria transmission.³

Robert Scholtens, a Doctor of Veterinary Medicine and eminent American epidemiologist at the Centers for Disease Control (CDC), was tasked with overseeing US-assisted malaria eradication programmes in 18 endemic countries. In 1972, Scholtens and co-authors, Robert Kaiser and Alexander Langmuir, both senior infectious diseases epidemiologists at CDC, opined on the methodology and successes of the Global Malaria Eradication Program (GMEP) in an article entitled “*An epidemiologic examination of the epidemiology of malaria eradication*”. Their paper was published in the first issue of the *International Journal of Epidemiology*⁴ and is reprinted alongside our contemporary reflection. By the time the original article appeared in press, the GMEP had been credited with eliminating malaria from 15 countries and reducing incidence in several other endemic regions.⁵ However gains were not universal, the incidence of malaria stagnated or increased in many areas, particularly in sub-Saharan Africa. There was “*general disappointment*” with overall progress and the WHO had already realised that eradication was not going to be achieved and had abandoned the programme.⁶ Two-thirds of the

world's population remained at risk of malaria and Scholtens, Kaiser and Langmuir had settled on a decidedly pessimistic outlook on the prospects of malaria eradication.

What went wrong? Early spread of parasite and mosquito resistance to compounds that had previously been effective certainly contributed, as did other world *"problems clamoring for attention"*, but ultimately, the authors laid the blame squarely at the feet of humankind. *"Whether the immediate cause [for the lack of success] is political conflict, social upheaval, inadequate commitment, lack of sustained effort, or some other human deficiency the problems are omnipresent."* Policymakers grossly underestimated malaria transmission intensity and the scale of effort required to eradicate malaria in Africa and malaria control activities were not prosecuted sufficiently vigorously to impact meaningfully on incidence in high transmission settings. Scholtens, Kaiser and Langmuir called for a re-examination of classical antimalaria methodology and development of new approaches to malaria control based on greater understanding of the epidemiology and biology of the disease. They recommended greater integration of malaria control objectives and activities into other health programs as a means of achieving *"continued progress in coping with the disease problems of the malarious world."* Sadly, much of this advice has gone unheeded.

Progress since the Global Malaria Eradication Program

In the 15 years following formal cessation of the GMEP and reorientation of targets towards containment, 7 further countries and one territory (Australia, Brunei, Cuba, Mauritius, Portugal, Réunion, Singapore and the former Yugoslavia) were certified malaria free.⁵ All of these regions had relatively robust health systems, and low receptivity to re-establishment of transmission and therefore could be considered 'low-hanging fruit'.

Elsewhere, malaria resurged as political commitment waned and antimalarial and insecticide resistance spread across the endemic world. Two independent foci of chloroquine resistance emerged in Southeast Asia and South America in the late 1950s, with Cambodian strains arriving in Africa during

the 1960s.^{7–11} Chloroquine resistant parasites spread rapidly throughout sub-Saharan Africa during the 1980s. Sulfadoxine-pyrimethamine was introduced in the late 1960s with resistance appearing almost immediately in Southeast Asia and spreading throughout Africa during the 1990s.¹² During this time, antimalarial clinical efficacy trials were generally conducted with only 14 days of follow-up to avoid confounding from reinfections. Studies of such short duration were inadequate to detect early signs of recrudescence and emerging drug resistance, thus delaying recognition and timely public health interventions to avert the impending crisis. Sustained use of failing drugs fuelled further spread of drug resistant parasites and resulted in childhood malaria-related mortality in Africa almost doubling between the 1980s and 1990s.^{13,14} Meanwhile, important vectors of malaria such as *Anopheles gambiae sensu stricto* in West and Central Africa developed high-level resistance to DDT with accumulating evidence of possible chronic human health effects leading to bans or restrictions on its use in many countries.¹⁵ By the turn of the millennium, 106 countries remained endemic for malaria with an estimated 262 million malaria cases and 839,000 deaths globally.¹⁶

Disastrous trends in the burden of malaria catalysed important scientific discoveries (**Table 1**). In the 1970s, re-evaluation of modern and ancient pharmacopoeia led to the isolation and purification of artemisinin from the herb *Artemisia annua*,¹⁷ the parent compound for the most potent class of antimalarial drugs ever discovered. Coformulations of one of the artemisinin derivatives and a longer-acting partner drug were developed to shorten treatment regimens and reduce the risk of parasite resistance.¹⁸ Antigen-based rapid diagnostic tests (RDTs) were developed in the 1990s and iterative refinement led to sensitive and easy-to-use tools for accurately diagnosing falciparum malaria where blood film microscopy was unavailable.¹⁹ Highly mosquitocidal synthetic pyrethroids were formulated for use as indoor residual sprays and in impregnated bednets.^{20–23} Subsequent chemical manipulation and altered impregnation processes produced long-lasting insecticide treated nets with more sustained protective effectiveness and greater practicability.

98 The resurgence of malaria eventually spurred political and scientific bodies to rekindle their
99 commitment to reducing its global burden. In 1993 the World Health Assembly adopted a new WHO
100 Global Malaria Control Strategy.²⁴ In 1998 the Roll Back Malaria initiative was created with a target of
101 halving the global burden of malaria by 2010.²⁵ At the turn of the millennium, the United Nations
102 Millennium Development Goals called for a reversal of the increasing trend in malaria incidence by
103 2015.²⁶ New funding agencies were formed, such as the Bill & Melinda Gates Foundation (2000), the
104 Global Fund to Fight AIDS, Tuberculosis and Malaria (2002), the US President's Malaria Initiative (2005)
105 and UNITAID (2006). Total annual spending on malaria in endemic countries increased from 1.2 billion
106 USD in 2000 to 3.5 billion in 2016.²⁷ Despite highly-publicised commitments, institutional inertia and
107 financial roadblocks delayed the introduction of new malaria control tools. High-level resistance to
108 chloroquine and sulphadoxine-pyrimethamine was widespread by the late 1990s, but despite this, the
109 WHO vacillated for several years before revising its antimalarial guidelines to recommend artemisinin-
110 based combination therapies (ACTs) for firstline treatment of falciparum malaria. Almost a decade
111 later, ACTs were being used in less than 50% of endemic African countries.²⁸ Intravenous artesunate
112 was shown to be superior to intravenous quinine for severe malaria in southeast Asia in 2005²⁹ and
113 Africa in 2010³⁰ but despite its potential to save lives, its widespread use only began in 2013.³¹

114 Lack of adequate national reporting systems and a series of changes in the methods used for
115 quantifying disease burden have confounded interpretation of global malaria trends. Whilst malaria
116 deaths may have almost halved over the last 20 years,³² the global incidence of malaria has remained
117 largely unchanged (**Figure 1**).³³ In 2019 an estimated 212 million cases were reported from 87 malaria
118 endemic countries and nearly half the world's population remained at risk of malaria (**Figure 2**³⁴).³³
119 These global trends hide significant discrepancies in progress. Almost 94% of cases and deaths still
120 occur in Africa, where the burden of malaria has risen by more than 20% in 10 countries over the last
121 decade.³³

Many high profile groups and individuals continue to advocate strongly for a recommitment to a time-limited goal for global malaria eradication,^{16,35,36} expounding the economic and humanitarian imperatives of this approach. As yet no globally-endorsed commitment has eventuated and the malaria community remains divided on whether eradication is even feasible. Scholtens, Kaiser and Langmuir outlined many obstacles to malaria eradication. Several of these remain relevant, and in many cases have been accentuated by new challenges.

Modern barriers to malaria eradication

Evolution

Parasite and mosquito vector evolution continue to inhibit progress. Artemisinin-based combination therapies were introduced with much optimism and have had a significant impact.^{37,38} Within 20 years of widespread use, *P. falciparum* resistance to the artemisinins emerged in Cambodia and has since spread throughout the Greater Mekong Subregion.^{39–41} Inappropriate use of single-agent artemisinins as well as counterfeit^{42,43} and substandard products have catalysed the natural selection process. Resistance to artemisinins and their partner drugs results in delayed parasite clearance and recrudescence, both of which increase the risk of parasite transmission.⁴⁰ In Thailand, Cambodia and Vietnam, clinical failure rates following standard ACTs in some areas now exceed 50%.⁴⁰ Artemisinin resistance has now emerged independently in Africa, the prevalence of resistance-conferring *kelch13* mutations in *P. falciparum* isolates in Northern Uganda increasing from 3.9% in 2015 to 19.8% in 2019.⁴⁴ Triple artemisinin-based combination therapies,⁴⁵ longer treatment courses³⁹ and higher artemisinin doses⁴⁶ are being trialled to salvage these critical drugs. Sadly, development and testing of novel strategies by researchers and action from policy-makers, such as banning all individually packaged artemisinins and prioritising elimination efforts to hotspot areas of artemisinin resistance, have failed to keep pace with the evolving problem. The delays in the international response mirrors the lethargic approach to addressing chloroquine resistance at the end of the 20th Century. If this is

not rectified with a sense of urgency, the consequences for the current malaria eradication programme will be similarly grim.

Most RDTs for *P. falciparum* malaria rely on detection of *P. falciparum* histidine-rich protein 2 (*PfHRP2*) or its structural homolog *PfHRP3* – both of which have significant naturally-occurring genetic diversity.^{47,48} Disproportionately increased exposure of parasites with unmutated *PfHRP2/3* genes to antimalarial drugs through use of RDTs targeting these antigens has led to natural selection and propagation of parasites with mutated or absent *PfHRP2/3* genes. These mutated parasites may escape detection by RDTs leading to increasing prevalence in areas where *PfHRP2/3*-based RDTs have been used extensively.^{49–51} The ability of *Plasmodium* species to evolve rapidly, combined with substantial antigenic diversity, also undermines vaccine development. Despite huge investment, only two malaria vaccines have progressed through preclinical testing to late stage clinical trials, with the RTS,S vaccine finally achieving WHO approval in 2021.⁵² Both vaccines induce modest and short-lived protection against clinical malaria and little efficacy against asymptomatic parasitaemia.^{53,54}

Ongoing mosquito evolution is equally challenging. Until recently, malaria vector control was dominated by pyrethroid class insecticide use. Between 2010 and 2016, *Anopheles* resistance to at least one class of pyrethroid insecticide was recorded in 56 (77%) of the 72 countries with active monitoring systems.⁵⁵ The frequency of pyrethroid resistance increased to greater than 50% in some mosquito species during the same time period.⁵⁵ Insecticide treated bednets and indoor residual insecticide sprays are effective for killing *Anopheles* mosquito vectors that feed or rest indoors, particularly late at night. However, important *Anopheles* species are displaying behavioural resistance to these interventions by increasingly biting outdoors and earlier in the evening.^{56,57} Once these behaviours predominate, insecticide treated nets and indoor residual spraying will no longer be effective and vector control interventions will need to target outdoor transmission sites.⁵⁸

Capacity for vector control

One of the biggest threats to modern vector control has been the restrictive endorsement of residual spraying and bednets as the only evidence-proven means of achieving good vector control. The Global Malaria Program has recently departed from this prescriptive approach by advocating stratification of interventions based on local ecology and malaria epidemiology. This harkens back to the pre-DDT era when engineered solutions and larval control by habitat modification were adapted to local conditions and were effective in reducing malaria on a programmatic basis. Today, these ecological approaches have “no recommendation” due to “very low-certainty evidence” in WHO malaria guidelines.⁵⁹ Consequently, there is now limited capacity to react to areas of residual malaria transmission on the cusp of elimination because of (1) a lack of WHO-recommended vector control interventions that appeal to international funders,⁵⁹ (2) diminishing numbers of well-trained vector control specialists⁶⁰ and (3) failure of programmes to monitor vector surveillance indicators to provide the evidence on which decisions might be made to select supplemental interventions.⁶¹

Non-falciparum Plasmodium species

Over the last two decades, there has been increasing recognition of the clinical importance and comparative refractoriness to standard malaria control measures of the non-falciparum *Plasmodium* species (**Figure 3**⁶²).⁶³ *Plasmodium vivax* can cause significant morbidity and associated mortality.^{64,65} It is one of two human *Plasmodium* species, the other being *P. ovale*, that relapses from latent liver forms (hypnozoites). Standard treatment of blood stage *P. vivax* parasites with either chloroquine or ACT has little impact on transmission because these drugs do not kill hypnozoites and therefore do not prevent relapses. Primaquine is the only widely available drug that can kill hypnozoites, but its use is limited because it can cause severe oxidative haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency; an enzymopathy that has co-evolved to be prevalent in malaria endemic areas.⁶⁶ Several studies have shown that in areas co-endemic for both *P. falciparum* and *P. vivax*, malaria control activities have a greater impact against *P. falciparum* than *P. vivax*.^{38,63,67,68}

Similarly, conventional antimalaria methodology will have little impact on several recently discovered zoonotic *Plasmodium* species such as *P. knowlesi*⁶⁹ and *P. cynomolgi*⁷⁰ which are dependent on definitive monkey hosts. Although relatively infrequent causes of human malaria, these *Plasmodium* species will likely be ineradicable without exterminating the monkeys.

Competing problems

Scholtens and colleagues described several competing health and social problems that drew focus and resources away from malaria control during the GMEP period. Since then, major new health challenges have arisen. HIV was unknown in 1972, but has since infected 77.5 million people and caused 34.7 million deaths.⁷¹ 18.6 billion US dollars was spent on this disease in 2019 alone. More recently, the global COVID19 pandemic has caused seismic impacts on health systems with reorientation of resources away from other conditions such as malaria.^{72–74} Modelling suggests that an increase in malaria incidence is possible due to the carry-on effects of the COVID19 response.⁷⁵

Anopheles mosquitoes thrive in warm environments. Global warming from human activity has the potential to facilitate spread of malaria vectors to new areas with previously hostile climatic conditions.⁷⁶ The predicted population growth on the African continent in the next 30 years⁷⁷ coupled with climate change is likely to facilitate transmission through increased interaction between mosquitoes and human hosts and will further strain financial resources.

Bureaucratic and system-based roadblocks

Scholtens and colleagues implored the research community to gain a better understanding of malaria epidemiology and to use this knowledge to optimise malaria control strategies and tools. Unfortunately, malaria researchers today face burgeoning bureaucratic processes and inefficiencies associated with fund-seeking, ethical and regulatory board approval, compliance monitoring and interval reporting. Research costs have risen hugely. Once new products have been trialled, formal

regulatory approval is often prolonged and expensive and can be subject to coercive financial forces and conflicts of interest. These bureaucratic processes and institutional inefficiencies delay both acquisition of scientific knowledge and release of new malaria control tools and techniques. The increased costs of research have impacted public sector outputs. Malaria is a disease of impoverished countries that yields little financial reward for big pharma and therefore the malaria community is disproportionately reliant on not-for-profit institutions for research advances.

Priorities for maximising prospects of malaria eradication

Despite the huge challenges, significant progress towards the global and equitable control of malaria is possible. If current trends continue, mathematical modelling predicts that malaria transmission will fall but still be widespread in 2050.¹⁶ Enhanced access to existing tools for diagnosis, treatment and vector control will achieve greater reductions, but pockets of low-level transmission in sub-Saharan Africa are likely to persist.¹⁶ These models assume that no major new competing problems will arise to derail control efforts – a prediction that is far from certain, particularly in view of the ongoing COVID19 pandemic. New malaria control interventions and technologies that transcend the insoluble human inadequacies that have confounded malaria control for more than a century will be critical if eradication is to be achieved within our lifetimes. We believe the following are the highest priority areas for development:

Information technology must be harnessed much more effectively to enable internationally co-ordinated, real-time, comprehensive and geospatially granular malaria surveillance. Access to quality data on hotspots of malaria transmission will underpin all existing and future malaria eradication strategies. Mobile phones are widely available, even in resource poor settings,⁷⁸ and have potential to improve surveillance, mapping and active case detection. Integration of malaria surveillance with other infectious and non-communicable diseases would enable efficient and targeted use of malaria control resources, particularly once transmission has receded to low levels.

Mass drug administration (MDA) reduces clinical malaria and hidden asymptomatic parasite reservoirs.⁷⁹ Of all currently available strategies, MDA holds the greatest promise for accelerating the final stages of malaria eradication. Campaigns should target geographic areas and seasons of high transmission based on enhanced surveillance and be delivered consistently and vigorously. New combination drug regimens that include a minimum of three drugs given in one or two doses, and avoidance of drugs used for management of symptomatic malaria, would be preferable. In a recent trial from Burkina Faso and Mali, impressive seasonal malaria prevention was achieved using a combination of the RTS,S malaria vaccine with monthly mass administration of sulphadoxine-pyrimethamine and amodiaquine, and was more effective at preventing clinical malaria, hospitalisation and death than either intervention alone.⁸⁰ If replicated in non-trial settings, this combination of strategies holds great promise for reducing malaria morbidity in areas with intense *P. falciparum* transmission.

Parasite and host diagnostics must be improved for both clinical applications and screening of asymptomatic individuals. RDTs are convenient for detecting clinical *P. falciparum* malaria, but their sensitivity must be improved for diagnosing non-falciparum malaria and low-level asymptomatic infections. As malaria recedes, high throughput, ultra-sensitive and affordable serological or molecular assays will be needed to screen populations for residual reservoirs of infection. This will help target control strategies such as active case detection and mass drug administration to eliminate transmission hotspots. Robust and affordable host diagnostics for G6PD deficiency are needed for safe antirelapse treatment of patients with *P. vivax* malaria. Whilst point-of-care G6PD assays have been developed and licensed, their reliability and cost-effectiveness in remote areas, where the greatest burden of malaria resides, are not known.

Technological advances in vector control and improved understanding of the vectors have huge potential to transform the fight against malaria. Propagation of genes that confer sterility or immunity to *Plasmodium* parasites through competent *Anopheles* mosquito populations (the 'gene-drive'

process) and novel strategies that attack mosquito behavioural vulnerabilities, such as attractive targeted sugar baits, may have significant effects on malaria transmission.^{81–83} The potential detrimental ecological effects of these and other future vector control strategies will need careful consideration prior to their introduction.

Lastly, decisive national and international leadership is needed to ensure timely and dynamic use of malaria control resources. Action is needed to reduce current inefficiencies in discovery, approval and deployment of novel antimalaria strategies. To bypass high-level bureaucratic roadblocks, responsibilities need to be delegated and redundant processes culled. Ultimately, the many authorities making policy decisions need to be held to account for their actions, for the good of the malarious world, rather than the benefit of reputations.

Conclusion

At the end of their treatise, Scholtens, Kaiser and Langmuir called for “*a policy for the future*” of malaria control. We believe that such a policy must acknowledge and accept the fallibility of human-led interventions and the inevitability of competing interests. The tools employed henceforth must counter the deficiencies of humankind by harnessing communication technology and minimising human labour. They must also suit remote, impoverished regions where the main burden of malaria resides. Scholtens, Kaiser and Langmuir lamented the “diminishing number of ‘malariologists’ and proliferation of ‘eradicationists’” as an impediment to progress. We agree that a blinkered focus on the eradication endgame may distract from the necessary work of genuine scientific discovery and quality malaria control. Strong commitment to prompt and sustained deployment of optimal interventions will be far more important than unrealistic and unenforceable eradication goals. If the business of malaria eradication continues as usual, malaria will undoubtedly still be rife in sub-Saharan Africa in 50 years’ time. However, accelerated scientific progress and dogged determination, coupled with a degree of luck, still offer great hope of eradicating malaria from the globe within a generation.

297

298 **Acknowledgements**

299 We thank many colleagues in the global malaria community who have committed their careers to
300 tackling the burden of malaria. Over the last decade many have raised significant concerns that the
301 unique opportunities offered by the global elimination campaign will be squandered unless there is
302 urgent remedial action on the current trends. RNP is a Wellcome Trust Senior Fellow in Clinical Science
303 [200909]. For the purpose of Open Access, the authors have applied a CC BY public copyright licence
304 to any author accepted manuscript version arising from this submission"

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1. Tognotti E. Program to eradicate malaria in Sardinia, 1946-1950. *Emerg Infect Dis.* 2009;15:1460–6.
2. WHO Expert Committee on Malaria (1956; Athens, Greece). WHO expert committee on malaria, Athens, 20-28 June 1956: sixth report [Internet]. World Health Organization; 1956. Available from: <https://apps.who.int/iris/handle/10665/64537>
3. Holmes KK, Bertozzi S, Bloom BR, Jha P. Major infectious diseases. Disease control priorities, third edition, volume 6 [Internet]. Washington D.C.: World Bank; 2017. Available from: <https://elibrary.worldbank.org/doi/abs/10.1596/978-1-4648-0524-0>
4. Scholtens RG, Kaiser RL, Langmuir AD. An epidemiologic examination of the strategy of malaria eradication. *Int J Epidemiol.* 1972;1:15–24.
5. World Health Organization. Eliminating malaria. Geneva: World Health Organization; 2016.
6. World Health Organization. Re-examination of the global strategy of malaria eradication. Twenty-second World Health Assembly, part I. WHO official records number 176, annex 13. Geneva: World Health Organization; 1969.
7. Lasch EE, N’Guyen TL. Observations on an apparent chloroquine-resistant strain of *Plasmodium falciparum* in West Africa. *Br Med J.* 1965;2:1219–22.
8. Chulay JD, Spencer HC, Warshow MM, Saio MA, Musoke SS, Masembe JB, et al. Chloroquine-resistant *falciparum* malaria. *N Engl J Med.* 1983;308:781.
9. Plowe CV. The evolution of drug-resistant malaria. *Trans R Soc Trop Med Hyg.* 2009;103 Suppl 1:S11-14.
10. Payne D. Spread of chloroquine resistance in *Plasmodium falciparum*. *Parasitol Today.* 1987;3:241–6.
11. Wernsdorfer WH, Payne D. The dynamics of drug resistance in *Plasmodium falciparum*. *Pharmacol Ther.* 1991;50:95–121.
12. Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR. Epidemiology of drug-resistant malaria. *Lancet Infect Dis.* 2002;2:209–18.
13. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW. Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy. *Lancet Infect Dis.* 2003;3:349–58.
14. Attaran A, Barnes KI, Curtis C, d’Alessandro U, Fanello CI, Galinski MR, et al. WHO, the Global Fund, and medical malpractice in malaria treatment. *Lancet.* 2004;363:237–40.
15. van den Berg H. Global status of DDT and its alternatives for use in vector control to prevent disease. *Environ Health Perspect.* 2009;117:1656–63.
16. Feachem RGA, Chen I, Akbari O, Bertozzi-Villa A, Bhatt S, Binka F, et al. Malaria eradication within a generation: ambitious, achievable, and necessary. *Lancet.* 2019;394:1056–112.

17. Qinghaosu Antimalaria Coordinating Research Group. Antimalaria studies on qinghaosu. *Chin Med J (Engl)*. 1979;92:811–6.
18. White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci*. 1999;354:739–49.
19. World Health Organization. Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: round 8 (2016-2018). Geneva: World Health Organization; 2018.
20. Dolan CB, BenYishay A, Grépin KA, Tanner JC, Kimmel AD, Wheeler DC, et al. The impact of an insecticide treated bednet campaign on all-cause child mortality: A geospatial impact evaluation from the Democratic Republic of Congo. *PLOS ONE*. 2019;14:e0212890.
21. Zamawe COF, Nakamura K, Shibamura A, Jimba M. The effectiveness of a nationwide universal coverage campaign of insecticide-treated bed nets on childhood malaria in Malawi. *Malar J*. 2016;15:505.
22. Maxwell CA, Msuya E, Sudi M, Njunwa KJ, Carneiro IA, Curtis CF. Effect of community-wide use of insecticide-treated nets for 3-4 years on malarial morbidity in Tanzania. *Trop Med Int Health*. 2002;7:1003–8.
23. Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. *Cochrane Database Syst Rev*. 2018;11:CD000363.
24. World Health Organization. A Global strategy for malaria control [Internet]. World Health Organization; 1993 p. 1–40. Available from: <https://apps.who.int/iris/handle/10665/41785>
25. Nabarro DN, Tayler EM. The 'Roll Back Malaria' Campaign. *Science*. 1998;280:2067–8.
26. United Nations. Millennium Development Goals - UN Millennium Project [Internet]. Millennium Development Goals. [cited 2021 Jul 8]. Available from: <https://www.mdgmonitor.org/>
27. Haakenstad A, Harle AC, Tsakalos G, Micah AE, Tao T, Anjomshoa M, et al. Tracking spending on malaria by source in 106 countries, 2000-16: an economic modelling study. *Lancet Infect Dis*. 2019;19:703–16.
28. Bosman A, Mendis KN. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. *Am J Trop Med Hyg*. 2007;77:193–7.
29. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005;366:717–25.
30. Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. 2010;376:1647–57.
31. Clinton Health Access Initiative, Unitaid. Injectable artesunate assessment report [Internet]. Clinton Health Access Initiative and Unitaid; 2019 p. 1–79. Available from: <https://www.severemalaria.org/sites/mmv-smo/files/content/attachments/2020-02-07/Injectable%20artesunate%20report.pdf>

32. World Health Organization. World malaria report 2016. Geneva: World Health Organization; 2016 p. 1–150.
33. World Health Organization. World malaria report 2020. Geneva: World Health Organization; 2020 p. 1–250.
34. Weiss DJ, Lucas TCD, Nguyen M, Nandi AK, Bisanzio D, Battle KE, et al. Mapping the global prevalence, incidence, and mortality of *Plasmodium falciparum*, 2000–17: a spatial and temporal modelling study. *Lancet*. 2019;394:322–31.
35. Gaye O. There should be a World Health Assembly resolution for malaria eradication. *Malar J*. 2019;18:352.
36. Rabinovich RN, Drakeley C, Djimde AA, Hall BF, Hay SI, Hemingway J, et al. malERA: An updated research agenda for malaria elimination and eradication. *PLoS Med*. 2017;14:e1002456.
37. Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, et al. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. *PLoS Med*. 2005;2:e330–e330.
38. Kenangalem E, Poespoprodjo JR, Douglas NM, Burdam FH, Gdeumana K, Chalfein F, et al. Malaria morbidity and mortality following introduction of a universal policy of artemisinin-based treatment for malaria in Papua, Indonesia: A longitudinal surveillance study. *PLoS Med*. 2019;16:e1002815.
39. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*. 2014;371:411–23.
40. Woodrow CJ, White NJ. The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. *FEMS Microbiol Rev*. 2017;41:34–48.
41. Ashley EA, Pyae Phyo A, Woodrow CJ. Malaria. *Lancet*. 2018;391:1608–21.
42. Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, et al. Fake artesunate in southeast Asia. *Lancet*. 2001;357:1948–50.
43. Newton PN, White NJ, Rozendaal JA, Green MD. Murder by fake drugs. *BMJ*. 2002;324:800–1.
44. Balikagala B, Fukuda N, Ikeda M, Katuro OT, Tachibana S-I, Yamauchi M, et al. Evidence of Artemisinin-Resistant Malaria in Africa. *N Engl J Med*. 2021;385:1163–71.
45. van der Pluijm RW, Tripura R, Hoglund RM, Pyae Phyo A, Lek D, Ul Islam A, et al. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated *Plasmodium falciparum* malaria: a multicentre, open-label, randomised clinical trial. *Lancet*. 2020;395:1345–60.
46. Bethell D, Se Y, Lon C, Tyner S, Saunders D, Sriwichai S, et al. Artesunate dose escalation for the treatment of uncomplicated malaria in a region of reported artemisinin resistance: a randomized clinical trial. *PLoS ONE*. 2011;6:e19283.
47. Nderu D, Kimani F, Thiong'o K, Karanja E, Akinyi M, Too E, et al. *Plasmodium falciparum* histidine-rich protein (PfHRP2 and 3) diversity in Western and Coastal Kenya. *Sci Rep*. 2019;9:1709.

48. Willie N, Zimmerman PA, Mehlotra RK. Plasmodium falciparum Histidine-Rich Protein 2 Gene Variation in a Malaria-Endemic Area of Papua New Guinea. *Am J Trop Med Hyg.* 2018;99:697–703.
49. Prosser C, Gresty K, Ellis J, Meyer W, Anderson K, Lee R, et al. Plasmodium falciparum Histidine-Rich Protein 2 and 3 Gene Deletions in Strains from Nigeria, Sudan, and South Sudan. *Emerg Infect Dis.* 2021;27:471–9.
50. Góes L, Chamma-Siqueira N, Peres JM, Nascimento JM, Valle S, Arcanjo AR, et al. Evaluation of Histidine-Rich Proteins 2 and 3 Gene Deletions in Plasmodium falciparum in Endemic Areas of the Brazilian Amazon. *Int J Environ Res Public Health.* 2020;18:E123.
51. Iriart X, Menard S, Chauvin P, Mohamed HS, Charpentier E, Mohamed MA, et al. Misdiagnosis of imported falciparum malaria from African areas due to an increased prevalence of pfhrp2/pfhrp3 gene deletion: the Djibouti case. *Emerg Microbes Infect.* 2020;9:1984–7.
52. WHO recommends groundbreaking malaria vaccine for children at risk [Internet]. 2021 [cited 2021 Oct 13]. Available from: <https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk>
53. Datto MS, Natama MH, Somé A, Traoré O, Rouamba T, Bellamy D, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. *Lancet.* 2021;397:1809–18.
54. RTS,S Clinical Trials Partnership, Agnandji ST, Lell B, Fernandes JF, Abossolo BP, Methogo BGNO, et al. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. *N Engl J Med.* 2012;367:2284–95.
55. World Health Organization. Global report on insecticide resistance in mosquito vectors: 2010–2016. Geneva: World Health Organization; 2018 p. 1–72.
56. Sougoufara S, Doucouré S, Backé Sembéne PM, Harry M, Sokhna C. Challenges for malaria vector control in sub-Saharan Africa: Resistance and behavioral adaptations in Anopheles populations. *J Vector Borne Dis.* 2017;54:4–15.
57. Russell TL, Beebe NW, Cooper RD, Lobo NF, Burkot TR. Successful malaria elimination strategies require interventions that target changing vector behaviours. *Malar J.* 2013;12:56.
58. Pollard EJM, MacLaren D, Russell TL, Burkot TR. Protecting the peri-domestic environment: the challenge for eliminating residual malaria. *Sci Rep.* 2020;10:7018.
59. World Health Organization. WHO guidelines for malaria [Internet]. Geneva: World Health Organization; 2021 Jul p. 1–214. Available from: <https://app.magicapp.org/#/guideline/5700>
60. Russell TL, Farlow R, Min M, Espino E, Mnzava A, Burkot TR. Capacity of National Malaria Control Programmes to implement vector surveillance: a global analysis. *Malar J.* 2020;19:422.
61. Burkot TR, Farlow R, Min M, Espino E, Mnzava A, Russell TL. A global analysis of National Malaria Control Programme vector surveillance by elimination and control status in 2018. *Malar J.* 2019;18:399.

62. Battle KE, Lucas TCD, Nguyen M, Howes RE, Nandi AK, Twohig KA, et al. Mapping the global endemicity and clinical burden of *Plasmodium vivax*, 2000–17: a spatial and temporal modelling study. *Lancet*. 2019;394:332–43.
63. Price RN, Commons RJ, Battle KE, Thriemer K, Mendis K. *Plasmodium vivax* in the era of the shrinking *P. falciparum* map. *Trends in Parasitology*. 2020;36:560–70.
64. Douglas NM, Pontororing GJ, Lampah DA, Yeo TW, Kenangalem E, Poespoprodjo J, et al. Mortality attributable to *Plasmodium vivax* malaria: a clinical audit from Papua, Indonesia. *BMC Med*. 2014;12:217.
65. Douglas NM, Lampah DA, Kenangalem E, Simpson JA, Poespoprodjo JR, Sugiarto P, et al. Major burden of severe anemia from non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. *PLoS Med*. 2013;10:e1001575.
66. Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. *PLoS Med*. 2012;9:e1001339.
67. Oliveira-Ferreira J, Lacerda MV, Brasil P, Ladislau JL, Taui PL, Daniel-Ribeiro CT. Malaria in Brazil: an overview. *Malar J*. 2010;9:115–115.
68. Sattabongkot J, Tsuboi T, Zollner GE, Sirichaisinthop J, Cui L. *Plasmodium vivax* transmission: chances for control? *Trends Parasitol*. 2004;20:192–8.
69. Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S, et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. 2008;46:165–71.
70. Bykersma A. The New Zoonotic Malaria: *Plasmodium cynomolgi*. *Trop Med Infect Dis*. 2021;6:46.
71. UNAIDS. Global HIV & AIDS statistics — Fact sheet [Internet]. [cited 2021 Jul 11]. Available from: <https://www.unaids.org/en/resources/fact-sheet>
72. World Health Organization. Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report 27 August 2020. Geneva: World Health Organization; 2020 Aug p. 1–29.
73. Velavan TP, Meyer CG, Esen M, Kremsner PG, Ntoumi F, PANDORA-ID-NET and CANTAM consortium. COVID-19 and syndemic challenges in ‘Battling the Big Three’: HIV, TB and malaria. *Int J Infect Dis*. 2021;106:29–32.
74. Rogerson SJ, Beeson JG, Laman M, Poespoprodjo JR, William T, Simpson JA, et al. Identifying and combating the impacts of COVID-19 on malaria. *BMC Med*. 2020;18:239.
75. Weiss DJ, Bertozzi-Villa A, Rumisha SF, Amratia P, Arambepola R, Battle KE, et al. Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: a geospatial modelling analysis. *Lancet Infect Dis*. 2021;21:59–69.
76. Giesen C, Roche J, Redondo-Bravo L, Ruiz-Huerta C, Gomez-Barroso D, Benito A, et al. The impact of climate change on mosquito-borne diseases in Africa. *Pathog Glob Health*. 2020;114:287–301.

77. United Nations. World population prospects: the 2017 revision. New York: United Nations; 2017 p. 1–47.
78. World Bank. World development report 2016: digital dividends overview. Washington DC: World Bank; 2016 p. 1–58.
79. McLean ARD, Indrasuta C, Khant ZS, Phyo AK, Maung SM, Heaton J, et al. Mass drug administration for the acceleration of malaria elimination in a region of Myanmar with artemisinin-resistant falciparum malaria: a cluster-randomised trial. *Lancet Infect Dis.* 2021;S1473-3099(20)30997-X.
80. Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga R-S, Diarra M, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. *N Engl J Med.* 2021;385:1005–17.
81. James S, Collins FH, Welkhoff PA, Emerson C, Godfray HCJ, Gottlieb M, et al. Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group†. *Am J Trop Med Hyg.* 2018;98:1–49.
82. Hammond A, Galizi R, Kyrou K, Simoni A, Siniscalchi C, Katsanos D, et al. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nat Biotechnol.* 2016;34:78–83.
83. Fraser KJ, Mwandigha L, Traore SF, Traore MM, Doumbia S, Junnila A, et al. Estimating the potential impact of Attractive Targeted Sugar Baits (ATSBs) as a new vector control tool for *Plasmodium falciparum* malaria. *Malar J.* 2021;20:151.

Table 1. Availability of approved malaria control tools in routine use in 1972 and in 2021

		1972	2021
Diagnosis		Microscopy	Microscopy
			Antigen-based bedside rapid diagnostic tests
			PCR (predominantly in research and non-endemic settings)
			Point-of-care tests for G6PD deficiency
Drugs	Blood schizontocidal	Quinine	Quinine
		Chloroquine	Chloroquine
		Sulfadoxine-pyrimethamine	Sulfadoxine-pyrimethamine
		Tetracycline	Doxycycline
			IV artesunate
			Artemisinin-based combination therapies (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine)
	Hypnozoitocidal	Primaquine	Primaquine
			Tafenoquine
Drug treatment approaches		Treatment of symptomatic disease	Treatment of symptomatic disease
		Active case-finding and treatment	Active case-finding and treatment
		Mass drug administration	Mass drug administration
		Incorporation into foodstuffs	
			Seasonal malaria chemoprevention
			Intermittent preventive treatment in pregnancy
			Intermittent preventive treatment in infancy/childhood
Vector control	Larval source management	Engineering solutions	Engineering solutions
		Larvaciding (various chemical and biological agents used)	Larvaciding (various chemical and biological agents used)
	Mosquito control	Residual insecticide spraying (DDT and pyrethrum used)	Residual insecticide spraying (synthetic pyrethroids used)
			Long-lasting insecticide-treated bednets
Vaccines			RTS,S vaccine

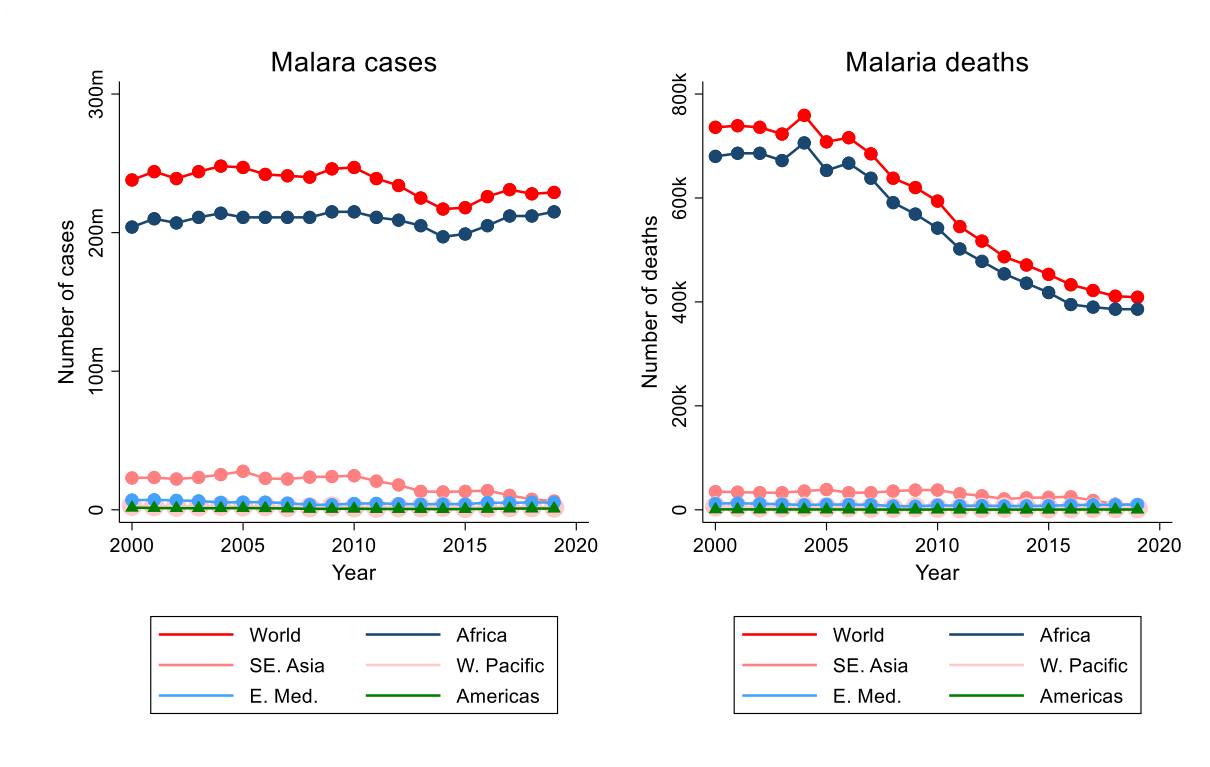


Figure 1. Trends in malaria incidence and deaths between 2000 and 2019. Data taken from World Malaria Report 2020. Abbreviations: SE., southeast; W., western; E. Med., Eastern Mediterranean

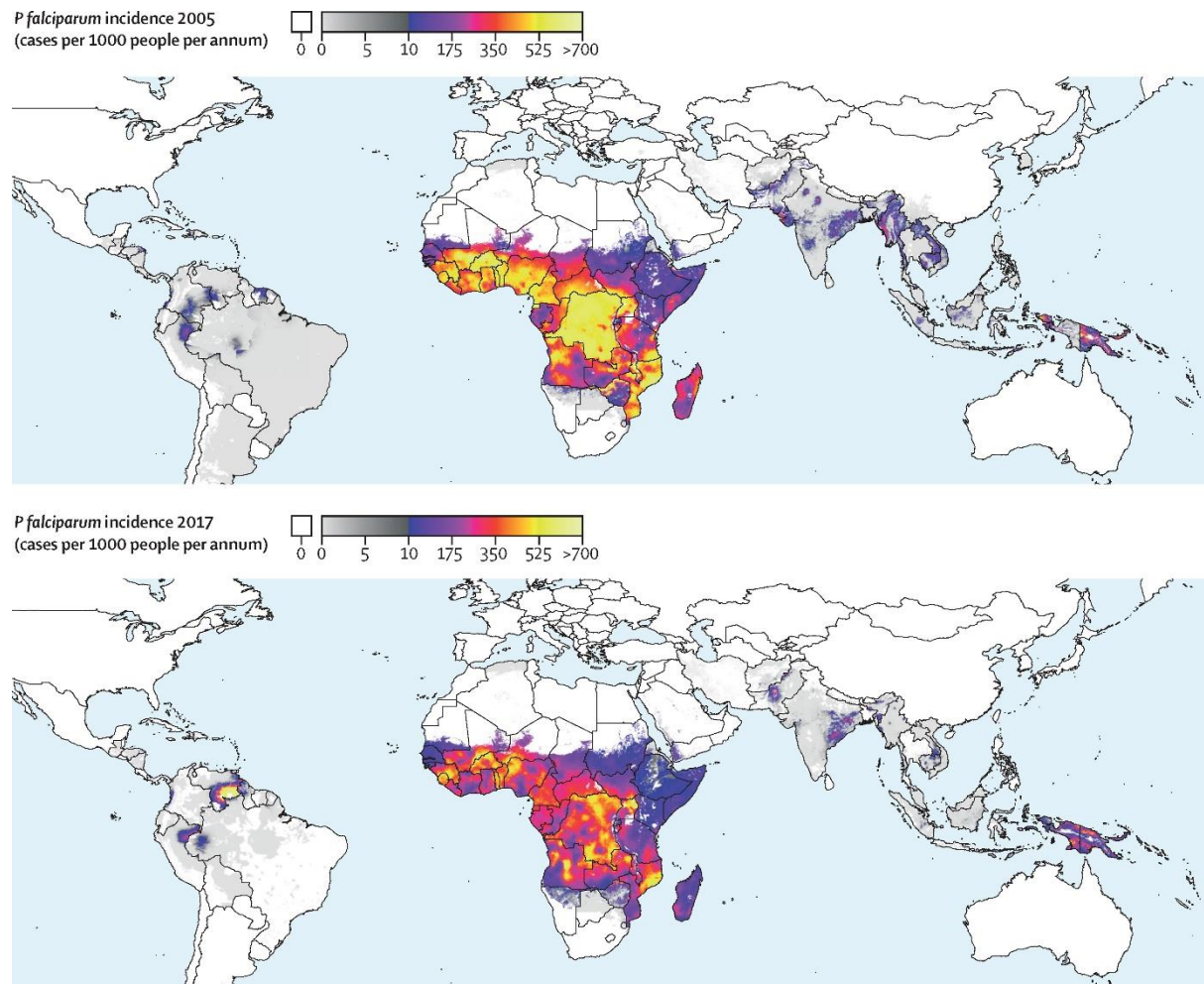


Figure 2. Global *Plasmodium falciparum* malaria incidence in cases per 1,000 people per year in 2005 (top) and 2017 (bottom). Most datapoints are modelled. Taken from Weiss DJ et al. Mapping the global prevalence, incidence, and mortality of *Plasmodium falciparum*, 2000-17: a spatial and temporal modelling study. 2019;394(10195), 322-31.

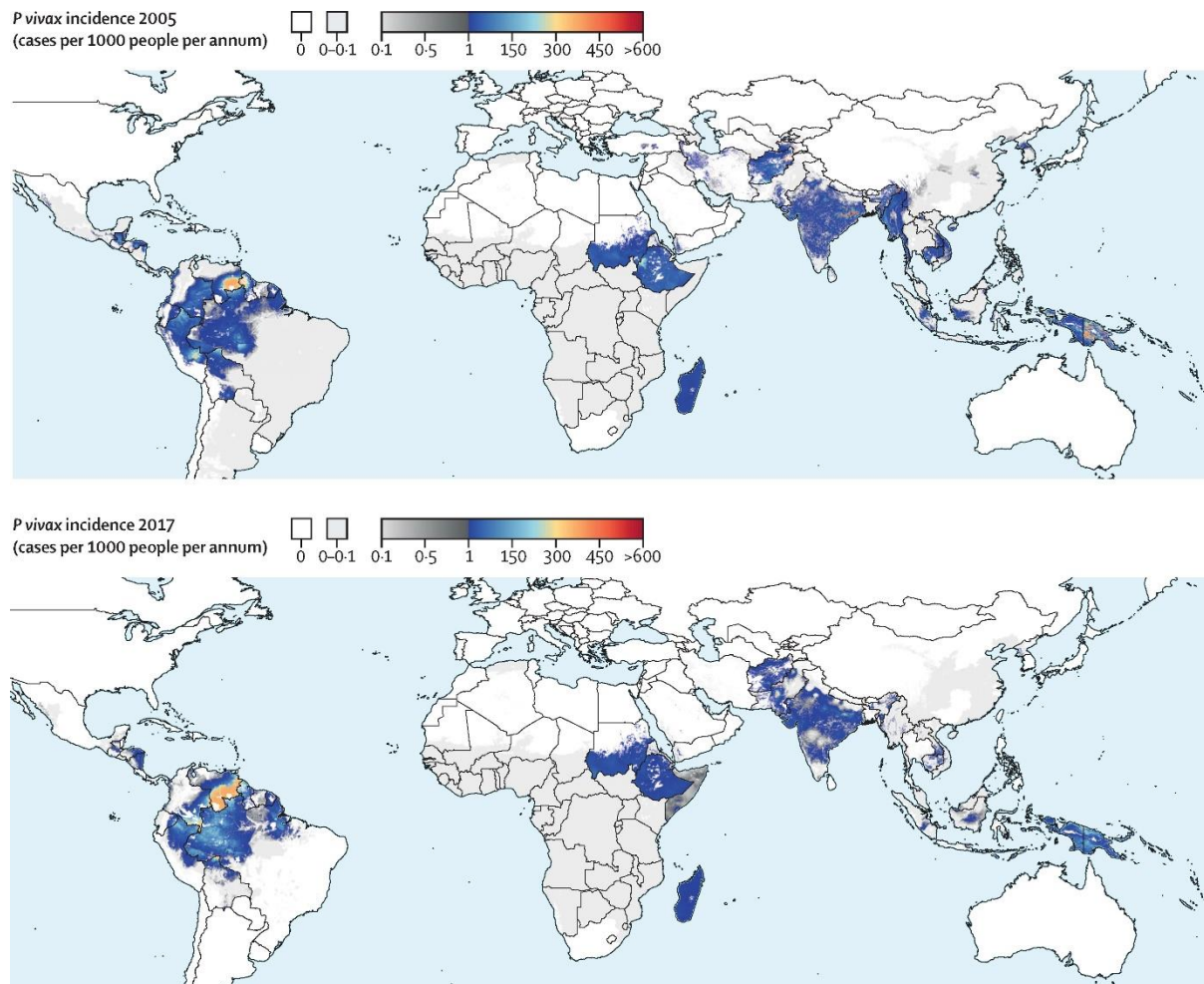


Figure 3. Global *Plasmodium vivax* malaria incidence in cases per 1,000 people per year in 2005 (top) and 2017 (bottom). Most data points are modelled. Taken from Battle KE et al. Mapping the global endemicity and clinical burden of *Plasmodium vivax*, 2000-17: a spatial and temporal modelling study. *Lancet* 2019;394(10195),332-43.