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MALARIA ERADICATION WITHIN A GENERATION

Malaria eradication within a generation: ambitious, achievable, and necessary

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Executive summary

50 years after a noble but flawed attempt to eradicate malaria in the mid-20th century, the global malaria community is once again seriously considering eradication. Momentum towards eradication has been building for decades, and more than half of the world's countries are now malaria free. Since 2000, a surge of global progress has occurred, facilitated by the roll-out of new technologies and the substantial growth in political and financial commitment by countries, regions, and their global partners. Annual domestic and international spending on malaria increased from roughly US$1·5 billion in 2000 to $4·3 billion in 2016. Simultaneously, the number of countries with endemic malaria dropped from 106 to 86, the worldwide annual incidence rate of malaria declined by 36%, and the annual death rate declined by 60%.

Inspired by these outstanding achievements, and troubled by a stagnation in progress that saw 55 countries report an increase in cases between 2015 and 2017, the *Lancet* Commission on Malaria Eradication (the Commission) was convened to consider whether malaria eradication is feasible, affordable, and worthwhile. In this report of the Commission, we synthesise existing evidence and new epidemiological and financial analyses to show that malaria eradication by 2050 is a bold but attainable goal, and a necessary one given the never-ending struggle against drug and insecticide resistance and the social and economic costs associated with a failure to eradicate.

Global social, economic, and environmental trends are, in most places, reducing malaria. Our models show that these trends alone will lead to greatly reduced but still widespread malaria by 2050. When the effects of enhanced access to high-quality diagnosis, treatment, and vector control are factored in, the 2050 projections show a world largely free of malaria, but with pockets of low-level transmission persisting in a belt across Africa, from Senegal in the northwest to Mozambique in the southeast. In view of these projections, we explore the responses to the operational, biological, and financial challenges that are required to bend the curve (ie, to accelerate the decline in malaria cases and deaths) and achieve elimination everywhere outside of Africa by 2030 and worldwide eradication by 2050.

Operational obstacles limit the success of malaria programmes in many countries, including ineffective management, inadequate use of data to inform strategies, poorly incentivised staff, and disengaged communities. Solutions to most of these challenges are available and inexpensive but require access to management training and tools, which many malaria programmes do not have. Strengthening programme management and improving the availability and use of data for decision making are operational priorities which, if addressed, would enhance programme effectiveness and accelerate the path to malaria eradication. Leveraging the expertise and comparative advantages of the private sector and forming close partnerships with private health-care providers will further strengthen performance.

Multiple challenges arise from the complexity of malaria biology: malaria parasites and their mosquito vectors are constantly evolving resistance to widely used drugs and insecticides, the most common methods of parasite detection are not sensitive enough to identify all infections, simian malaria is now common in humans in parts of southeast Asia, and the effectiveness of standard vector control interventions is low in areas with the highest transmission intensity and where outdoor biting is common. Encouragingly, the research and development pipeline for drugs, insecticides, diagnostics, and vector control tools is robust. Promising new products with strong potential to overcome existing challenges have become available in the past 5 years or are scheduled to roll

out over the next decade. Continued investment in research and development will be essential, with prioritisation of technologies that provide long durations of efficacy, do not require difficult or protracted compliance from individuals and households, and drive down malaria in high-transmission or otherwise problematic settings.

The cost of malaria eradication is not known and will be highly dependent on managerial efficiency, the efficacy and cost of new tools, and the degree to which interventions can be targeted. Estimates suggest that annual spending of $6 billion or more is required; current global expenditure is approximately $4·3 billion. The Commission believes that an additional investment of $2 billion per year is necessary, with a quarter of that coming from increased development assistance from external donors and the rest from government health spending in malaria-endemic countries. Securing additional funding will not be easy. Development assistance for health has plateaued since 2011, but opportunities exist for new and smaller donors to step in and fill the gap. In addition, our analyses show that government spending on malaria in high-burden countries has increased faster than their growth in gross domestic product, indicating that health in general, and malaria specifically, is a high priority. The opportunities for increased public expenditure on malaria and reduced reliance on donor funds need to be assessed and acted upon country by country. For both donors and countries, a shared and time-bound commitment to eradication will catalyse enthusiasm and financial support.

Strong and committed leadership and governance, reinforced through transparency and independent accountability mechanisms, are essential to ensure that eradication is achieved. Leadership and ambition are increasingly coming from the national and regional levels. Global malaria eradication will be achieved through regional elimination. Global organisations should focus on supporting and enabling countries and regions by developing guidance, coordinating across stakeholders, and advocating for sustained investment and research. There is value in closer collaboration and clearer definition of roles between the two apex organisations, WHO and the RBM Partnership to End Malaria. Opportunities also exist for greater alignment of policies and investment strategies between The Global Fund to Fight AIDS, Tuberculosis and Malaria and the US President's Malaria Initiative, the two major malaria funders. Finally, the Commission recommends the creation of an independent monitoring board for malaria eradication.

Beyond the obvious benefits of eradicating a disease that has caused untold morbidity and mortality throughout human history, malaria eradication also contributes to broader health and development goals. Strengthening global health security and meeting many of the Sustainable Development Goals—including achieving universal health coverage, promoting equity, and reducing poverty—are all supported and reinforced by progress towards malaria eradication, and vice versa. Malaria eradication has multiple benefits for human welfare and prosperity, the value of which will greatly exceed the investment required to get the job done.

In this report, the Commission concludes that malaria eradication is possible, worthwhile, and affordable, and that the alternatives to eradication are untenable. We identify opportunities for specific actions that will overcome challenges and accelerate progress, starting with an immediate, firm, global commitment to achieving eradication by 2050.

Introduction

This report by the *Lancet* Commission on Malaria Eradication (the Commission) addresses a bold proposition: malaria, one of the most ancient and deadly diseases of humankind, can and should be eradicated before the middle of the 21st century. Earlier eradication ambitions were put on hold in 1969, and the malaria community shifted its focus to reducing morbidity and mortality through implementation of prevention and control interventions. Malaria control programmes were often overwhelmed and underfunded, and, especially across Africa, a sense of fatalism existed that substantial progress would never be made. But around the turn of the century, the situation changed dramatically, with re-energised commitment, new and improved tools, and greatly increased funding. Between 2000 and 2017, the worldwide annual incidence of malaria declined by 36%, and the annual death rate declined by 60%.[1,2] In 2007, Bill and Melinda Gates proposed that merely controlling malaria was too modest a goal and that complete eradication was the only scientifically and ethically defensible objective. This ambitious goal was quickly embraced by WHO and other global stakeholders.[3–5] In 2015, the eradication agenda began to take definitive shape through the articulation of global strategies and—perhaps most importantly—a potential timeline for eradication.[6–8]

The Commission was launched in October, 2017, by the Global Health Group at the University of California San Francisco. The Commission builds on the 2010 *Lancet* Malaria Elimination Series, which evaluated the operational, technical, and financial requirements for malaria elimination and helped shape and build early support for the eradication agenda.[9] Malaria eradication, like all disease eradication efforts, is a daunting, long-term enterprise requiring the relentless commitment of multiple stakeholders until the task is complete. The Commission is contributing to this collective effort alongside other global bodies by synthesising the evidence needed to make the case that, despite the many challenges, malaria eradication is achievable within a generation, and that the world should commit to this audacious goal now.

The malaria eradication imperative

Countries and regions face many pressing problems in health and beyond, of which malaria is just one. Thus, a

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21st century commitment to malaria eradication must be justified on the basis of solid evidence that malaria eradication is achievable within a defined time period, that it is worthwhile in relation to the return on investment and multiple societal benefits, and that the alternative to eradication is untenable. We address each of these three assertions here, and indicate how the various sections of this report contribute to the evidence in support of the Commission's conclusions.

Is malaria eradication by 2050 possible?

Substantial progress towards malaria eradication has been made in the past 20 years, described in detail in section 1. The combined effect of global social, economic, and environmental trends and the scale-up of coverage of current interventions is projected to lead to low levels of malaria that persist in pockets across roughly ten countries in equatorial Africa in 2050. These modelled projections of the future are set out in section 2. The report highlights three ways to bend the curve to ensure a world free of malaria by 2050: improving management and operations and making better use of existing technologies, rolling out new technologies, and spending more money.

Section 3 outlines what we call the software of malaria eradication: inexpensive and readily adoptable approaches to strengthen the management, operational precision, and effectiveness of malaria programmes. Governments can overcome capacity challenges and further improve malaria programme performance by engaging with private health-care providers and leveraging private sector expertise in delivering interventions. Leadership and accountability at the country, regional, and global levels are also crucial elements for success, and we describe necessary actions in section 7.

We identify the most pressing biological challenges to eradication in section 4. Fortunately, as discussed in section 5, the tools needed to overcome these challenges—what we call the hardware of malaria eradication—are rolling out, and the research and development pipeline for new technologies has never been stronger. Three important tools—rapid diagnostic tests (RDTs), artemisinin-based combination therapy (ACT), and long-lasting insecticide-treated nets (LLINs)—were introduced early in the 21st century and are now ubiquitous and effective across the world. A variety of other tools have more recently become available and are increasingly being deployed, including information technology, molecular methods for diagnosis and surveillance, a new drug for *Plasmodium vivax* malaria, and two novel insecticides, all of which will accelerate progress. Most excitingly, the research and development pipeline is expected to yield additional new drugs and insecticides, innovative vector control strategies, and more sensitive and precise diagnostics over the coming decade. Further in the future is the radical potential of gene drive technologies to reduce transmission in the most challenging settings. The most promising and effective research and development targets for malaria eradication are discussed in section 5.

Both government and international spending on malaria have greatly increased since 2000. These investments have resulted in substantial reductions in global malaria burden and rapid progress towards regional elimination in Asia-Pacific and the Americas. Current spending now stands at about US$4·3 billion per year. To know with certainty how much money will be required to eradicate malaria is not possible, nor can we accurately disentangle malaria-specific costs from the overall costs of health systems. Annual spending of no less than $6 billion will probably be required. In section 6, we discuss initial ideas on how both donor and domestic sources can be enhanced to meet an estimated annual funding shortfall of approximately $2 billion. We also identify opportunities for more efficient and effective spending.

Is malaria eradication worthwhile?

Malaria eradication is an overwhelmingly worthwhile enterprise for multiple reasons. First, eradication will permanently end the historic toll of malaria sickness and death. Second, eradication is the only way to overcome the relentless evolution of malaria drug and insecticide resistance discussed in section 4. Third, as documented in section 6, malaria eradication will make a major contribution to welfare and economic prosperity in endemic countries and regions, and the benefits conferred by eradication will greatly exceed the costs. Once eradication has been achieved, the resources previously devoted to malaria can be allocated to other health priorities, further improving population health and strengthening economic development. Fourth, synergies exist between malaria eradication and broader health and development goals. As discussed in section 8, meeting several of the Sustainable Development Goals (SDGs)—including achieving universal health coverage, promoting equity, and reducing poverty—and building global health security are supported by malaria eradication, and vice versa. Malaria eradication is an excellent investment with benefits that reverberate throughout the health and development sectors.

What is the counterfactual scenario to malaria eradication?

The world could decide not to launch a bold initiative to eradicate malaria by 2050, and instead opt to maintain current efforts and wait until an unspecified time when the operational, technical, and financial requirements might be more strongly in place. We describe this alternative scenario and its implications in section 1 and argue that backing away from the pursuit of eradication by 2050 would be indefensible.

Section 1: context, lessons from the past, and alternatives to malaria eradication

In 1900, nearly all of the roughly 200 countries in the world had endemic malaria. Nowadays, 86 such

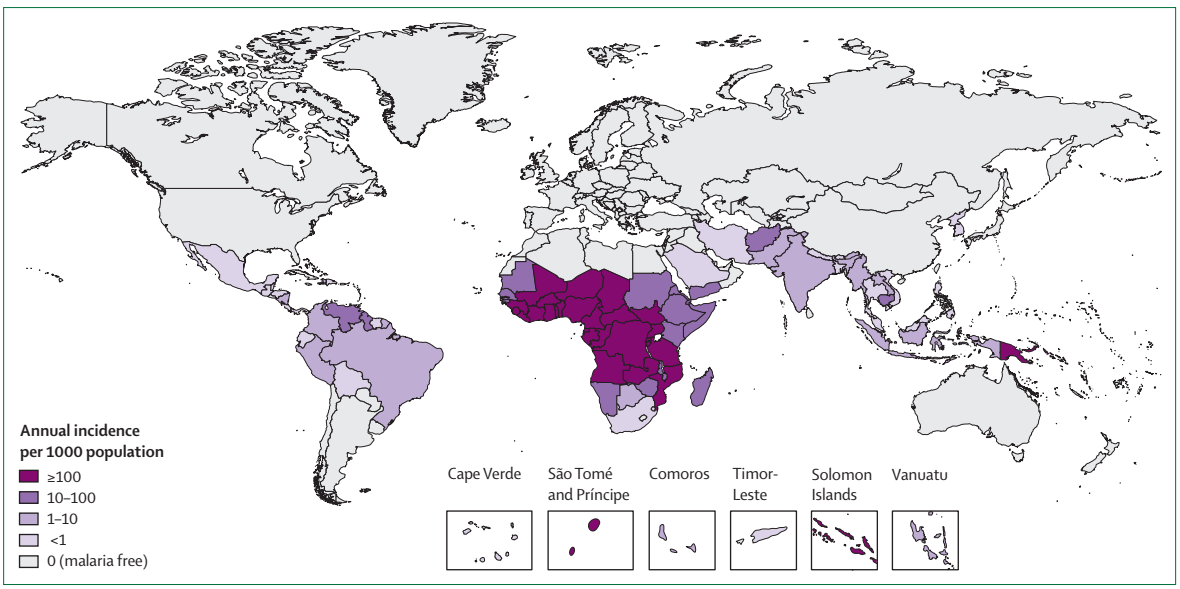

Figure 1: **Malaria cases per 1000 total population in 2017, by country**
The annual incidence was calculated on the basis of the number of cases caused by the four human malaria species—*Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae*, and *Plasmodium ovale*—in 2017 as reported in WHO's *World Malaria Report 2018*,[1] and the total population of each country in 2017 as reported by World Bank.[10]

countries exist, approximately 30 of which have particularly high rates of malaria (figure 1). Dozens of countries are working to end malaria transmission within the next decade, and support for eradication of the disease has grown. However, global progress has stalled since 2015 and the malaria community is now at a critical moment, faced with a decision to either temper its ambitions as it did in 1969, or recommit to an eradication goal. In this section, we describe the historical and current context for malaria eradication, contrast the circumstances in 2019 with those in 1969, and explore the counterfactual scenario to aggressive and immediate eradication efforts.

The continuum to eradication

Malaria endemic countries were previously classified by programmatic phase, primarily determined by national incidence.[11] Countries with high burdens were considered to be in the control phase, during which malaria programmes aimed to reduce morbidity and mortality through continued interventions. Programmes entered the elimination phase when incidence dropped below 1 case per 1000 population per year. The goal of elimination is to reduce the annual incidence of locally acquired cases to zero within a defined geographic area, typically a country.[11,12]

These classifications evolved as the malaria community began to seriously consider the goal of eradication and acknowledge the artificial dichotomy between control and elimination. Now, all endemic countries are thought to be on a continuum, with national elimination as the ultimate goal. Once a country has eliminated malaria, it enters the prevention of re-establishment phase. In this phase, continued interventions and vigilance are required to prevent resurgence and the re-establishment of transmission caused by imported cases.[13]

Malaria eradication is defined by WHO as the permanent reduction to zero of the worldwide annual incidence of malaria infection caused by all species of human malaria parasites: *P vivax*, *Plasmodium falciparum, Plasmodium malariae,* and *Plasmodium ovale*.[12] Interventions against these species will no longer be needed once we reach eradication, and the considerable human and financial resources required to achieve eradication can then be reallocated to other health priorities.[7,8] However, non-human malaria parasites infect humans in some regions, especially the simian species *Plasmodium knowlesi* in southeast Asia, and prevention and management of these cases will require ongoing interventions.[14] The implications of simian malaria are discussed in greater detail in section 4.

20 years of progress towards eradication

The most recent wave of progress began in the late 1990s with the launch of major global organisations that provide technical, operational, and financial support for malaria-endemic countries. Chief among these organisations are the RBM Partnership to End Malaria (the RBM Partnership; formerly the Roll Back Malaria Partnership), which was launched in 1998, the Bill & Melinda Gates Foundation (the Gates Foundation), launched in 2000, The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), launched in 2002, and the US President's Malaria Initiative (PMI), launched in 2005. The substantial influx of funding and technical and operational resources introduced by these

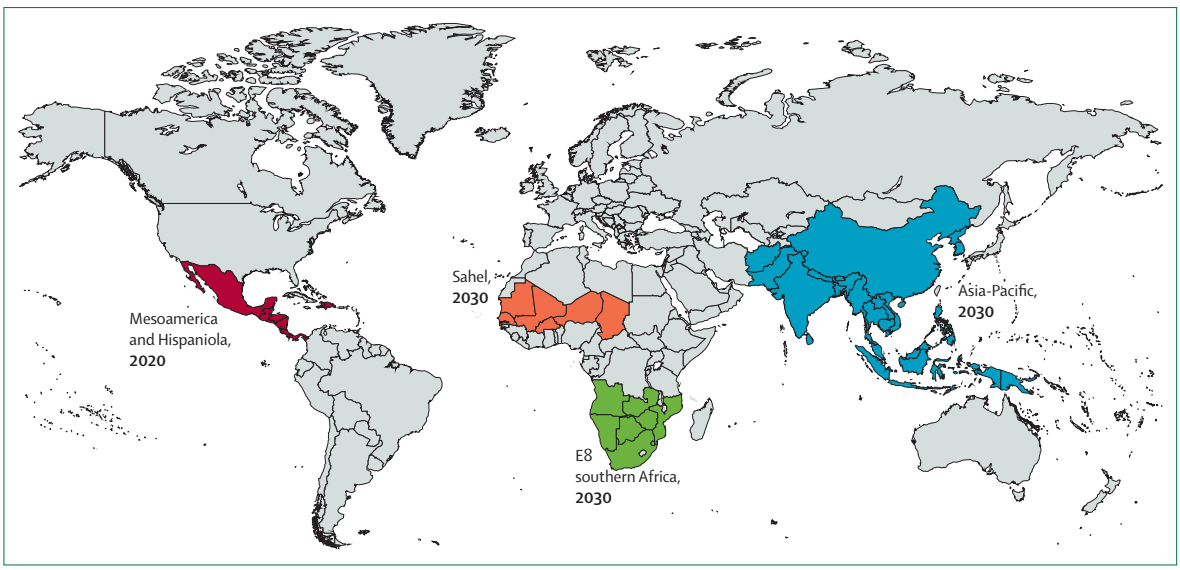

Figure 2: **Regional goals for malaria elimination**
Several regional networks and platforms for malaria elimination have been launched since 2008. The major initiatives are shown here, along with their respective elimination goals. These initiatives are described in more detail elsewhere in this report (panel 1). E8=Elimination 8.

organisations and others led to accelerated progress and the deployment of highly effective new tools, particularly ACTs, LLINs, and RDTs.

What have countries done?

Between 2000 and 2017, 20 countries—about one-fifth of the 106 malaria-endemic countries in 2000—eliminated malaria transmission within their borders, reporting zero indigenous malaria cases for at least 1 year.[1] In the past 10 years, dozens of countries have declared national elimination goals and some high-burden countries, such as Indonesia and Senegal, have begun setting subnational elimination goals for low-burden districts and provinces. In 2016, WHO identified 21 countries with the potential to eliminate malaria by 2020; seven of these countries (Algeria, China, El Salvador, Iran, Malaysia, Paraguay, and Timor-Leste) have eliminated malaria since that list was published.[15,16] Of the remaining 14 with ongoing transmission, seven (Belize, Bhutan, Cape Verde, Costa Rica, eSwatini, Saudi Arabia, and Suriname) reported fewer than 100 cases in 2018 and are on track to eliminate by 2020.[1] The other seven countries (Botswana, Comoros, Ecuador, Mexico, Nepal, South Korea, and South Africa) have had challenges and setbacks that have either slowed or reversed their progress in the past few years.[15]

Many high-burden countries also had declines in cases and deaths between 2000 and 2015. However, between 2015 and 2017, 55 countries had an increase in cases and 38 countries had an increase in deaths.[1,2] To what extent these increases reflect real epidemiological trends or improvements in surveillance, diagnosis, and access to malaria services is unclear. A thorough examination of the causes is warranted.

What have regions done?

In addition to setting national-level elimination goals, every malaria endemic region in the world has committed to malaria elimination. An early example of regional collaboration driving national progress towards elimination was in the WHO European region. Nine countries that were still endemic in 2005 committed to regional elimination by 2015, which was achieved when the final country with ongoing transmission, Tajikistan, reported its final indigenous case in 2014.[17,18] In 2016, recognising that remaining malaria-free requires ongoing vigilance and political and financial commitment, the same nine countries agreed to continue working together to prevent re-establishment of transmission in the WHO European region.[19]

Several regional networks and collaborative bodies have also launched in Africa, Asia-Pacific, and the Americas to enhance cooperation in achieving future national and regional elimination goals (figure 2). The networks have developed regional strategies and roadmaps to guide and monitor progress, and some have secured financial support through regional-level grants from external donors.[20–27] In many cases, participation in regional networks has driven countries to set more aggressive national elimination goals (panel 1).

In line with country-level trends, regions advanced steadily between 2000 and 2015 before a slowing of progress and some resurgence in succeeding years. All WHO regions, except for the European region and the South-East Asia region, had an increase in cases between 2015 and 2017, although deaths continued to decline in all regions except the region of the Americas and the Western Pacific region.[1]

What has the world done?

At the global level, WHO and the RBM Partnership published complementary documents in 2015, *Global Technical Strategy for Malaria 2016–2030*[6] and *Action and Investment to Defeat Malaria 2016–2030*,[7] which outlined 15-year technical, financial, and advocacy plans to accelerate progress towards eradication. The plans focused on interim elimination and burden reduction targets for 2020, 2025, and 2030.[6,7] A third global advocacy document—*From Aspiration to Action: What Will It Take to End Malaria?*—issued by the Gates Foundation and the UN Special Envoy for Malaria, went further by outlining technical, operational, and financial requirements for achieving eradication by 2040.[8]

In 2016, WHO convened the Strategic Advisory Group on Malaria Eradication to advise the Director-General on the feasibility of eradication and the merits of a World Health Assembly resolution on this subject.[31] Early 2017 saw the launch of the End Malaria Council, a group of public and private sector leaders supporting countries and regions in achieving elimination goals while advocating for increased commitment and investment to accelerate eradication at the global level.[32] Later that year, the Malaria Eradication Research Agenda published updated recommendations for eradication research.[33]

The current malaria situation

In 2017, 86 countries reported a total of 219 million malaria cases and 435 000 malaria deaths, down from 262 million cases and 839 000 deaths in 2000.[1] However, cases and deaths are not distributed evenly. The good news is that 38 countries had incidences of fewer than ten cases per 1000 population in 2017, with 25 countries reporting fewer than one case per 1000 population (figure 1).[1] The same 38 countries reported just 5% of total malaria deaths.[1] Nearly all of these low-burden countries are actively working towards national and regional elimination goals of 2030 or earlier.

Troublingly, 29 countries—all in Africa except Papua New Guinea and the Solomon Islands—had high rates of transmission in 2017, reporting more than 100 cases per 1000 population (figure 1) and accounting for 85% of total malaria deaths.[1] Ten countries currently account for two-thirds of global cases, and the top two alone, Nigeria and the Democratic Republic of the Congo, account for 36% (table 1).

In this report, we emphasise the need for simultaneous action both in countries that are nearing elimination and in countries with the highest malaria prevalence to achieve eradication by mid-century. 26 of the 29 high-burden countries had an increase in cases between 2015 and 2017, illustrating the urgent need for strenuous and effective action.[1] Momentum in high-burden countries is now gathering. In April, 2018, the Commonwealth of Nations (the Commonwealth) resolved to halve malaria cases in endemic member states by 2023.[34] Of the 53 Commonwealth countries, 25 have ongoing transmission and accounted for more than half of global malaria cases and deaths in 2017.[1] Eight of the 16 countries shown here (table 1) are part of the Commonwealth. In November, 2018, WHO and the RBM Partnership published *High Burden to High Impact: A Targeted Malaria Response*[35] to drive down malaria in

Panel 1: **Description of major regional malaria elimination initiatives**

Africa

- The African Leaders Malaria Alliance (ALMA) is a coalition of 49 African heads of state and government committed to ending malaria by 2030, a goal endorsed by the African Union; although the 2030 goal is unlikely to be attained on the basis of current trends, it serves an important aspirational purpose in rallying the support and participation of member countries; ALMA provides a forum to review progress and address challenges in meeting malaria targets, implement a monitoring and accountability system, and facilitate knowledge sharing[22,28]
- The Elimination 8 in southern Africa is working to attain zero malaria transmission through joint collaboration and strategic programming, with a focus on advocacy and accountability, mobile and migrant populations, monitoring and surveillance, and policy-harmonisation across the countries in the region; the four front-line countries aim to eliminate malaria by 2020; the second-line countries are targeting 2030[23]
- The Sahel Malaria Elimination Initiative is a regional platform developed to enable eight countries in west Africa to work together to eliminate malaria by 2030; the countries aim to scale up universal coverage of antimalarial drugs, mobilise financing for malaria elimination, strengthen cross-border collaboration, fast-track the introduction of innovative technologies to combat malaria, and develop a subregional scorecard to track progress[27]

Mesoamerica

- In June, 2013, the Council of Ministers of Health from Central America and Dominican Republic committed to eliminate malaria from the subregion's ten countries by 2020;[25] currently, the Regional Malaria Elimination Initiative builds on previous regional efforts and commitments, aiming to ensure that national strategic plans align with regional objectives and address programmatic and financial gaps, avoid duplication and overlap of efforts, coordinate all technical assistance, incentivise results-based performance, and strengthen partnerships[29]

Asia-Pacific

- The Asia Pacific Leaders Malaria Alliance (APLMA) is an affiliation of 22 heads of government, formed to accelerate progress and eliminate malaria in the region by 2030; APLMA facilitates high-level engagement for malaria elimination by tracking regional progress and brokering policy, technical, and financing solutions to regional and national challenges[21]
- The Asia Pacific Malaria Elimination Network works in partnership with APLMA, supporting implementation of the regional elimination roadmap by providing country partners a forum to discuss programmatic and technical challenges and successes[20]
- In the Greater Mekong Subregion, elimination has been identified as the only acceptable response to contain the threat of drug-resistant *Plasmodium falciparum* malaria; the WHO Regional Strategy for Malaria Elimination in the Greater Mekong Subregion outlines a phased approach to elimination, with *P falciparum* transmission eliminated in all six participating countries by 2025, and all forms of human malaria eliminated by 2030; this regional effort is supported, in part, by the Regional Artemisinin-resistance Initiative grant from The Global Fund to Fight AIDS, Tuberculosis and Malaria[26,30]

	Greatest number of cases		Highest annual incidence	
	Country	Cases, n (% of global total [N=219 million])	Country	Cases per 1000 total population
1	Nigeria	53·7 million (25%)	Rwanda	506
2	Democratic Republic of the Congo	25·0 million (11%)	Burkina Faso	412
3	Mozambique	10·0 million (5%)	Central African Republic	387
4	India	9·6 million (4%)	Mali	386
5	Uganda	8·6 million (4%)	Sierra Leone	380
6	Burkina Faso	7·9 million (4%)	Togo	371
7	Ghana	7·8 million (4%)	Benin	368
8	Niger	7·7 million (4%)	Niger	359
9	Cameroon	7·3 million (3%)	Equatorial Guinea	343
10	Mali	7·2 million (3%)	Mozambique	338

The top ten countries with the greatest number of cases were determined on the basis of total estimated cases caused by the four human malaria species—*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*—in 2017 by country, as reported in WHO's *World Malaria Report 2018*.[1] The top ten countries with the highest annual incidences were determined using the number of cases caused by the four human malaria species in 2017, as reported in WHO's *World Malaria Report 2018*,[1] and the total population of each country in 2017 as reported by World Bank.[10]

Table 1: **Countries with the highest malaria burden, 2017, ranked**[1,10]

the highest-burden countries, emphasising the need for strengthened political will, multisectoral coordination, and tailored, data-driven policies and strategies.

Lessons from the Global Malaria Eradication Programme (GMEP)

The WHO GMEP was launched in 1955 and formally ended at the 22nd World Health Assembly in July, 1969, after 15 years of notable successes and serious failures. The World Health Assembly's official record of proceedings contained a thorough review of the GMEP, including gains, setbacks, requirements, challenges, and outlook for the future of eradication.[36] The report identified key benefits of the eradication campaign, including the expansion of routine health services; the creation of essential infrastructure that benefited other vector-borne disease control programmes and the health system at large; improved economic development and the breaking of the vicious cycle of poverty and disease; and valuable advances in scientific research and technology. The biggest challenges at the time were considered to be complacency and absence of political will; poor leadership and management; inadequate tools to eliminate in high transmission areas, particularly sub-Saharan Africa; population movement and poor access to malaria services; minimal knowledge of vector behaviour; insufficient funds; and the early development and spread of insecticide and drug resistance. The report concluded that eradication should remain the long-term goal of the malaria community, but should not be actively pursued because of these seemingly insurmountable challenges.[36]

50 years later, the findings and conclusions of this final GMEP report are startlingly familiar. The known benefits of eradication remain the same, as do many of the operational, technical, and financial challenges. Despite the GMEP's successes—malaria elimination in 15 countries and substantially reduced transmission in several others—the World Health Assembly decided to close down the programme in 1969 because of stalled progress and scarcity of solutions to the challenges at hand.[36] In 2019, the world again faces a crucial decision on whether to launch a time-bound eradication effort now, despite the numerous challenges. Because of the similarities between past and present, it might be tempting to adhere to the World Health Assembly's conclusions of 50 years ago: keep eradication as a long-term vision but maintain a strategy of control where the feasibility of elimination has not yet been shown.

Yet, the world in 2019 is nothing like the world in 1969. The citizens of malaria-endemic countries are much wealthier, healthier, and better educated than they were 50 years ago.[37–39] In 1969, more than 80 countries had a per-capita gross domestic product (GDP) of less than $1000 per year; now, fewer than 30 such countries exist (in adjusted dollars), only 18 of which have a high burden of malaria.[40] Global development trends, especially urbanisation, are generally assisting the decline in malaria.[41] Technological capabilities have advanced beyond recognition compared with 1969, when the world was still 30 to 40 years away from widespread access to modern information and communications technology. As a result of substantial innovation, investment, and progress in malaria control, the world is now in a position to address many of the daunting challenges identified 50 years ago. New and highly effective tools, a strong product pipeline, five decades of scientific research and evidence generation, and invaluable lessons from previous and current disease eradication efforts are now available to guide decision making. Most importantly, the malaria community has renewed energy and commitment to confront challenges and pursue eradication. As noted in 1969, "ultimate success will depend on the determination to overcome obstacles."[36] A recommitment to eradicating malaria within a generation is powerful evidence of that determination.

The alternatives to eradication

The global malaria community might decide to follow the path taken 50 years ago at the close of the GMEP and postpone a time-bound commitment to malaria eradication until circumstances appear more favourable. Countries with very low transmission would be encouraged to continue making progress towards elimination, while in high-burden countries, the emphasis would be on mortality reduction. Under this counterfactual scenario, malaria will probably gradually decline in some areas where development and other socioeconomic factors contribute to a natural reduction in receptivity. However, in high-transmission countries, especially in Africa, malaria will continue to take its health and socioeconomic toll for

longer than necessary, particularly in the poorest and most marginalised communities. The risk of malaria resurgence in countries that have eliminated will be ever present, and the expensive and seemingly endless task of managing that risk will likely disincentivise countries from pursuing elimination. A world in which some low-income countries have eliminated malaria but others in the same region have persistent malaria is inherently unstable because resurgence is almost certain to occur. Resources to control malaria and prevent re-establishment will continue to be needed for a longer period and overcoming drug and insecticide resistance will become increasingly difficult.

Relatedly, advocating for the pursuit of eradication without setting a clearly articulated and widely endorsed time-bound goal will undermine the seriousness and credibility of the commitment. Defining a global trajectory for eradication, accompanied by a roadmap and regular milestones for assessing progress, is crucial for incentivising action, mobilising support, and ensuring that malaria eradication remains a high priority until the goal is reached. When time-bound smallpox and polio eradication efforts were launched (smallpox in 1966 and polio in 1988), global consensus on their prospects was less robust than is the case for malaria now. Yet stakeholders rallied behind the respective goals and made remarkable progress, remaining committed to eradication even during the difficult final stages. History in global health and many other arenas has taught that success follows bold commitments, and not vice versa.

Section 2: modelling the trajectory for malaria eradication

The current global distribution of malaria (table 1; figure 1),[42,43] results from a complex mixture of natural and anthropogenic environmental conditions and uneven deployment of malaria control measures. As a disease that disproportionately affects the rural poor, malaria epidemiology is affected by secular trends like urbanisation, reductions in poverty, and changing climate and land cover. To plan the path to eradication and optimise resource allocation, it is useful to model potential changes in the distribution and intensity of malaria on the basis of reasonable scenarios of future global socioeconomic and environmental trends and the effect of malaria-specific interventions. This approach can provide an indication of (1) whether reducing malaria transmission will become easier or more difficult over time and (2) where elimination might be hardest to achieve. Here, we show maps of the current endemicity of *P falciparum*[42] and *P vivax*[43] and generate estimates of *P falciparum* endemicity under plausible scenarios of global change in 2030 and 2050, with and without a scale-up of malaria interventions. We selected 2030 because it is a watershed year by which several regions have pledged to eliminate malaria, and 2050 because it is the putative date for global eradication proposed in this report.

To generate global maps of *P falciparum* endemicity for 2030 and 2050, we used the Malaria Atlas Project global database, which includes observations of infection prevalence or clinical incidence from thousands of locations since the 1990s.[42] Our analysis (appendix pp 1–2), consisted of four steps: (1) development of a machine-learning model to capture the complex associations between malaria endemicity data and a wide range of present-day socioeconomic and environmental geospatial covariates; (2) mapping of covariate estimates to the years 2030 and 2050 on the basis of projected global trends; (3) application of the associations learned in the first step to projected covariates generated in the second step to estimate the possible future global landscape of malaria endemicity; (4) use of a mathematical transmission model to explore the potential effect of differing levels of malaria interventions imposed on these future landscapes. This analysis has various limitations, and the results reflect major patterns and trends rather than granular forecasts of future malaria transmission.

See Online for appendix

The current situation

We used *P falciparum*[42] and *P vivax*[43] infection prevalence for 2017 to provide a baseline for the subsequent discussion of the situation in 2030 and 2050 (figure 3). Although much of Africa has seen a reduction in *P falciparum* prevalence since 2000,[44] numerous subnational regions with over 50% prevalence remain. In isolated pockets of Angola, Democratic Republic of the Congo, Mozambique, and Uganda, prevalence exceeds 70%.[42] In Asia-Pacific, the highest prevalence values are concentrated in Pakistan, Indonesia, and Papua New Guinea, but even these rarely exceed 30%.[42] In the Americas, substantial *P falciparum* malaria exists in Amazonian Colombia and Venezuela.[42] The high prevalence values in southern Venezuela, exceeding 50% in some places, are associated with economic and political breakdown over the past few years.

Concerning *P vivax*, distribution in Africa is restricted to parts of east Africa and Madagascar, with prevalence rarely exceeding 1%.[43] *P vivax* is widely distributed in Asia-Pacific, but substantial areas in excess of 5% prevalence are only found in Pakistan and the island of New Guinea.[43] In the Americas, the Venezuelan anomaly is clear, and small pockets of *P vivax* with prevalence above 5% are also found across the upper Amazon Basin.[43]

The impact of future global social, economic, and environmental trends

Our analysis indicates that, overall, global trends have a considerable positive impact on malaria endemicity, especially in Africa. Our models suggest that projected social, economic, and environmental trends are associated with reduced *P falciparum* prevalence and R_c (basic reproductive number under control) values, even when keeping constant the current level of coverage with key

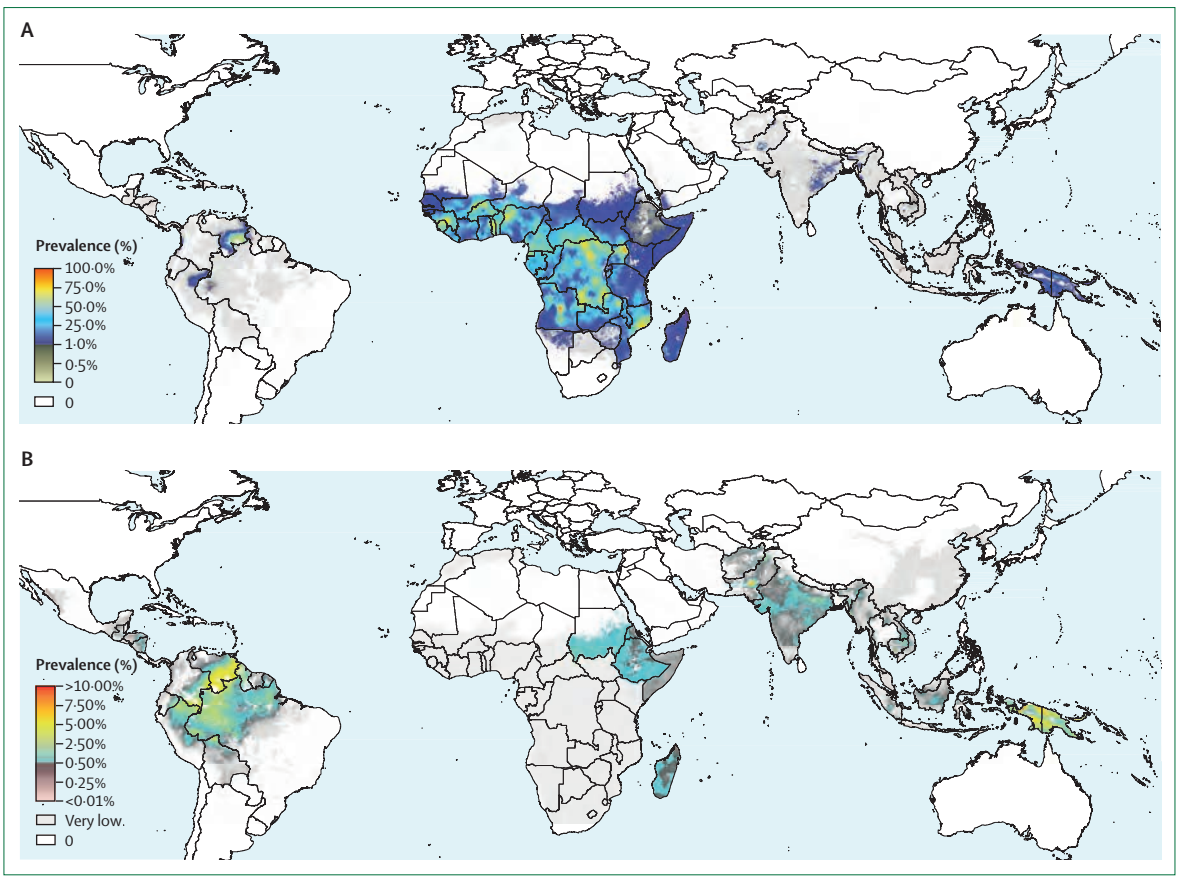

Figure 3: **Global malaria endemicity in 2017**[42,43]
(A) *Plasmodium falciparum* infection prevalence (children aged 2–10 years). (B) *Plasmodium vivax* infection prevalence (individuals aged >1 year) estimated for each 5 km^2 grid cell globally. Note different colour scales are used for each map and both feature a two-part scale to enhance differentiability of values near zero.

malaria interventions (figure 4). By 2030, the distribution of higher prevalence is substantially reduced, with 90% of endemic areas falling below 30% prevalence. Further progress is seen in 2050, with 90% of endemic areas falling below 22% prevalence and half below 4% prevalence, along with the establishment of many new areas of zero transmission. Areas of higher prevalence are concentrated in Angola, Democratic Republic of the Congo, and Mozambique, together with some additional foci in west Africa. Outside of Africa, global trends have a smaller effect but, by 2050, very low prevalence is nevertheless seen nearly everywhere, with 90% of endemic areas (excluding Venezuela) falling to less than 1% prevalence. Concerning R_c in Africa, in 2050, very few areas have a value of over 3 and only 1% of endemic areas are above a value of 7. Outside of Africa, again with the exception of Venezuela, only 1% of endemic areas exceed a value of 2. Socioeconomic development in Africa drives these projected declines in transmission, including urbanisation, improvements in housing, and improved physical infrastructure. In some parts of South America and the Horn of Africa, our forecasted global socioeconomic and environmental trends contribute to increased malaria, driven primarily by rising temperature and precipitation.

The added effect of increased coverage

When the potential effects of global trends are combined with high coverage of malaria control interventions, our analysis indicates a potentially dramatic effect (figure 5). Outside of Africa, we project *P falciparum* elimination by 2030, with the exception of small pockets in Brazil and the island of New Guinea. In Africa, 95% of previously endemic areas are projected to fall below 0·5% prevalence by 2030 and below 0·1% prevalence by 2050. Remaining pockets of transmission will be scattered in small foci across the belt from west Africa to northern Mozambique. The transmission focus in central Brazil expands somewhat between 2030 and 2050, reflecting the role of projected increases in precipitation in this region. Regarding R_c in 2050, almost all values are below 1, indicating the natural die-away of the disease everywhere except in the African foci and central Brazil. Even in Africa, R_C values above 1·4 in 2050 are found in only 1% of the formerly endemic regions.

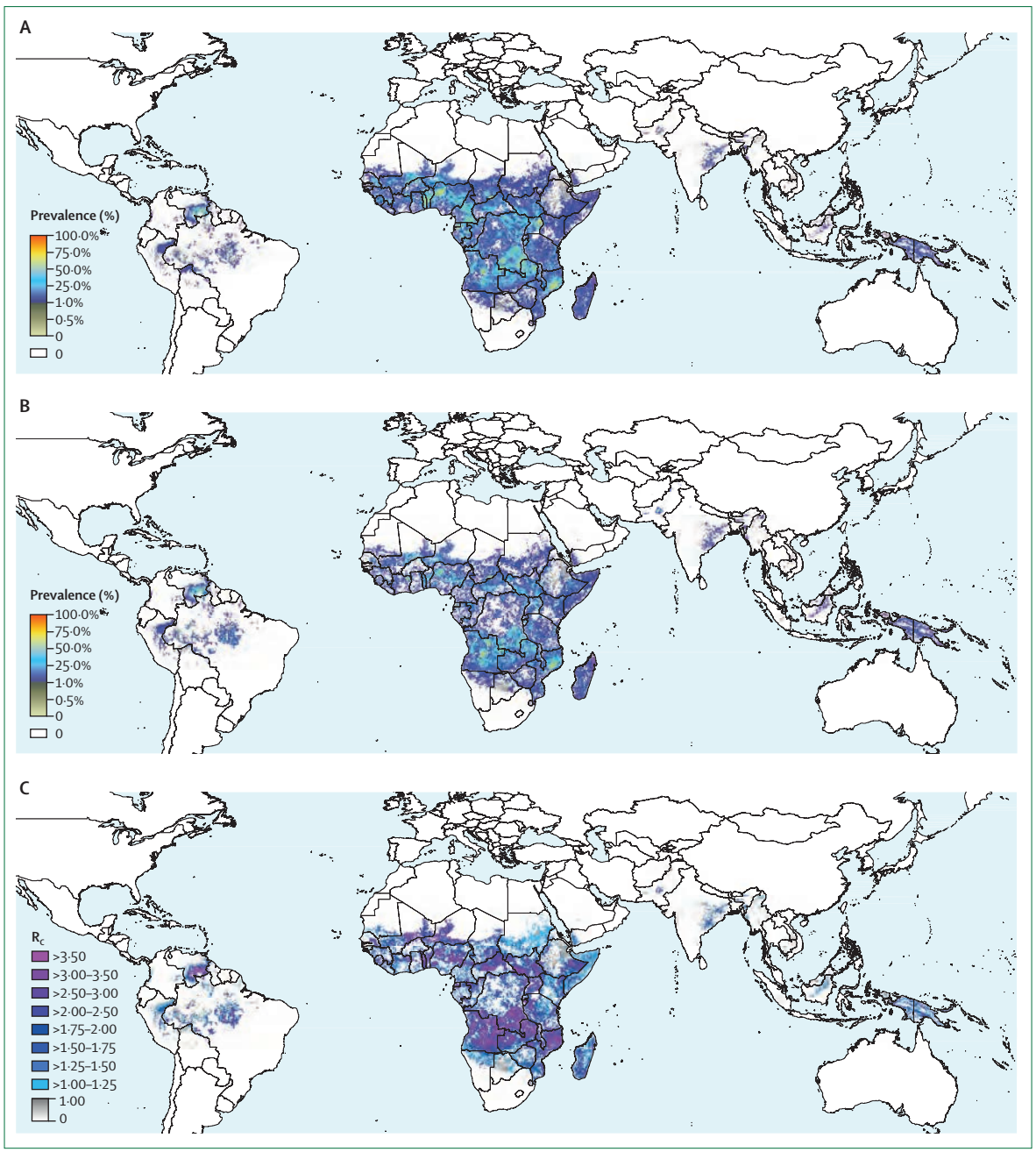

Figure 4: **Projected future effect of global trends on malaria endemicity**
Plasmodium falciparum infection prevalence (children aged 2–10 years) projected for the years 2030 (A) and 2050 (B), and *P falciparum* R_c for 2050 (C). In these projections, malaria intervention coverage was held constant to 2017 levels. R_C=basic reproductive number under extant control conditions.

We simulated very high levels of malaria control using combined ACTs, LLINs, and indoor residual spraying (IRS) at 80% effective coverage (appendix pp 1–2). We do not suggest that high coverage levels for these three interventions, and especially for LLINs and IRS in combination, are either feasible or desirable across a wide area. In practice, the mix of interventions and the desirable coverage levels will need to be targeted and responsive to local conditions. Rather, we use 80% coverage with currently available interventions, which have known and well modelled relationships with malaria transmission and prevalence, as a proxy for enhanced treatment (thus reducing the parasite reservoir) and vector control (thus reducing transmission). In practice, we imagine these reductions in the future being achieved by increased and better-targeted coverage with contemporary interventions,

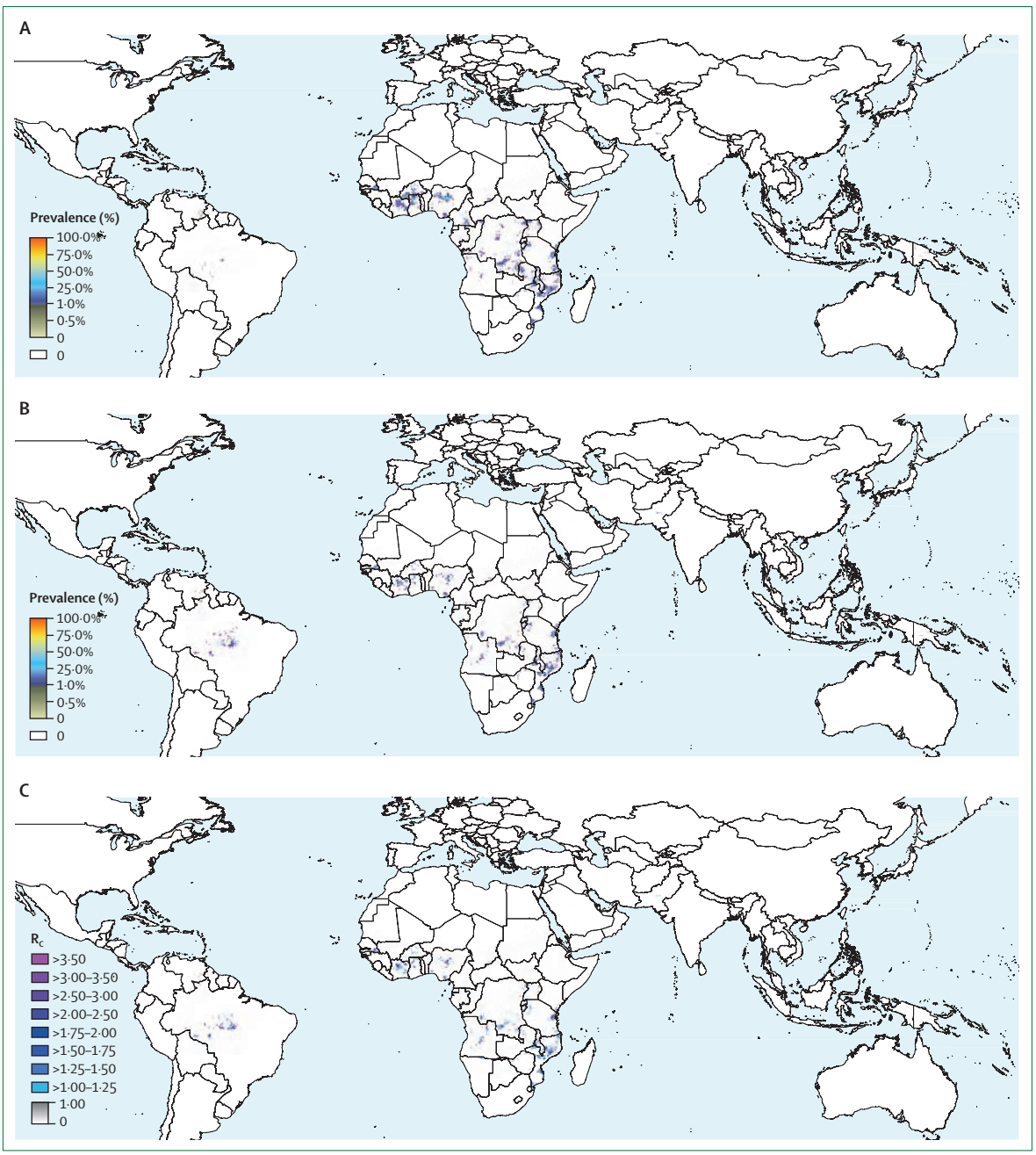

Figure 5: **Projected future effect of global trends and enhanced malaria control on malaria endemicity**
Maps show *Plasmodium falciparum* infection prevalence (children aged 2–10 years) projected for the years 2030 (A) and 2050 (B), and *Plasmodium falciparum* R_c for 2050 (C). In these projections, malaria intervention coverage was enhanced above 2017 levels to reach 80% effective coverage of insecticide-treated nets, indoor residual spraying, and artemisinin-based combination therapies. R_c=basic reproductive number under enhanced control conditions.

combined with progressive use of new interventions that are reasonably expected to become available.

Interpretation

Combining the effect of global trends and enhanced interventions shows a world with almost no *P falciparum* malaria outside of Africa in 2030, and a world with very little malaria in Africa by 2050. Although complex and regionally varying, the global trends generally have a positive effect, especially as a result of changes to the human environment stemming from underlying socioeconomic development. The addition of enhanced malaria control yields a proportionally larger effect than the global trends alone; however, we emphasise that this situation reflects a combined effect: the global trends reduce transmission to a level where scaled malaria

control can be much more impactful, and eradication becomes more technically feasible.

We have probably underestimated the effect of malaria-specific interventions (figure 5) for two reasons. First, our analysis is based on previous relationships between key interventions and malaria transmission during a time when many national malaria programmes have been suboptimally resourced and staffed and have not exploited new opportunities for data-driven management and targeting. Adaptive management through the improved use of data for decision making and the targeting of interventions is expected to strongly increase the effect of current interventions. Second, the 2030 and 2050 projections take no account of new interventions that are likely to become available. For example, outdoor biting is a key variable in explaining the residual pockets of malaria in 2030 and 2050. We currently have no effective and widely deployable outdoor biting technologies, but we expect these to be available within the next decade. Furthermore, past relationships do not capture the effect of mass drug administration or mass chemoprevention because these interventions are either relatively new or have yet to be applied widely. These underestimates might be counteracted by the absence of drug or insecticide resistance from our projections, which result in overly optimistic estimates for the continued efficacy of current tools (see section 4).

We show Asia-Pacific as *P falciparum*-free by 2030 with the exception of the island of New Guinea, although even here we project transmission to be on the brink of elimination. In the Americas, remaining transmission should be dealt with by 2030. A return to stability and economic growth in Venezuela could lead to rapid elimination, and Brazil is well able to deal with its stubborn Amazonian foci. The scattered malaria foci we predict will remain in Africa in 2050 could readily be extinguished with plausible improvements in both management and technology of the kind described in sections 3 and 5 of this report.

Our analyses are subject to many cautions and caveats (appendix p 2). To state with confidence what the environmental, political, or global health landscape will look like decades in the future is impossible, and these maps only explore a small subset of possibilities. They represent plausible future scenarios based on associations between global trends and malaria, and between malaria interventions and malaria, observed over the past two decades. Parallel improvements in modelling methods and data collection systems will allow us to evaluate, revise, and improve these scenarios in the future.

P vivax maps for 2030 and 2050 could not be included at this time, but are anticipated. We show that for the Americas, Asia-Pacific, the Horn of Africa, and Madagascar, *P vivax* elimination is a major task (figure 3). Knowledge from many countries fighting both *P falciparum* and *P vivax* indicates that *P falciparum* typically declines more rapidly, and that *P vivax* becomes a larger share of all malaria as elimination approaches.[45] However, evidence from the past few years shows that the lag time between eliminating the two parasite species is short. The time between the final indigenous case of *P falciparum* and of *P vivax* was only 1 year in China, 5 years in El Salvador, and under 1 year in Malaysia and Sri Lanka.[1,46] Pending modelling of *P vivax* in 2030 and 2050, the *P falciparum* results we provide here are likely to be a close proxy.

Bending the curve

Our model shows scattered pockets of malaria, with low prevalence and low R_C, persisting in 2050. The focus of the remainder of this report is on how to deliberately bend the curve to ensure that the world is malaria free by 2050 or sooner. As outlined in the introduction, we propose that enhanced software (sections 3, 7), new hardware (section 5), and increased investment (section 6) should be more than sufficient to transform a modelled future into an engineered future of a world free of malaria by 2050.

Section 3: management and operations

Effective management and implementation of malaria programmes are the most important requirements for national and regional elimination and eventual global eradication. The current slowing of progress is not primarily the result of biological challenges, it is caused by an inability to deliver key services and interventions where they are needed most.

Copious guidance on operational requirements and approaches is provided by WHO and others, and we do not attempt to synthesise this advice here.[6,13,47] Rather, we emphasise the overwhelming importance of improved management capacity and the need for data to inform decision making. We then discuss operational issues that are controversial or insufficiently addressed. We briefly examine challenging economic, social, and political circumstances that could throw eradication off track, and finally, we comment on the country, regional, and global endgames.

Management matters

In malaria elimination, as in all other endeavours, well managed programmes are likely to succeed even with severe challenges, while poorly managed programmes might fail even in favourable circumstances.[48,49] Management is a generic skill, independent of the precise design of the malaria programme or whether the country is early or late in the elimination continuum—it is the ability to assemble and direct human and financial resources to achieve specific and quantifiable goals in a set timeframe.[13] Management can be taught, but general management training is not widely available to national malaria programme managers and staff. This topic is almost never spoken about at malaria conferences, and management

strengthening receives little explicit support from the major donors.

Global approaches to management training have been proposed and could have a role in creating a senior leadership cadre with strong networks and connectivity to colleagues in other countries and regions.[50] Such an initiative should be led by institutions in endemic countries and supported by their non-endemic country partners. The programme should avoid an overly academic curriculum and employ faculty from the world of implementation, rather than research. The contributions of business schools and the private sector will be essential. This training programme should emphasise practical leadership and management skills. Over time, this initiative will create a global network of malaria eradication professionals who are interconnected and speak a common language. Investment in ongoing alumni interaction, mentoring, and periodic reconvening is a priority.

Most management training must take place at national and subnational levels and be tailored to particular institutional, cultural, and economic settings. The Asian Collaborative Training Network for Malaria, in partnership with the Bureau of Vector-Borne Disease, Ministry of Public Health, Thailand, hosts a training programme for malaria managers that covers relevant entomology, epidemiology, and programme management. The network of alumni includes programme managers across the Asia-Pacific region.[51] National malaria programmes have the opportunity to both offer and require management training at all levels, including for middle management and team leaders on the front line.[52]

Lessons from the Global Polio Eradication Initiative indicate that the suboptimal and variable performance of local teams is stalling progress towards eradication of polio.[53] Strengthening subnational management capacity will probably be crucial for malaria eradication as well. In Zimbabwe, a programme to build leadership and management capacity among district-level malaria leaders is currently being piloted. Initial results indicate increased productivity, coverage, and quality of malaria programme operations, strengthened management and leadership, and improved team performance (Gosling R and Chung A, University of California San Francisco, personal communication). Additional pilots in malaria and other health areas have had similar results, but the evidence-base needs to be strengthened.[52,54] More programmes of this kind are required, with rigorous measurement of outcomes and the scale-up of successful management training models.

Managing sector-wide change

In addition to a focus on managing the national malaria programme, management training should prepare participants for the planning and management of malaria services within the context of sector-wide change. Two specific sector-wide disruptions are occurring or are foreseen in most countries: integration of malaria services within the broader health system, and decentralisation of responsibility for malaria to subnational levels.

Integration and decentralisation present serious operational and structural challenges to malaria programming.[48,55] Once countries eliminate malaria and enter the prevention of re-establishment phase, there will be pressure to shrink or close the national programme and integrate malaria services into the general health system.[13] Although this decision might be prudent from a resource allocation perspective, full integration presents risks, including the erosion of malaria expertise and the loss of capacity to prevent imported cases from triggering resurgence.[47] Decentralisation poses its own set of challenges, including overwhelming subnational health units with new technical, administrative, and financial responsibilities.[48,56] These two reform processes can be dangerous in the absence of proper planning, delineation of clear roles and responsibilities, establishment of effective accountability arrangements, and ample and ongoing staff training.[48]

Strong management of both the malaria programme and the health sector will be essential to navigate integration or decentralisation while maintaining momentum and effectiveness in the fight against malaria. Improving management capacity at the subnational level might help to mitigate at least some of the common pitfalls associated with decentralisation.[56,57] To counter certain challenges posed by integration, countries might consider maintaining a small, core team to manage domestic malaria issues, such as the one that exists at the US Centers for Disease Control and Prevention. In addition, countries that achieve elimination can serve as a technical resource for other eliminating countries through regional initiatives like the Asia Pacific Malaria Elimination Network (APMEN) or the Elimination 8 (E8), or through bilateral and multilateral agreements, such as the Australia-China-Papua New Guinea Trilateral Malaria Project.[58]

Management and operational opportunities

Managerial and operational requirements for effective programme delivery are numerous. Here, we highlight six issues of particular importance in achieving eradication.

Better data for decision making

On the road to eradication, managers and front-line staff must have access to accurate, granular, and timely data to deploy interventions efficiently and effectively. Incomplete data or data that are primarily used for reporting purposes only can prolong transmission, especially in marginalised communities with a self-perpetuating cycle of inadequate malaria services, underdetection, and under-reporting.[59] The malaria surveillance system and the data it collects serve as the basis for all programme policies, strategies, and implementation activities. Malaria data must inform

the characterisation of geographical foci of transmission and populations at higher risk, guide the response to cases reported from both public and private facilities, and support supply chain management, monitoring of resistance, entomological surveillance, the assessment of programme performance, and more.[47]

Data completeness and quality at the national level is improving with the roll-out of tools such as District Health Information System 2 and other electronic health information systems.[60] Digital platforms and tools make it easier to collect, share, and interpret data, but they are not the entire solution. Policy obstacles remain, for example, in relation to cross-border data sharing. The collection of some data will continue to depend on scarce local expertise, such as in entomological surveillance.[61] Additionally, programmes will need to develop capacity in data analysis and information technology. While expertise and experience, especially at subnational levels, will continue to be invaluable in the interpretation of results, the Commission anticipates a revolution in data collection, analysis, and use in the next decade with profound effects on programme management and effectiveness.

Targeting and tailoring interventions

Data have an essential role in stratification, which in turn facilitates better targeting of interventions. Even in high-burden countries, malaria is heterogeneous: some communities and households have more malaria than others, and some groups of people have more malaria than others. The degree of heterogeneity increases rapidly as malaria transmission approaches elimination levels.[61] Data completeness, and supporting information such as a population census, are essential to detect marginalised communities at high risk, some of which might not be well known to government agencies.

There is no doubt that in lower-burden countries moving towards elimination, malaria programmes have to be highly focused, not just in vector control but also in the active and reactive detection of cases and infections and subsequent responses. What is less clear is the extent to which programmes in higher burden countries should adopt at least a partially targeted response, concentrating resources on places or populations with particular characteristics, even in areas with stable, widespread transmission.[62,63] Rapid improvement in the capture and analysis of real-time geospatial data on cases, intervention coverage, genetic epidemiology, and human behaviour will allow programme managers to evaluate different packages of interventions, levels of coverage, and targeting approaches. This exemplifies the learning-while-doing approach, which we discuss here.

Interventions must be tailored to improve access by target groups. Innovative strategies targeting populations at risk are being adapted to support malaria elimination, such as expanding Integrated Community Case Management (iCCM) to include additional active case detection or providing malaria testing for all ages (panel 2). Targeting and tailoring interventions require not only good data, but adaptive management, which in turn requires local flexibility and discretion in the use of financial and human resources. At the national level, funders should allow for reprogramming and reallocation of resources, while still ensuring financial due diligence.

Prioritising human resources

Deploying sufficient numbers of well trained and motivated staff at all levels is essential for subnational and national malaria elimination. This need is self-evident, but difficult to achieve in many countries because of more pervasive health system challenges. Community health workers (CHWs), including village malaria workers and volunteers, can complement an overstretched health workforce and increase access to basic health services, especially among remote and underserved communities.[73] For countries that rely on CHW programmes, malaria elimination and eradication will require adaptive programming that responds to changing circumstances on the ground. Innovative strategies are being explored, including expanding the scope and remit of CHW activities to support malaria elimination (panel 2).

Policies and procedures for human resources within ministries of health might need to be modified to ensure that malaria programmes will succeed. For example, the common practice of regular transfer of staff away from malaria and into new departments depletes the national malaria programme of expertise and often leaves key posts vacant for long periods. The formulaic allocation of staff numbers to different subnational administrative units might not account for the realities of malaria programme requirements, including the need to adequately staff locations with particularly challenging epidemiologies or large geographic scope. Additionally, prohibiting CHWs from either testing or treating malaria will limit the potential effectiveness of community case management. Human resources policies and procedures need to be carefully reviewed and pragmatically modified to ensure that they are suited to the very specific requirements of malaria elimination.

Incentives

Incentives and the autonomy to use them are an important tool for managers, especially as managers must motivate their workers on the front line to make a special effort to achieve eradication.[49,74] Employees are motivated when their working conditions include a safe and enabling environment, adequate supplies, job security, supportive colleagues, autonomy, and a manageable workload.[75] Similarly, front-line workers benefit from training opportunities and skill development. Creative incentives based on local circumstances can also be leveraged.[76] For example, motivation is improved when programmes promote meaningful engagement with data collection,

Panel 2: Innovative strategies for improving access to quality care

Ensuring access to quality, community-based care is a core element of malaria elimination. However, malaria eradication will require these evidence-based strategies to be adapted to the local context and responsive to changing circumstances. Two examples of such an approach are provided here.

Expanding integrated community case-management activities in Mali

Integrated Community Case Management (iCCM) is a strategy targeted at children, using community health workers (CHWs) to diagnose, treat, refer, and report cases of malaria, pneumonia, and diarrhoea among populations with poor access to facility-based health care.[64] When implemented and managed well, the iCCM model has led to remarkable success: the percent mortality reduction among children younger than 5 years attributable to iCCM after 4 years of implementation was 14% in Democratic Republic of the Congo, 11% in Nigeria, and 6% in Niger.[65] Other benefits conferred by iCCM include increased care-seeking behaviour for fever from CHWs or at local facilities, and reduced care seeking at higher-level facilities which lowers overall costs of care and increases the cost-effectiveness of case management.[66,67]

However, despite their many strengths, iCCM programmes have had major obstacles in achieving national scale, primarily because CHWs in many countries are not provided with adequate support, oversight, or material resources to do their duties or provide high-quality care.[68] In addition, iCCM targeted at children only will have a suboptimal effect on malaria transmission; the model needs to be expanded to include people of all ages to accelerate elimination efforts.

In Mali, the Ministry of Health and the non-governmental organisation (NGO) Muso have collaborated to implement proactive community case management, an expanded approach that includes active detection of febrile cases among all age groups at the household level. CHWs use mobile tools and receive monthly dedicated supervision with real-time performance dashboards. Other features include removal of user fees, primary care infrastructure improvements, and staff capacity building.[69] Studies assessing proactive community case-management efficacy since its 2008 launch show increased access to care and reductions in child mortality. In addition, prevalence of febrile illnesses in children younger than 5 years decreased by 55% over the study period.[70,71] This example suggests that proactive malaria case detection via in-home diagnosis and treatment as part of a larger integrated strategy could be a model for promoting malaria elimination in challenging health settings.

Adapting community-based malaria services to sustain uptake in Burma/Myanmar

In Burma/Myanmar, as in many other endemic countries, the greatest malaria burden is borne by remote communities. The country's health system infrastructure is poor and, until 2011, most remote villages relied on informal health-care providers who do not have the training and expertise necessary to detect and treat malaria.[72] With the support of international donor funds, the public health sector and partner NGOs have increased investments in rural health services, establishing networks of CHWs who provide early diagnosis and treatment for malaria and assist in the distribution of long-lasting insecticide-treated nets at the community level. This approach has helped halve the malaria incidence rate in Burma/Myanmar between 2012 and 2015, from 8·1 to 4·2 cases per 1000 population per year.[72]

However, as incidence declines, a smaller percentage of febrile patients will be diagnosed with malaria, and CHWs will not be able to provide alternative diagnosis or treatment, probably leading to a decline in service uptake. For this reason, the NGO Medical Action Myanmar supported implementation of a basic health-care package among a network of 1335 CHWs between 2011 and 2016. Extended services included the management of diarrhoea and skin and respiratory tract infections, detection and treatment of acute malnutrition, active case finding of suspected tuberculosis, and referral of severe illness to the nearest government hospital. Uptake of malaria-specific services, measured by monthly blood examination rate, was compared before and after expansion of the package. The addition of the basic health-care package was associated with an immediate and sustained increase in blood examination rates, and in every year of the study, incidence of *Plasmodium falciparum* and *Plasmodium vivax* declined (*P falciparum* by an average of 70% and *P vivax* by 64%).[72] In the villages where monitoring continued from January, 2017, to June, 2018, no *P falciparum* cases were detected.[72]

These results show that a community-based service model can dramatically reduce overall malaria incidence and eliminate *P falciparum* malaria from large areas in rural Burma/Myanmar. Expanding the remit of malaria-only CHWs to include general health-care interventions is important to sustain community uptake of malaria services and will improve rural health beyond malaria. This model should be piloted more widely in malaria-endemic countries in Asia and other regions.

tailor strategies to the local context, and are responsive to community-generated ideas.[77] Financial incentives might be considered if used with caution. The withdrawal of salary top-ups can have a negative effect on staff motivation, and income differences can create disharmony.[78] However, financial incentives have shown positive effects, particularly when eradication is near; both the smallpox and Guinea worm eradication programmes implemented cash awards for reporting cases.[79,80]

Active and sustained community participation

For decades, policy and discourse have stressed the importance of community participation as a means to improve health knowledge, service quality, and

health-related outcomes.[74] Few examples of effective and sustained community engagement strategies at scale have been documented for malaria elimination. One exception is the case of subnational elimination in Vanuatu. On the island of Aneityum, early and ongoing community leadership has been crucial for malaria elimination and prevention of re-establishment, and was credited with containing a potential outbreak 10 years after elimination.[81] In 2015, the RBM Partnership called on the malaria community to more effectively involve communities in the design and implementation of malaria interventions and innovations.[7]

The nature of malaria interventions makes community participation especially important. IRS is intrusive and becomes unpopular over time.[82] Bed net distribution must be accompanied by constant efforts to encourage the regular and appropriate use of nets.[83] Mass drug administration requires a high level of community trust in health services and an understanding of the role of asymptomatic infections.[84] Participation will be further challenged by changes in epidemiology associated with decreasing transmission, and declining perceptions of personal risk will hamper the maintenance of community engagement.[74,85] As malaria becomes increasingly concentrated in remote and marginalised population groups, the barriers to participation will become greater and more specific, as has been the case with polio eradication.[86–88] Lessons from polio indicate that an iterative community engagement strategy that uses existing community structures, including community health workers, can increase demand for health services and improve participation, even among mobile populations and those that are hard to reach.[89,90]

Learning by doing

Given the plethora of management and operational challenges, implementation research is essential.[91] So-called learning by doing is a rapid, iterative approach to generating and evaluating local solutions to local problems. A prime example was the development of the ring vaccination strategy to contain smallpox transmission, which transformed the trajectory of smallpox eradication.[92,93] This research model has also enhanced the effect of malaria interventions, such as the adoption of iCCM across much of sub-Saharan Africa and the roll-out of the China 1-3-7 surveillance and response policy.[93,94] In India, two separate pilots in high-endemic areas in the states of Madhya Pradesh and Odisha are being evaluated; lessons learned will inform elimination planning across the country.[59,95]

The Structured Operational Research and Training Initiative (SORT IT), led by the Special Programme for Research and Training in Tropical Diseases (known as TDR), supports countries and institutions to do operational research around their own priorities, build sustainable operational research capacity, and make evidence-based decisions for improving programme performance. Since 2009, the programme has trained more than 700 health workers from 90 countries in a range of public health topics, with over half of SORT IT studies contributing to a change in policy, practice, or both. Since partnering with the Global Malaria Programme in 2014, 28 studies on malaria have been published, 15 in 2018 alone.[96] NGOs and academic institutions have embraced the SORT IT approach, and its adoption in other contexts, such as regional initiatives for malaria elimination, can be expected to improve the capacity of national malaria programme staff to do implementation research.[96]

Leveraging the private sector

To date, the approach to fighting malaria across low-income and middle-income countries has been focused on the role of the public sector, resulting in missed opportunities to engage with the private sector. Private health-care providers have important roles in malaria diagnosis and treatment in many countries. We address the need to ensure adequate stewardship of private providers in section 8 and the financial implication of out-of-pocket payment in section 6. Here, we explore the possibilities for harnessing commercial markets and for outsourcing.

LLIN procurement and distribution

The initial roll-out of bed nets generated much interest in demand-driven approaches to distribution, emphasising their purchase by individual households from local stores and vendors. Voucher systems were introduced in Tanzania and elsewhere to allow poorer households to acquire nets either free of charge or at a greatly subsidised price.[97] In 2007, in response to growing evidence on the personal and community-wide protection offered by LLINs, international targets were expanded to 80% coverage of all populations at risk of malaria. To address market failures that could have caused LLINs to be underprovided, universal coverage was recommended to be pursued primarily through mass procurement and distribution of free LLINs.[98]

The global malaria community has since mounted an unprecedented effort to purchase hundreds of millions of bed nets with international public funds, ship them to endemic countries, and distribute them to households free of charge. As of 2019, 2 billion nets are estimated to have been purchased and distributed at a total cost approaching $11 billion.[99] Still, universal coverage has not been achieved in most countries.[1] The current discourse on global malaria strategy assumes that this massive programme of procurement and distribution of nets will not only continue, but expand to fill the large, unmet need.[100] The realism of this assumption should be explored. Almost all LLIN procurement and distribution is funded by donors, and the willingness of countries to make these investments is untested. Yet, some degree of targeted LLIN coverage is probably required throughout elimination and into the prevention of re-establishment

phase, and as countries transition to complete reliance on domestic resources.

New market analyses and projects investigating the viability of private sector supply chains and demand creation for retail sales of nets are being funded by at least one major international donor.[101] An analysis of the incremental effect of and resource implications for achieving universal coverage is being led by WHO.[102] The Commission recommends that this issue be revisited, both globally and at regional and national levels. What is the appropriate scale and scope of international procurement and distribution? To what extent, where, and how quickly can and should this approach be complemented or replaced by a private market for high-quality LLINs, subsidised when appropriate for poorer families or populations at higher risk of malaria? This shift from supply side to demand side might be especially pressing in countries nearing elimination and countries losing eligibility for donor financing.

Outsourcing

In most countries, the national malaria programme within the ministry of health seeks to fund and deliver all or most malaria services and interventions. However, in many malaria endemic countries government capacity limits the reach and quality of those services. Interest is growing in public-private partnerships in health care and there are many instances where contracting out certain services has improved access, quality, and accountability at similar or lower cost than the previous arrangements.[103] Much potential exists for public-private partnerships and outsourcing in malaria. Although the Global Fund and PMI have embraced this approach, governments are typically less enthusiastic and might terminate outsourcing when donor funds are withdrawn.

IRS is highly effective when well executed, but is a complex task requiring skilled management of human resources, commodities, and logistics.[104] In some high-burden countries, a range of IRS activities are contracted out by PMI to international non-governmental organisations (NGOs).[105] A more sustainable approach, with greater benefit to the local economy, is for the ministry of health to contract with local for-profit or not-for-profit entities to provide IRS services.

Resources from the Global Fund are often used to contract with NGOs, faith-based health systems, and others to expand the provision of malaria services, including diagnosis and treatment.[106] In some places, NGOs provide services to communities where governments either cannot or do not go, or where community mistrust of public services would limit their effectiveness.[107] In other settings, private partners are contracted to expand the volume and quality of malaria diagnosis, treatment, and prevention. When the Global Fund withdraws, these contractual arrangements are at risk of ending. In the Greater Mekong Subregion, academia, civil society, and domestic and international NGOs work with remote communities and mobile and migrant populations to eliminate malaria.[108] That the national malaria programmes could replicate these services or engender the community trust built up by private partners is unlikely. Continuing or expanding the outsourcing of malaria services might be essential for malaria elimination in some countries, and desirable in most.

The Commission recommends the vigorous exploration of outsourcing IRS and other services to local contractors, especially in countries with a strong private sector and in countries transitioning away from donor finance. Such arrangements require governments to manage contracts effectively, set and monitor targets, and use penalty clauses to incentivise performance. New outsourcing arrangements should be closely monitored to assess quality, coverage, and cost-effectiveness.

Complex emergencies

Complex emergencies such as war, political and economic instability, mass migration, and natural disasters can have a profound effect on the health-care system.[109] Depending on the strength and flexibility of the malaria programme, these events can disrupt malaria service delivery and lead to increases in malaria cases and deaths.

An example of this situation is in Venezuela, which is currently facing its worst malaria epidemic in history.[110] Since roughly 2012, the country has been challenged by economic collapse and political instability, with rapidly declining GDP and soaring inflation. Malaria has simultaneously resurged due to stock-outs of diagnostics and drugs, interruptions to surveillance and vector-control activities, and an overall deterioration of the health system.[111] Population movement in and out of highly endemic parts of the country has facilitated the spread of transmission to areas previously declared malaria-free, and malaria cases have spilled over into neighbouring Brazil, Colombia, and Guyana.[110,111] In 2017, Venezuela had the highest case rate per population at risk in the Americas and accounted for 84% of the increase in malaria cases in the region.[1]

A malaria programme's ability to respond and adapt to potential disruptions is dependent on the overall strength and resilience of the larger health system, as well as the nature of the crisis. Frameworks and plans for emergency preparedness and recovery can be incorporated into malaria elimination strategies to guide response in the event of acute crises such as natural disasters or disease outbreaks.[112–114] More protracted crises such as armed conflict, economic instability, or political upheaval might require the development of alternative delivery strategies, novel interventions, or both, if standard approaches are no longer viable. In the Central African Republic, a programme was established to provide prompt diagnosis and treatment of malaria in the context of frequent population displacement.[115] During the 30-year civil war in Sri Lanka, the malaria

programme formed partnerships with NGOs to maintain malaria prevention, case management, and surveillance in conflict districts.[116,117] Once the civil war came to an end, the country achieved national elimination within 3 years.[117,118]

Prioritising implementation research in complex emergencies now can help inform strategies to avoid unnecessary malaria cases and deaths in future events and might also mitigate delays to eradication in the final stages. Similarly, strategies that effectively address the challenges presented by human mobility, border malaria, hard-to-reach populations, and outdoor transmission in more stable contexts can be adapted to emergency settings. Regional and cross-border initiatives can also have an important role during these events.

The three endgames

For malaria eradication, there are three endgames: the country elimination endgame, the regional elimination endgame, and the global eradication endgame. We discuss these final stages briefly here.

Over 100 countries have already eliminated malaria and passed into the prevention of re-establishment phase, and several others are due to eliminate in the next few years.[15,119] The key requirements for national elimination are well described in WHO publications and elsewhere in the literature, and we highlighted some major operational considerations earlier in this section.[6,13,86,120,121] However, relatively little guidance or documented experience exists on the prevention of re-establishment in different epidemiological and economic contexts. This situation is concerning. On the road to eradication, prevention of re-establishment is at least as important as elimination. If resurgence occurs in countries that have previously eliminated malaria, the political and financial momentum behind eradication will be seriously undermined.

The risks of resurgence and re-establishment in countries that have eliminated in the past decade are much higher now than previously. The countries that eliminated in the 1950s and 1960s were mainly temperate, with low and often seasonal transmission. Many were also high-income countries, with well developed health systems and a strong capacity to implement effective public health programmes. By contrast, current and future eliminators are mainly in tropical areas, with high receptivity. Increasingly, and by 2030 entirely, these countries will be low-income and lower-middle-income. This reality combined with the exponential growth in international movement of people, including from endemic countries (such as India and Indonesia), to countries that have eliminated (such as Sri Lanka and Malaysia), creates a situation of unique jeopardy. Some low-income countries that achieve elimination with support from the Global Fund are unlikely to be able to sustain the surveillance and response systems necessary to prevent re-establishment without external assistance.

Countries must develop effective strategies and financial plans for the prevention of re-establishment before they eliminate. Important technical and operational questions remain, including when and how to scale back malaria interventions, such as vector control, and what level of surveillance is necessary in different places. Malaysia has developed a system to address these questions in an efficient and locally appropriate manner. The country reported zero indigenous human malaria cases for the first time in 2018 but is at risk of re-establishment due to its proximity to high-burden countries.[46] The malaria programme began stratifying foci in 2016 on the basis of vulnerability and receptivity using a web-based application, targeting interventions and resources according to risk (Rose NBM and Jenarun BJ, Ministry of Health [Malaysia], personal communication). Although countries approaching elimination can learn from the experiences of new eliminators like Malaysia, WHO and other technical agencies must be proactive in providing guidance on prevention of re-establishment. Major funders, especially the Global Fund, should be willing to continue to co-finance prevention of re-establishment in vulnerable settings where resurgence will have substantial regional and global consequences (section 6).

The next major endgame is the achievement of regional elimination. Every region will reach a point in which a small number of countries struggle to eliminate while all other countries in the region are preventing re-establishment. At this stage, a collective interest exists in bringing maximum financial and technical support to the last endemic countries to help them reach elimination and thereby achieve freedom from malaria for the whole region.[122] Taking the example of the Asia Pacific Leaders Malaria Alliance (APLMA) countries, India, eastern Indonesia, and Papua New Guinea will struggle to meet the elimination deadline of 2030 on the basis of current trajectories.[1] Regional support, such as peer country technical assistance, should be increasingly focused on these countries.

Finally, and most challengingly, is the global eradication endgame. This endgame is the battle in the most difficult places to treat the last human *Plasmodium* infections. Much can be learnt from smallpox and polio in this regard.[87,123] The main message is to identify, now, those countries which will prove most problematic in 2030 and 2050 and to invest in creating a pathway to successful elimination there. In section 2, we map the places where malaria is likely to persist in 2030 and 2050 despite our best efforts. These projections highlight a small number of countries, including Democratic Republic of the Congo, Mozambique, and Nigeria, that, with strong international support, will need to identify innovative ways to accelerate the decline of malaria and achieve elimination on or before the target date. One approach, especially in large countries such as Nigeria, is to select several subnational units, perhaps states, for intensified efforts with the goal of early elimination.[124] These

locations would be the testing grounds for innovative approaches and would show what is possible in very challenging circumstances. Emergency Operations Centers (EOCs), centralised command posts to manage and coordinate public health threats, might be equally advantageous in the endgame stages for malaria eradication as they have been for polio.[125] A second challenge for the global endgame is those countries which (unpredictably and for reasons that are political, economic, and social rather than biological) fall behind their elimination schedule. Global attention and support will be required to assist these countries in achieving elimination. Ensuring the necessary systems for elimination are in place as early as possible, such as robust surveillance and response, will increase the likelihood of success and shorten the final stage of malaria eradication.

Section 4: biological challenges to eradication

Humans, *Anopheles* mosquitoes, and *Plasmodium* parasites have coexisted for tens of thousands of years, evolving and adapting together. The ancient evolutionary association between human beings and *Plasmodium* is manifested by the existence of common red blood cell genetic disorders, thought to have evolved to provide partial protection against fatal malaria.[126] Malaria parasites and vectors also evolve, sometimes quickly, to evade the interventions used against them. The fight against malaria will always be challenged by this so-called evolutionary arms race, requiring ongoing investment and innovation that can only stop once all four species of human malaria parasites are eradicated.

This section examines the biological challenges that present the most serious threats to eradication, including parasite challenges, vector challenges, and endgame challenges. These challenges can be addressed through research, innovation, and the development of new operational and technical tools, as described in sections 3 and 5. We also examine the potential threat of zoonotic spillover and its implications for a malaria eradication goal, which does not include simian species of malaria.

Parasite challenges

Malaria eradication requires the extinction of four human malaria parasite species, *P falciparum*, *P vivax*, *P ovale*, and *P malariae*. While *P falciparum* malaria now causes the most malaria sickness and death, followed by *P vivax*, the distribution and relative importance of these species are changing, and will continue to change as progress is made towards eradication.[14] Parasite-specific challenges to eradication include the predictable and repeated evolution of drug resistance, and limitations in our ability to detect low-density and latent infections.

Drug resistance

In the past 60 years, three waves of *P falciparum* drug resistance have occurred. From 1957 to the late 1970s, resistance to chloroquine spread from southeast Asia to most parts of the world.[127] Sulfadoxine-pyrimethamine was introduced in 1981, and again resistance spread from southeast Asia to cover most of the malaria-endemic world by the early 2000s, contributing to an increase in deaths from *P falciparum* malaria.[128] An urgent search for new antimalarial drugs led to the development of ACTs.[129] First deployed in southeast Asia in the late 1990s, ACTs are now the first-line treatment for uncomplicated *P falciparum* malaria in nearly all countries.[130]

Resistance to artemisinin and its partner drugs is now common and increasing in the Greater Mekong Subregion, prompting an emergency response by WHO.[131,132] In keeping with historical trends, artemisinin resistance is expected to spread to or emerge in south Asia, Africa, and the Americas. When drug resistance first appears in new regions, it usually undergoes a slow emergence over several years, followed by rapid onset of widespread resistance. Africa and Latin America are now in the early stages of this process, with artemisinin-resistant parasites detected in Guyana in 2010 and Equatorial Guinea in 2012.[133,134] Drug resistance is also a problem for *P vivax* malaria; chloroquine-resistant *P vivax* is widespread in Asia, Africa, and the Americas.[135] Resistance has not yet been documented in *P ovale* and *P malariae*, but it can be anticipated if their distribution and relative frequency increase. Until eradication is achieved, the response to drug resistance must be vigorous and continuous.

Detection

Malaria often presents as a non-specific febrile illness, and confirmed diagnosis is important for effective treatment and accurate surveillance. Current diagnostic methods—microscopy and RDTs—are generally adequate for routine malaria case management, although improvements to RDTs are necessary to increase diagnostic accuracy and sensitivity, and strengthen active surveillance as an elimination strategy.

Notably, most of the current RDTs for *P falciparum* malaria detect antigens to histidine-rich proteins 2 and 3 (PfHRP-2 and PfHRP-3). Following nearly 20 years of widespread RDT use, *P falciparum* parasites have evolved to delete genes that express PfHRP-2 and PfHRP-3, thereby escaping detection. These gene deletions are increasing in frequency and have been reported from countries in the Americas and the Horn of Africa. Diagnostic tests that do not rely on the detection of PfHRP-2 and PfHRP-3 are urgently needed.[136]

In addition to presenting as febrile illness, all malaria parasite species can cause afebrile infections that are of such low density in the blood that they are undetectable by microscopy and RDTs.[137] Furthermore, afebrile parasite carriers typically do not feel ill and do not seek treatment. These undetected low-density infections probably have a major role in sustaining transmission. Highly sensitive tests are needed, alongside active

surveillance strategies to find infected individuals who are not sick.[138]

Improved RDTs for *P vivax* malaria are also necessary because current products are hampered by detection limits that are approximately 25-fold lower than *P falciparum* RDTs.[139] More sensitive *P vivax* RDTs will accelerate malaria elimination efforts in the Americas and Asia-Pacific (figure 3), and might also be essential for eradication efforts in Africa. In Africa, most individuals have acquired partial genetic resistance to *P vivax* infection through a red blood cell adaptation called Duffy antigen negativity.[126] However, evidence suggests that *P vivax* malaria in Africa is more common than previously thought, often occurring at low densities in individuals who are negative for Duffy antigen.[140] The eradication endgame will therefore require highly sensitive RDTs that can detect afebrile, low-density *P vivax* infections.[141]

The persistent liver forms of *P vivax* and *P ovale*, known as hypnozoites, are responsible for relapsing infections and are not affected by asexual blood stage antimalarials. Because their density in the liver is very low and they are metabolically dormant,[142] diagnostics specifically detecting hypnozoites are unlikely to ever be a product development priority. Instead, presumptive treatment with drugs that target hypnozoites is a more viable solution to this challenge, which we discuss in more detail in section 5.[14]

Vector-related challenges

Approximately 40 important species of *Anopheles* are capable of transmitting malaria, each of which is distinct in its efficiency as a malaria vector, its ability to survive and propagate in various environments, and its preferences for breeding and biting.[143,144] In any given location, malaria transmission is usually driven by a few primary vector species that should be targeted according to behaviour.[144] As progress towards eradication proceeds, vector species composition and distribution will change in response to the interventions used against them, driving shifts in transmission patterns.[14] Major vector-related challenges to eradication include resistance to insecticides and outdoor transmission.

Insecticide resistance

Over the past 60 years, the evolution of insecticide resistance has largely paralleled that of drug resistance. The first insecticide widely used for malaria, dichlorodiphenyltrichloroethane (known as DDT), was discovered in 1939.[145] Heavy agricultural use drove the emergence of resistance, first documented in 1951, followed by its subsequent spread.[146,147] The next major class of insecticides deployed were the pyrethroids.[148] Widely used in IRS and LLINs since the 1990s, pyrethroid resistance has now been observed in Africa, Asia, and the Americas.[149] The constant threat of resistance will require ongoing investment in insecticide development, rigorous surveillance, and the implementation of resistance mitigation strategies until eradication is achieved.

Outdoor transmission

Outdoor biting and resting happens all over the world, and current interventions are limited in their ability to target this mode of transmission, threatening regional elimination efforts in Asia and the Americas where most vectors primarily feed outdoors.[150] The primary vectors in Africa are traditionally indoor biting, but are now increasingly biting and resting outdoors to avoid contact with LLINs and IRS, a phenomenon known as behavioural resistance.[151,152] Behavioural resistance among primary vectors in Africa is expected to increase. In addition, several secondary vectors on the continent are outdoor feeders.[153] Eradication will require new approaches and products that target outdoor transmission.

Endgame challenges

To accelerate malaria eradication, the malaria community must prepare now for future challenges. Polio eradication teaches us that focusing on especially challenging locations early has potential to prevent a long, drawn out, and extremely expensive endgame. While exact endgame locations are unpredictable, they will probably include

Panel 3: The potential threat of urban malaria

Malaria is generally characterised as a rural disease, and in much of the world nowadays, this assessment is accurate.[154] India is the major exception. In 2017, 71% of malaria cases in the state of Tamil Nadu (population 79 million) occurred in the capital city, Chennai (population 7 million).[155] The main malaria vector in India, *Anopheles stephensi*, is particularly suited for Indian urban environments that provide ideal breeding habitats: water storage containers, wells, gutters, and construction sites. Elimination of malaria transmission in urban settings poses unique challenges and requires strategies and interventions beyond those typically deployed in rural settings. In urban India, a priority intervention is the improvement of municipal water supply infrastructure, reducing the need for rooftop storage of water.[154]

Beyond India, the threat of urban malaria is unclear. The countries with the highest malaria burden (table 1) have rapid urban population growth rates of 3–5% per year, and by 2050, the populations of Cameroon, Equatorial Guinea, Ghana, and Nigeria are expected to be at least 70% urban.[156] Although the projections in section 2 suggest that urbanisation will decrease the burden of malaria, potential also exists for urban malaria to increase depending on the *Anopheles* vectors present and their ability to survive in changing urban environments.[157] *An stephensi* is found throughout Asia and has also now been identified in Djibouti and Ethiopia; further spread of this vector in Africa might lead to greater challenges as urbanisation increases.[158-160] Worryingly, traditionally rural vectors in Africa might already be adapting to urbanisation. *An funestus* has shown an ability to survive in peri-urban environments in Uganda, and *Anopheles gambiae* sensu stricto mosquitoes, which typically prefer to breed in clean water, have shown an ability to adapt to polluted water in urban areas of Côte D'Ivoire, Ghana, Kenya, and Nigeria.[157]

Close monitoring of vector behaviour and geographical distribution will be essential in the coming decades, particularly in areas undergoing urbanisation. If malaria transmission emerges in urban settings, programmes will need to rapidly deploy interventions that reduce breeding sites and reach individuals at risk in densely populated areas.

areas in Africa currently facing exceptionally high levels of transmission, together with countries challenged by conflict, instability, or natural disaster. Urban malaria is another potential endgame challenge (panel 3).

High transmission of malaria occurs across a wide belt of equatorial Africa, from southern Senegal in the northwest, to Mozambique in the southeast (figure 3). In these locations, the number of infective bites per person per year are commonly around 100–150 and, in some settings, exceed 400.[161] Reducing transmission will require the relentless implementation of multiple interventions, with particular emphasis on addressing the highly abundant and competent vectors in these regions: *Anopheles gambiae* sensu stricto (ss), *Anopheles coluzzi*, *Anopheles funestus*, and *Anopheles arabiensis*.[162] Although the precise combination of interventions required for malaria elimination in these settings is unclear, research in Uganda offers promise, showing the ability to reduce high levels of transmission almost to zero in the presence of three of these vector species (panel 4).

There is an urgent need for more evidence on transmission reduction strategies in various high-transmission settings, alongside the development of endgame tools specifically suited for this purpose. High-burden countries should no longer focus primarily on mortality reduction, but also on the radical and sustainable reduction of transmission. This focus will foster alignment with eradication goals, and will present multiple opportunities for operational research to determine the optimal management strategies and combinations of interventions required to suppress transmission in the most challenging circumstances.

Panel 4: Overcoming holoendemic malaria in Uganda

Uganda has one of the highest malaria burdens in the world (table 1). Malaria transmission occurs throughout the year in 95% of the country, and in the remaining highland areas, transmission is unstable and epidemic-prone. *Anopheles gambiae* sensu stricto is the dominant malaria vector species in most places; other common vectors are *Anopheles arabiensis* and *Anopheles funestus*. Although all four species of human malaria are present, *Plasmodium falciparum* is responsible for over 90% of reported cases.[163] Artemisinin-based combination therapy (ACT) is the first-line treatment for uncomplicated malaria in Uganda.

Tororo District is a high-endemic, rural area in eastern Uganda, with an estimated entomological inoculation rate of 310 infective bites per person per year in 2011–12.[164] The Government of Uganda has implemented several population-level malaria control interventions in this district, including long-lasting insecticide-treated net (LLIN) distribution campaigns in 2013 and 2017, and indoor residual spraying (IRS) in 2014. The first three rounds of IRS were done every 6 months using the carbamate insecticide bendiocarb.[165] The next three rounds of IRS were done every 12 months using Actellic (Syngenta; Rosental, Switzerland), a long-lasting organophosphate.

Researchers have been studying malaria in cohorts of young children in Tororo District since 2007.[166–169] Children enrolled in these studies were given LLINs and free care 7 days a week at dedicated study clinics, and routine evaluations were done every 1–3 months regardless of symptoms, including the detection of submicroscopic parasitaemia using molecular techniques. In addition, a group of young children were randomised to receive intermittent preventive treatment with standard doses of dihydroartemisinin-piperaquine, given monthly between 6 months and 2 years of age.[170]

From August, 2007, through January, 2015, the burden of malaria was consistently very high in Tororo, with young children having an average of five episodes of malaria per year and a parasite prevalence of 35%.* After the first four rounds of IRS, the incidence of malaria was reduced by 92% and parasite prevalence by 93%.* The addition of monthly dihydroartemisinin-piperaquine administration led to near-complete elimination of both symptomatic malaria and afebrile parasitaemia, and continuation of IRS through rounds five and six led to further reductions of 99% in malaria incidence and 98% parasite prevalence.* These data suggest that a combination of case management using ACTs, universal LLIN distribution, and IRS can dramatically reduce the burden of malaria among young children in high-transmission settings. These declines might be further accelerated by population-wide chemoprevention strategies.*

*Dorsey G, University of California San Francisco, personal communication.

Zoonotic spillover

The definition of malaria eradication is confined to human malaria parasites, yet some species of simian malaria can infect humans, a phenomenon known as zoonotic spillover. While human-to-human transmission of these species in nature has not been proven, the potential for such transmission to occur has implications for eradication efforts.

To become a human malaria parasite, simian malaria species must undergo three stages of evolution: (1) parasites are transmissible within the animal reservoir; (2) parasites are transmissible naturally from animals to humans; and (3) parasites are transmissible among humans, thereby becoming human malaria parasites.[171] Currently, four species of simian malaria are thought to be at stage 2 of this pathway: *P knowlesi* and *Plasmodium cynomolgi* in southeast Asia and *Plasmodium brasilianum* and *Plasmodium simium* in South America.[172] Among these species, *P knowlesi* malaria is by far the most prevalent, and presents the most imminent risk of becoming a human malaria parasite; although difficult to prove, human-to-human transmission might have already occurred (panel 5). If any species of simian malaria has proven human-to-human transmission, the malaria community will need to then include this species in eradication targets.

For any species of simian malaria, prevention of human-to-human transmission depends on the same combination of vector and parasite interventions used to eradicate the four human species. However, true eradication would require the extermination of the parasite reservoir in wild monkeys, and overcoming this challenge will probably require game-changing technologies. Thus, ongoing measures to detect, treat, and reduce transmission will be required. This problem will be limited by the geographical distribution of the particular monkey hosts and will primarily affect humans who live or work in close proximity to these hosts. In these settings, we anticipate that most transmission will remain monkey-to-monkey, followed by monkey-to-human, human-to-human, and lastly human-to-monkey. *P knowlesi* in humans is likely to be a

challenge only in countries with substantial populations of long-tailed and pig-tailed macaques and competent mosquito vectors, and primarily among people who live or work near or in forests, or in areas that have been colonised by monkeys driven to new habitats and behaviours by deforestation. We see no danger of *P knowlesi* beyond southeast Asia. Furthermore, given that the dominant reservoir of these parasites is in monkeys with no exposure to anti-malaria drugs, the evolution of drug resistance is unlikely.

Section 5: innovations and new tools

Innovations and new tools are essential for malaria eradication by 2050. To warrant their development and deployment, innovations must overcome the operational and biological challenges noted in sections 3 and 4. New tools will be especially valuable if they improve surveillance, counter drug and insecticide resistance, have long durations of efficacy, and do not require difficult or protracted compliance by individuals or households. Particular emphasis should be given to the identification and development of endgame tools that can reduce malaria burden in the highest transmission areas or prevent re-establishment. Interventions from the malaria toolbox must always be used in combinations that are tailored to local epidemiological and social contexts.

Here, we examine the innovation pipeline, reviewing the areas that received the most funding in 2018, and identifying additional innovations that are attracting interest. Within these areas, we identify priorities that are essential for addressing the major challenges to eradication, and discuss the implications for malaria research and development funding allocations.[181] A comprehensive set of research and development recommendations for malaria elimination and eradication were published in 2011 and updated in 2017 by the Malaria Eradication Research Agenda.[142,182]

Information technology

The global information technology revolution can greatly accelerate malaria eradication. Smartphones and powerful computers are widely available, and access to the internet is increasing. Huge amounts of geospatial data from satellites and other sources are readily accessible, providing unprecedented levels of information on where people live, how they are connected, and to which services they have access. Powerful software applications can be quickly developed and deployed. National malaria programmes and ministries of health are beginning to make use of these technologies, which can enable front-line health workers to access and interact with data, facilitate community participation, improve programme management, and allow healthcare providers—including private providers—to report malaria cases in real time. These technologies, strategically applied, can facilitate a transformation in the data-driven design, management, and evaluation of malaria programmes by the mid-2020s. In addition, the unique ability of social media to propagate information about malaria and to stimulate action by individuals and communities remains largely untapped.

Data hubs

The power of data to accelerate malaria eradication depends on their quality and prompt and widespread availability through national or regional data hubs. The timely acquisition of accurate and complete data can improve programme management at the national and subnational levels and enable strategic decision making at the regional and global levels. These developments can encourage accountability at all levels, track progress to eradication, and enable global and regional leaders to facilitate cross-border collaborations, initiate outbreak responses, expedite regulatory processes, and provide surge funding when necessary.

Panel 5: Zoonotic knowlesi malaria

Human infections with simian malaria parasites were thought to be extremely rare until a large number of human *Plasmodium knowlesi* infections were reported in 2004 in Sarawak, Malaysian Borneo.[173] Cases have since been reported in Brunei, Cambodia, Indonesia, Laos, Burma/Myanmar, the Philippines, Singapore, Thailand, Vietnam, and in the Andaman and Nicobar islands of India, although Malaysia has reported the highest *P knowlesi* incidence to date.[174–176] Despite achieving zero transmission of human malaria, Malaysia reported 4131 *P knowlesi* cases in 2018.[46]

Mosquitoes belonging to the *Anopheles leucosphyrus* group are the main malaria vectors in Peninsular Malaysia, Malaysian Borneo, and Vietnam. These mosquitoes are forest-dwelling and primarily feed on monkeys, although they are also attracted to humans in the outdoors.[177] *Macaca fascicularis* (long-tailed macaques) and *Macaca nemestrina* (pig-tailed macaques) are the most common non-human primates in southeast Asia, and the main natural hosts for *P knowlesi*.[177] *P knowlesi* has also been identified in banded leaf monkeys (*Presbytis melalophos*) in Peninsular Malaysia and in a dusky leaf monkey (*Trachypithecus obscurus*) in Thailand.[174]

The true prevalence of *P knowlesi* malaria in southeast Asia is largely unknown due to diagnostic challenges. When using microscopy, the early blood stages of *P knowlesi* resemble those of *P falciparum,* while all other stages are similar to *P malariae*.[173] Malaria rapid diagnostic tests have poor sensitivity to *P knowlesi* malaria, and evidence exists of misdiagnosis as *P falciparum*.[178,179] Currently, molecular detection methods are necessary to ensure the accurate identification of *P knowlesi*, but these assays are not routinely used in rural areas.[174]

Most infected individuals are adults who spend time in or near forests. Disease outcomes are variable, ranging from low-density, afebrile infections to life-threatening illness. *P knowlesi* infections can be treated effectively with ACTs or chloroquine. Because LLINs are not effective against forest-dwelling *An leucosphyrus* vectors, personal protection from being bitten while outdoors and chemoprophylaxis are the best options for prevention.[174]

P knowlesi malaria has the potential to become a confirmed species of human malaria infection in the near future. Human-to-human transmission of *P knowlesi* was shown under experimental conditions in the 1960s using *Anopheles balabacensis*, the main vector of human malaria in Sabah, Malaysian Borneo.[180] Human-to-human transmission in natural settings might already occur, but this hypothesis is difficult to prove since human *P knowlesi* infections happen in areas where macaques are common.

Some countries already have reasonably accurate and timely data but many do not, and most countries do not make full use of available data to support programme management. Prompt and transparent reporting by countries should be encouraged by the two big funders, the Global Fund and PMI, the latter of which is currently supporting quarterly reporting in its 24 focus countries. Once collected, a wide range of data should be quickly shared through data hubs with standardised rules and structures. Several of these hubs can probably be established by 2025. All partners have an important role in encouraging data sharing and transparency, ensuring interoperability, and creating quality-control mechanisms.

The establishment of a single global malaria data repository should also be considered. Although the details of its design, hosting, operations, and launch timing are matters for deliberation by experts, a global data hub will probably be essential for the final stages of eradication. In these end stages, the inclusion of molecular surveillance data at high geospatial resolution will facilitate the implementation of rapid, tailored responses to address persisting or emerging pockets of transmission (panel 6).

Panel 6: Molecular diagnosis and surveillance

Since the early 2000s, rapid advances in molecular biology have enabled the development of new techniques that amplify, detect, and characterise the DNA of malaria parasites and vectors. These techniques provide high-resolution insight into the specific epidemiological and entomological challenges in any given location, thereby enhancing precision in the design and deployment of malaria interventions.[183,184] Molecular diagnosis and surveillance have proven essential for the final stages of polio eradication and will probably have a similar role for malaria.[185]

Current applications of molecular diagnosis and surveillance

- Detecting and tracking the emergence and geographical distribution of drug and insecticide resistance to ensure appropriate and timely response[186,187]
- Determining the prevalence of low-density, afebrile infections and identifying the primary vector species responsible for transmission to optimise intervention selection[188,189]
- Ensuring the accurate diagnosis of *Plasmodium knowlesi* malaria, which is otherwise routinely mistaken for either *Plasmodium falciparum* or *Plasmodium malariae* using microscopy and rapid diagnostic tests[190]

Future applications of molecular surveillance that might be essential for malaria eradication

- Tracking progress to eradication, including the ability to monitor the prevalence of *Plasmodium vivax* and *Plasmodiun ovale* infections by distinguishing re-infection from homologous relapse[191]
- Mapping the flow of specific parasite strains to understand sources of transmission, such that malaria hotspots and sources of importation can be rapidly targeted[183]
- Monitoring the effect of interventions in locations with persistent malaria transmission to characterise challenges and guide the deployment of targeted response strategies that eliminate remaining infections[192]
- Preventing malaria re-establishment in locations with high malariogenic potential, a threat that will inevitably grow as eradication nears

The development of molecular methods is a major priority. In the coming years, further progress and improvements to sequencing, analytical methods, sampling frameworks, and field-friendly technology can be expected to make an important contribution to malaria eradication.

Diagnostics

Malaria eradication requires the identification of low-density, afebrile infections caused by all species of human malaria, including the detection of *P falciparum* without *pfhrp2* and *pfhrp3* genes. Operationally, malaria diagnostic tests will be used more widely if they do not require a finger-prick blood sample, particularly in settings where community health workers or informal private providers have a major role in diagnosis and treatment. Fever panels that can detect other diseases will also be useful, especially in areas where malaria is no longer common.

The malaria diagnostics pipeline, supported by the Foundation for Innovative Diagnostics, is mainly focused on developing highly sensitive field-friendly tests.[193] Two new RDTs are expected to become available in around 2021. The first will detect *P falciparum* with and without *pfhrp2* and *pfhrp3* genes, and the second will offer improved sensitivity for the detection of *P vivax* infections, both of which align with eradication requirements. Ideally, these tests will function well across various settings and populations, and will be able to detect low-density, afebrile infections, as well as malaria infection in pregnancy.[194,195] In the future, as parasite distributions change, ultrasensitive RDTs that can differentiate between all species of malaria parasites that infect humans will probably be necessary. If their development begins shortly, such RDTs can be expected to become available in the 2026–28 timeframe.

Medicines

Eradication will require staying ahead of drug resistance, eliminating all parasite lifecycle stages including hypnozoites, and deploying medicines at the population level to prevent and treat infection and reduce transmission. In addition, medicines will be easier to use if they require fewer doses over fewer days. Prospects for overcoming these challenges are high, and the malaria drug pipeline, overseen by Medicines for Malaria Venture, has never been more promising.[196]

Overcoming resistance

New medicines with novel mechanisms of action are essential for overcoming drug resistance. As of March, 2019, the malaria drug pipeline had five compounds in phase 2 clinical studies and three compounds in phase 1 studies.[196] A new drug combination might become available by 2024 or soon thereafter.

In addition to strengthening drug discovery and development, changing how drugs are used can prolong the lifetime of existing antimalarial drugs. The early detection of drug resistance through molecular surveillance can trigger mitigation strategies that involve changing the drugs to which parasite populations are exposed by rotating drugs, using multiple first-line

therapies, and using combination therapies.[197] Triple ACTs are in development, and are expected to be available between 2020 and 2024.[198]

Killing hypnozoites

The treatment of hypnozoites is challenging but possible. Tafenoquine, a drug approved by the US Food and Drug Administration in 2018 for this indication, is expected to greatly assist the regional elimination of *P vivax* malaria from Asia-Pacific and the Americas by 2030, and the global eradication of *P vivax* and *P ovale* malaria by 2050.[199] Given in a single dose, tafenoquine replaces the previous regimen of 7–14 days of primaquine. However, like primaquine, tafenoquine is an 8-aminoquinoline that can cause severe haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency, a genetic condition that is common in malaria-endemic countries.[126] Two new point-of-care quantitative G6PD tests are expected to facilitate tafenoquine deployment and inform alternative regimens if necessary.[200–202] Concurrent with the roll-out of tafenoquine, drug discovery research for hypnozoite clearance must continue, targeting products that are safe for use in all individuals.

Simplifying regimens

Short drug regimens with few pills lead to better compliance, improving treatment outcomes and decreasing opportunities to fuel drug resistance. In 2007, Medicines for Malaria Venture described the ideal treatment for malaria as single exposure radical cure and prophylaxis, where a single pill could target all lifecycle stages of all human malaria parasites.[203] Although research has since revealed that this ideal treatment is unlikely to be achieved, Medicines for Malaria Venture continues to support the development of new drugs and formulations that require fewer doses over fewer days. Tafenoquine represents a notable success, and five compounds in the pipeline aim to achieve single-dose efficacy.[196,203] Simplified regimens will greatly improve the clinical, preventive, and presumptive use of medicines to fight malaria and are a high priority for eradication.

Drug deployment strategies

Antimalarial medicines are not only useful for clinical case management, but can be used in population-scale interventions to accelerate subnational and national elimination. These interventions include mass drug administration, seasonal malaria chemoprevention, intermittent preventive therapy for children (panel 4) and pregnant women, focal drug administration, and chemoprophylaxis.[204] We anticipate that these strategies will become more widely used as evidence is accumulated to inform their optimal deployment.

Endectocides

Endectocides are antiparasitic drugs that are active against both endoparasites and ectoparasites, including mosquitoes. Widely used for onchocerciasis and lymphatic filariasis, ivermectin is an endectocide that can kill mosquitoes that feed on anyone who has taken the drug in the past 28 days.[205] Decades of ivermectin use show it to be extremely safe, with new evidence indicating safety at the higher doses required to kill mosquitoes.[205,206] Due to its promising safety profile and additive value to population-level strategies for malaria, ivermectin presents a low-risk investment that should be pursued. Pending further supportive evidence, registration of ivermectin as an endectocide is expected around 2024.

Monoclonal antibodies

Monoclonal antibodies are injectable proteins that can offer longer durations of protection than medicines and are potentially safe for use during pregnancy.[207] Two monoclonal antibodies are in early preclinical stages of development, each with a one in four chance of completing the development pipeline by around 2026.[208] We recommend their continued development. If 3 months of efficacy can be achieved with minimal cold chain requirements, monoclonal antibodies could reduce dosing during seasonal malaria chemoprevention three-fold. Furthermore, these products could serve as endgame tools, potentially reducing transmission in the highest endemic locations in Africa, preventing infection among hard-to-reach populations, and preventing re-establishment of malaria where elimination has been achieved. Safety in pregnancy would offer further benefits, including increased levels of coverage in population-wide drug-based strategies.

Vaccines

In highly endemic areas of Africa, children who survive constant *P falciparum* malaria infections develop substantial protection against death, moderate protection against illness, and little or no protection against infection.[209] This state is short-lived, waning quickly once regular exposure to infection ceases. Malaria vaccine development is limited by this biology, constraining the ability to achieve long-term protection.[209] Nonetheless, a malaria vaccine has been the holy grail of malariologists since the 1970s, in the hope that a potent adjuvant could stimulate a stronger immune response.[210]

50 years on, one malaria vaccine has been successfully developed. In 2015, the RTS,S/AS01 vaccine was approved by the European Medicines Agency for the prevention of *P falciparum* in young children.[211] This vaccine induces an immune response that is boosted by a powerful adjuvant, and by the fusion of the circumsporozoite protein to hepatitis B surface antigen.[212,213] Results from phase 3 trials in Africa show that three doses given over 18 months provided 46% protection from clinical malaria in children aged 5–17 months, with a fourth booster dose given at 20 months providing 36% protection over 4 years.[214,215] Low efficacy is partly due to vaccine strain specificity, because natural *P falciparum* infections have

high antigenic variation.[216,217] Development of RTS,S/AS01 for paediatric use continues, with pilot introduction and evaluation underway in Ghana, Kenya, and Malawi to assess its potential for routine widespread use in children.[218] If this vaccine could be used across all age groups and prevent infection by *P falciparum*, it could serve as an endgame tool, offering applications similar to those of monoclonal antibodies previously described. Efforts to assess this potential are ongoing, including further investigation of a fractional dose regimen of RTS,S/AS01 that had improved efficacy in human challenge trials.[219] Results are expected around 2024.

Malaria vaccine development has been a long, expensive, and challenging journey. Parasite biology is complex, limiting the possible duration of vaccine efficacy.[209] These limitations apply to all types of malaria vaccines in development. Other antigen-based vaccines could offer higher levels of initial efficacy than RTS,S/AS01, provided they are not challenged by strain specificity. Although multivalent and multistage vaccines in development offer promise, their efficacy will also decrease rapidly with time.[220–222] The leading weakened whole-parasite vaccine, *P falciparum* sporozoite (PfSPZ) Vaccine, which uses attenuated sporozoites, has shown mixed efficacy in phase 2 trials and will commence phase 3 trials in Bioko, Equatorial Guinea, in 2020.[223,224] PfSPZ Vaccine is delivered by four intravenous injections and has stringent cold chain requirements, limiting its widespread implementation. Transmission blocking vaccines are in earlier stages of development, with two candidates in phase 1 trials.[221] These vaccines do not protect individuals from disease, and determination of their efficacy will be particularly expensive and challenging, requiring large cluster-randomised trials that measure transmission at a community level.[225] Beyond *P falciparum*, little progress has occurred in the development of vaccines against other species of malaria.

A malaria vaccine with high efficacy and long duration of protection is not likely to become available before 2035, if ever. Future investment opportunities are two-fold. First, fundamental research to better understand the human immune response to infection would help to guide future vaccine development efforts.[142,226] Second, the exploration of new technologies that can increase the duration of protection, including slow release delivery mechanisms, could alleviate the greatest weakness of current approaches.[227] We recommend re-examination of the development pipeline for malaria vaccines, which, as of April, 2019, included sixteen candidates—PfSPZ Vaccine, and RTS,S/AS01 and its fractional variant among them.[221] We encourage the further development of fractional dose RTS,S/AS01 and caution against continued investment in other candidate vaccines unless they have a clear likelihood of offering substantial benefits over RTS,S/AS01. Decisions to further pursue the development of transmission-blocking vaccines must be made carefully, with development costs and timelines being key factors for consideration.

Insecticides

Insecticide-based vector-control tools have saved more lives from malaria than any other set of interventions and will be essential for eradication. New tools must address insecticide resistance, be longer lasting, and target outdoor-biting mosquitoes. The Innovative Vector Control Consortium oversees the pipeline in this area, and we describe prospects for addressing these challenges.[228]

Overcoming resistance

New insecticides with novel mechanisms of action are essential for overcoming insecticide resistance.[229] Encouragingly, 2017 marked the release of the first new insecticides for malaria in more than 30 years. Clothianidin is available for IRS, and chlorfenapyr is under evaluation for IRS, and available in a dual-ingredient LLIN that is awaiting a WHO policy recommendation.[230–232] In April, 2019, three candidate insecticides with novel modes of action were under development, suggesting that an additional new insecticide could become available between 2022 and 2025.[228] Prospects for maintaining this pipeline were boosted in April, 2018, with the launch of the ZERO by 40 initiative by the Innovative Vector Control Consortium and the Gates Foundation. This initiative brings together the world's five largest agrochemical companies that have committed to providing additional resources, expanding research and development, and increasing technical collaboration to achieve malaria eradication.[233]

In countries where pyrethroid resistance has been documented, the use of LLINs that include piperonyl butoxide are particularly promising, as exposure to this synergist compound can restore pyrethroid susceptibility in mosquitoes.[234] Elsewhere, the emergence of resistance can be delayed by rotating insecticide use in a mosaic pattern, using insecticide combinations, or both.[235] Products using combinations of insecticides are increasing in number, with a new IRS product now available, and two LLINs undergoing large-scale pilot studies scheduled for completion in 2022.[236,237]

Longer-lasting insecticides

The development of longer-lasting insecticides could reduce the need for LLIN replacement and the frequency of IRS implementation, offering substantial cost savings given that these interventions account for over 50% of malaria programme costs (section 6).[238] Products that prolong the efficacy of IRS and LLINs by using slow-release technologies have become available in the past few years.[239,240] Insecticides in the development pipeline might also offer longer durations of efficacy than those that are currently available, as most insecticides now

used against malaria were repurposed from agriculture, and were deliberately designed to degrade after a few weeks in the environment.

Products for outdoor transmission

Although tools that target outdoor-biting mosquitoes have long been available for consumer use, their application to malaria public health efforts is relatively novel. A variety of personal protection methods are available, including insecticide-treated clothing, blankets and tarps, bite-proof clothing, and the use of topical repellants.[241] However, these methods are limited by cost and the need for compliance, and most have not been used widely. Insecticide-treated hammocks are an exception and have been procured by the Global Fund for use among high-risk populations in southeast Asia.[242]

Two types of products that offer area-wide protection are in the development pipeline. Attractive targeted sugar baits specifically target mosquitoes by incorporating a membrane designed to fit the mosquito proboscis. A prospective product offering 6 months of efficacy is currently undergoing field trials and might be available by 2023.[243] These products will probably be most effective in arid African environments, where other sources of sugar are scarce and where mosquitoes are increasingly biting outdoors.[244,245] Spatial repellants are also in development for use against both indoor and outdoor transmission. These products might be available by 2023 and can be useful in more tropical, lush areas where attractive targeted sugar baits are not effective. However, current evidence suggests that the leading spatial repellants in development will only provide 2–4 weeks of efficacy.[246]

Additional investment in products that target outdoor biting is essential for eradication, including outdoor residual spraying, the use of insecticide-treated screening and fencing, and the use of endectocides on livestock.[241] Non-insecticide based products should also be explored, including the use of larvicides, larvivorous fish, and sound traps.[247] Any product that will be used outdoors must be carefully evaluated for its effect on the ecosystem, as reductions to biodiversity can result in unintended consequences to human and environmental health.[248]

Gene drive

Gene drive systems for mosquitoes work by editing mosquito genes that confer specific traits, such as sterility or immunity to malaria, and propagating the edited genes through entire mosquito populations.[249] Development of these systems has progressed rapidly in the past five years, providing prospects for a new technology that can overcome major challenges to eradication.

The most advanced gene drive system for *Anopheles* vectors prevents reproduction in *An gambiae* ss.[250] Early evidence suggests that this gene drive system might also be effective in *An coluzzi* and *An arabiensis*, expanding its potential as an endgame tool in high-endemic areas. Development of this gene drive system is supported by Target Malaria, a non-profit research consortium that is following a development pathway for gene drive systems, in which the successful field testing of more conservative, non-propagating approaches to genetic modification is required before the field testing of gene drive technologies.[249,251] A second gene drive system in development prevents *P falciparum* malaria infection in *Anopheles stephensi*, offering the potential to address urban malaria in India (panel 3).[252]

Genetic modification is controversial and gene drive technologies will face substantial challenges with regard to public trust and acceptance. Early dialogue on these topics has commenced. Stakeholders agree that individuals who live in endemic countries must be involved in decision-making processes, that development and deployment must include comprehensive monitoring and evaluation systems, that long-term studies are needed to evaluate the effect of gene drives on genetic diversity within and among species, and that if these systems are to be used, the benefits must clearly outweigh the risks.[249,253–255] An analysis on potential environmental effects offers promise, showing that reductions to *An gambiae* sensu lato mosquito populations are unlikely to cause major ecosystem-level consequences.[255] Dialogue on these topics must continue alongside the establishment of a regulatory pathway for gene drive systems for malaria.[249]

The scientific challenges to gene drive systems must also be addressed. Foremost is resistance, as mosquitoes have shown an ability to evolve to stop the propagation of the gene in the population.[256] Many strategies to combat resistance are being explored although eventual resistance to each gene drive system should be expected, necessitating its targeted use where modelling and analysis suggest its greatest possible benefit.[256] The development of risk-mitigation strategies will also be important, in particular for the establishment of systems that can reverse the original drive, restoring traits to their previous natural states.

Pending resolution of regulatory, ethical, and community issues, gene drive systems for *An gambiae* ss and *An stephensi* might become available for roll-out by 2030. Given their potential to address key biological and operational challenges to eradication, investments in gene drive technologies should continue, with substantial allocation to stakeholder engagement, regulatory capacity building, and the further development of systems to modify vectors that present major challenges to eradication. Gene drive systems that target the vector species responsible for *P knowlesi* transmission provide a prospect for the elimination of this species of malaria, a challenge for which solutions are otherwise unclear.

Product availability

Products that successfully traverse the product development pipeline have a number of regulatory obstacles to overcome before they become available for widespread

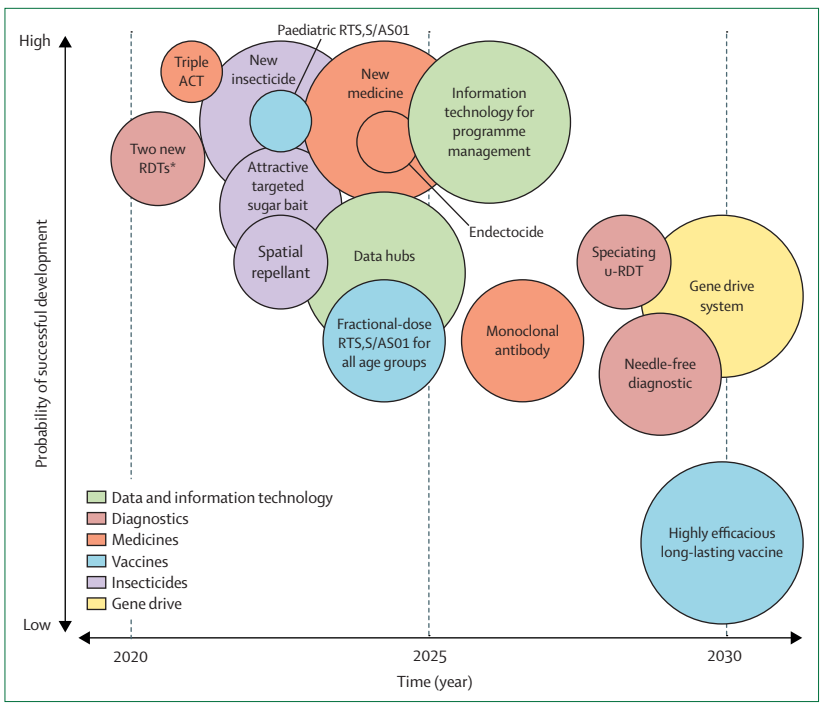

Figure 6: **Research and development framework for malaria eradication**
This framework shows innovations according to the probability of successful development (vertical axis), the timeline of availability (horizontal axis), and their relative effect on accelerating eradication efforts (size of coloured circle). Investment opportunities should be prioritised on the basis of the relative size of the coloured circle and its probability of successful development. Product availability is based on prospective registration dates. ACT=artemisinin-based combination therapy. RDT=rapid diagnostic test. u-RDT=ultrasensitive rapid diagnostic test. *These include a *Plasmodium falciparum* RDT that does not rely on the detection of *pfhrp2* and *pfhrp3*, and a *Plasmodium vivax* RDT.

use. We make three recommendations that can speed this process. First, when products are within 2 or 3 years of availability (for example, a drug in phase 3 trials), policy discussions, modelling, and implementation research concerning their use scenarios and financing should commence. These discussions can reduce the typical lag between the availability of a new product and its use. Second, the international approval process for new products must be expedited where possible. This process might soon improve, as WHO is doing a prequalification and policy process review with the aim of reducing delays to product access.[257] Regional approval processes offer yet another avenue to expedite regulatory approvals. Third, close collaborations within and between the public and private sectors, exemplified by product development partnerships such as Medicines for Malaria Venture and Innovative Vector Control Consortium, are essential to ensure that intellectual property is used as an aid to innovation and access.

Additionally, drugs, insecticides, and other commodities must be quality assured and the increasing number of substandard and counterfeit products combated. This issue is of the utmost importance for public health generally and requires vigorous, collective action at the global level.[258]

Managing the research and development portfolio

The malaria product development pipeline summarised here offers the potential to address a multitude of eradication-related challenges. We present a framework for these research and development priorities (figure 6), including approximate timelines for availability, probability of successful development, and relative ability to address major impediments to eradication. Although this framework provides initial insights for investment priorities for malaria eradication, in which products with high potential to accelerate eradication should be prioritised, it is subject to numerous judgment calls and should continue to be debated and updated as progress is made towards eradication.

Investments in malaria research and development have been roughly constant since 2010 at approximately $600 million per year, about 90% of the recommended spend of $673 million per year.[1,238] Allocations in 2018 were for medicines (35%), preventive vaccines (28%), basic research (22%), diagnostics (5%), and vector-control products (5%).[181] Examining our framework (figure 6) in relation to these allocations, four conclusions arise. First, large returns are likely to result from investments in information technology, data hubs, and molecular surveillance, and therefore these technologies merit greater emphasis. Second, high priority should continue to be given to diagnostics, drugs, and vector control. Third, vaccines might warrant lower levels of investment. Fourth, gene drive is a high-risk, high-reward endeavour that should be vigorously pursued, while recognising the many associated challenges. We also stress the importance of ongoing clinical research, especially into the treatment of severe and complicated malaria in children and other vulnerable individuals. Additionally, we emphasise the power of basic research, and research into radical new approaches, to be unpredictably transformative. Continued or increased investment by the US National Institutes of Health, the Gates Foundation, and private companies, which have provided close to 70% of total malaria research and development funding in the past few years, will be crucial for achieving malaria eradication.

Section 6: financing malaria eradication

An examination of the financial and economic dimensions of malaria eradication is of utmost importance. What will it cost? Who will pay for it? Is it affordable? Is it a good investment? In this section, we address these questions, with an initial focus on reporting how much is currently spent on malaria and who is financing that spending.

Spending on malaria control and elimination to date

We start by examining actual expenditures on malaria since 2000 and the decline in malaria over this period (figure 7). In the 106 countries that had endemic malaria in 2000, total malaria spending (excluding resources spent on administration and global functions) rose from $1·2 billion in 2000 to $3·5 billion in 2016.[259] This rise

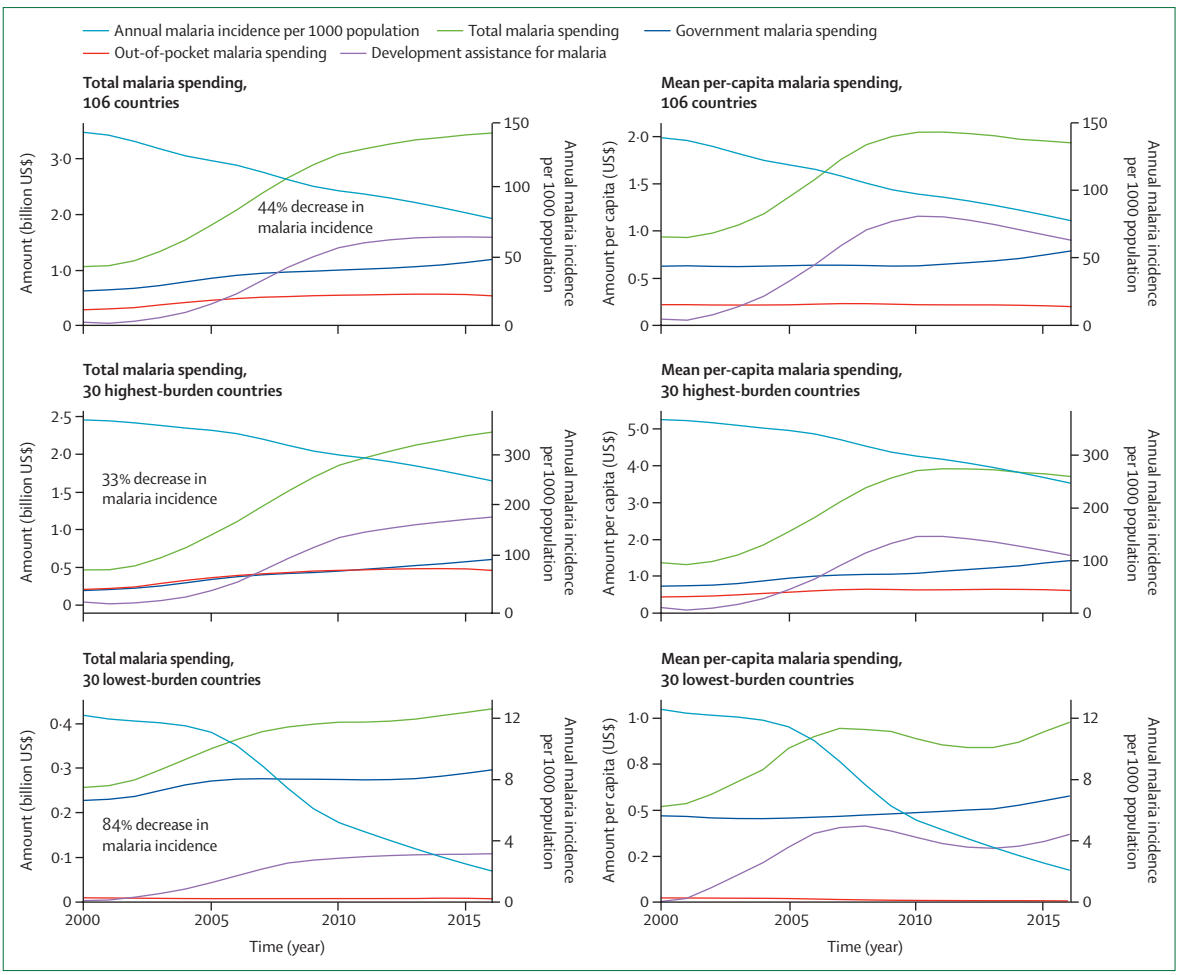

Figure 7: **Total and per-capita malaria spending by source and malaria incidence for the 106 countries with endemic malaria in 2000 and for the 30 highest-burden and lowest-burden countries, 2000–16**[1,259]

Prepaid private spending is included in total spending but not shown on graphs. Development assistance for malaria includes only the amount spent in support of programmes in the 106 countries and excludes spending for administration and global purposes. Spending per capita is per capita of total population. Malaria incidences are per 1000 total population. All dollars are 2018 US$. Per-capita spending and malaria incidences are means of the country values for each group of countries. Definitions and methods are described in the appendix (pp 9–11).The 106 countries are those with malaria in 2000 (appendix p 12). The 30 highest-burden and lowest-burden countries are defined by annual incidence and are selected from the 86 countries with malaria in 2017 (appendix pp 13–15).

was driven mainly by development assistance for malaria, which grew rapidly from 2002 to 2012 and overtook government malaria spending in about 2008. On a per-capita basis, average total malaria spending grew from roughly $1·2 in 2000 to $2·1 in 2016. Government malaria spending rose steadily during 2000–16. Out-of-pocket malaria spending has risen slightly since 2004, but declined as a proportion of total malaria spending.[259]

The 30 countries with the highest annual incidences in 2017 (appendix pp 13–15) have 86% of all malaria cases and receive 75% of development assistance for malaria. Malaria financing in these countries is similar to the global patterns, with development assistance exceeding government malaria spending in 2006. Average annual per-capita malaria expenditure rose to $4 in 2016 in these countries. In the 30 countries with the lowest incidence, the pattern is different. Most spending on malaria comes from government, and funds from this source rose steadily during this period. For these countries, development assistance for malaria increased since 2000, but remained well below government spending. Out-of-pocket malaria spending has been low and flat. Average annual per-capita malaria spending was around $1 in 2016. These investments were associated with substantial declines in average malaria incidence between 2000 and 2016 (figure 7), ranging from 33% in the 30 highest-burden countries to 84% in countries with the lowest incidences, with an overall average decline in the 106 countries of 44%.

We present here estimates of current malaria spending from both international and domestic sources in 2016 (table 2).[259] In summary, current total spending on malaria is around $4·3 billion per year, of which roughly 57% comes from development assistance. Focusing on

	Amount (million $)	Proportion of total amount (%)
Government	1204	28%
Out-of-pocket	556	13%
Prepaid private	99	2%
Development assistance	2418	57%
In-country	1668	40% (69% of development assistance)
Administration	473	11% (20% of development assistance)
Global	277	5% (11% of development assistance)
Total	4277	100%

All spending in 2018 US$. Definitions and methods are described in appendix (pp 9–11).

Table 2: **Malaria spending in 2016 by source in the 106 countries with malaria in 2000[259]**

in-country spending (excluding development assistance for administration and global purposes), development assistance is 47% of total malaria spending. For these 106 countries, reliance on development assistance for malaria is higher than for the health sector as a whole (14%) or for HIV (45%).

We examined development assistance for malaria in 2018 by source and channel. The US Government provides 43% of all development assistance for malaria, followed by the UK Government (14%), the Gates Foundation (13%), and the French Government (3%). Eighty percent of all international malaria funding is channelled through the Global Fund, US Government bilateral programmes, and NGOs, which are in turn largely funded by the US Government.

The malaria financing gap

The most recent and comprehensive attempt to estimate the future cost of malaria control and elimination involved complex modelling of the costs of scaling up all currently recommended malaria interventions to high-coverage levels in order to achieve the *WHO Global Technical Strategy for Malaria 2016–2030* targets.[238] Spending in 2015 was estimated at $2·9 billion and modelling suggested that this will need to increase to $6·4 billion by 2020, $7·7 billion by 2025 and $8·7 billion by 2030, with an estimated total cost of $102 billion between 2015 and 2030. These estimates are for programme costs only, and the additional costs of research and development were not included. The 20 highest-burden countries account for 88% of the total investment, and 63% of the total investment is required for Africa. High levels of coverage (90% of the population at risk by 2025) with both LLINs and IRS were assumed to be necessary everywhere with ongoing transmission, and accounted for 55% of total costs.

Unfortunately, the cost of malaria eradication is unknown. Neither the smallpox, polio, nor Guinea worm eradication campaigns had, in their early stages or subsequently, accurate estimates of total costs over the medium term. Even now, cost estimates are frequently revised upwards because of changing circumstances and new challenges. But, we can assert that malaria eradication will not cost less than the $4·3 billion per year that is currently spent.

The financing gap can be narrowed by increased efficiency and innovation. Improved data-driven management, better targeting, especially of vector-control interventions, and leveraging private markets and outsourcing, discussed in section 3, all have the potential to achieve more with less money. Additionally, some of the new technologies discussed in section 5, such as longer-lasting fabrics and insecticides for LLINs, have the potential to enhance cost effectiveness.

Nonetheless, the Commission concludes that total malaria spending needs to increase, preferably by about $2 billion per year. In order not to increase dependency on development assistance, most of this increase, say $1·5 billion, would ideally come from increased government malaria spending. Development assistance must at least maintain its current real value and preferably be increased by around $0·5 billion per year. Additionally, potential exists for development assistance for malaria to be spent more effectively and also for increased contributions from innovative finance mechanisms.

Increasing government health spending

Government malaria spending has increased steadily since 2000 (figure 7),[259] although additional and more rapid increases in government malaria spending are required. A dominant role for government malaria spending shows country-level commitment to elimination, makes countries more independent and less vulnerable to changing aid policies in donor countries, and prepares countries for transitions out of eligibility for resources from the Global Fund and PMI (panel 7). Elaborating, in detail, plausible scenarios for increases in government spending for malaria in individual countries in differing economic and epidemiological circumstances is an important exercise that we recommend. This work should fully account for the opportunity costs of increased malaria expenditure in relation to other health priorities and broader development goals.

To assess the potential for a scale-up in government spending on malaria, we examined the average annual rate of change between 2000 and 2016 of GDP per capita, government health spending per capita, and government malaria spending per capita for the 30 countries with the highest rates of malaria in 2017.[259] Annual growth rates per capita over this period were 2·1% for GDP, 2·8% for government health spending, and 4·3% for government malaria spending.[259] As countries grew more wealthy, higher proportions of their wealth were

invested into the health sector, and even higher proportions on malaria. Although these averages are encouraging for malaria eradication, these numbers disguise wide variation among individual high-burden countries. Ghana adopted prohealth and promalaria policies, with the post-2000 annual per-capita rates of growth in GDP at 3·5%, government health spending at 6·1%, and government malaria spending at 8·9%. Nigeria chose a neutral policy position, with the rates of growth in GDP at 3·5%, government health spending at 3·0%, and government malaria spending at 3·1%. By contrast, Uganda had a 3·6% annual increase in GDP, but government health spending declined by 0·7% per year and government malaria spending increased by a modest 0·6% per year.

To further illustrate the scope for different policy choices, we examined government malaria spending as a percentage of GDP for the 30 high-burden countries. The median country devoted 0·07% of GDP to government malaria spending, whereas in the 75th percentile country, the proportion was 0·13%. If all 30 high-burden countries were capable of reaching or exceeding the median proportion, billions of additional dollars would be available to fight malaria. For Nigeria alone, moving from its current government malaria spend of 0·01% of GDP to the median figure would generate an additional $0·3 billion per year. Attaining the 75th percentile would increase Nigerian Government spending on malaria nearly ten-fold, yielding an additional $0·7 billion and more than doubling the combined malaria expenditure of all governments of the 30 highest-burden countries (appendix pp 13–15).

Co-funding policies of the Global Fund have attempted to catalyse increased government malaria spending. In addition to meeting baseline domestic financing prerequisites, countries are incentivised to increase domestic finance in exchange for accessing their full allocation from the Global Fund. The co-financing incentive is at least 15% of the country's total allocation. If the Global Fund and PMI joined in encouraging and incentivising increased government health and malaria spending, the effect could be even more substantial.

Future investment priorities for development assistance for malaria

Development assistance in high-burden countries

The dominant use of development assistance in high-burden countries is to co-finance national malaria programmes. Substantial development assistance to high-burden countries will need to be accompanied by requirements and incentives to increase government malaria spending so that it progressively becomes a larger proportion of total national spending on malaria.

In addition, other important uses for development assistance exist in high-burden countries. For example, elimination has not been shown to be feasible in very high-transmission areas in equatorial Africa (figures 1, 3). Development assistance can be used to fund demonstration projects to establish the mix of interventions and management approaches that can drastically reduce malaria cases and deaths even in the most difficult

Panel 7: Country transitions from external to domestic financing

With rising economic growth and declining disease burden, many countries will lose eligibility for donor financing and transition to full domestic financing. These changes risk slowing global progress towards malaria eradication if countries are not equipped to sustain necessary financial, technical, and programmatic resources after transition.

Transition challenges for malaria

Malaria programmes undergoing transition have various strategic challenges. Key among these challenges is the need to mobilise domestic resources to close funding gaps after the end of donor support. Resource mobilisation is particularly difficult for countries close to elimination where the malaria burden is less visible and declining political awareness of malaria threatens programme budgets. Transition has other health system implications, as donor financing often supports important malaria programme infrastructure, personnel, and activities. In addition, strategic planning for transition can be complicated by multiple, overlapping changes in epidemiology and health system structure. As programmes prepare for transition, they need to revise their national strategies to reflect changing disease burden and identify opportunities to leverage health systems changes, such as the expansion of universal health coverage or integrated health system approaches. The pressures on domestic health budgets and delivery systems are further compounded in countries with simultaneous transitions across disease areas or from multiple funding agencies.

Donors have an important role in ensuring transition does not disrupt progress towards elimination and eradication. The Global Fund to Fight AIDS, Tuberculosis and Malaria has taken positive steps through its Sustainability, Transition and Co-Financing policy, which supports countries as they strengthen long-term sustainability, increase domestic financing, and prepare to transition from external support.[260]

Policy priorities for malaria transition planning

Managing transitions to ensure continued progress towards eradication requires consideration of malaria programme strategy, structure, and operations. Evidence from transition readiness assessments for malaria in the Philippines, Sri Lanka, and Thailand (Beyeler N and Fewer S, University of California San Francisco, personal communication) identifies four action areas for countries and their partners to consider:

- Determine the scale, scope, and strategy of the malaria programme: evaluate the programme to identify essential functions for the future and opportunities for greater efficiency to ensure transition planning meets future needs, not the status quo
- Maintain the essential workforce for malaria: modify workforce plans and policies to respond to changing programmatic needs and secure financing for key positions, including essential externally financed roles
- Mobilise and allocate domestic resources to malaria: at both national and subnational levels, increase capacity for effective budgeting and financial management, improve programme efficiency, and sustain political will for malaria despite declining burden
- Integrate externally supported systems into national structures: develop the management and technical capacity and policies to operate robust surveillance, supply, and other systems

If managed effectively, transition offers an opportunity to strengthen health systems and build domestic capacity and political will to finance and manage malaria programmes. Malaria eradication will advance if transition risks are mitigated by thorough and thoughtful planning several years in advance of expected transition, strong technical assistance to implement country-owned transition plans, and domestic resource mobilisation to continue effective malaria control and elimination programmes.

settings. Such programmes will also identify collateral requirements, such as particular features of health-care infrastructure that are essential if malaria is to be effectively tackled. Development assistance can then be invested in this infrastructure to better prepare countries for the final effort towards elimination.

Development assistance in low-burden countries

The use of development assistance for malaria in low-burden countries should distinguish between low-income countries (such as Nepal and Timor-Leste) and middle-income countries (such as Namibia and Sri Lanka). In low-income countries, a substantial proportion of total malaria programme costs will have to be met by development assistance for the foreseeable future. Maintaining development assistance flows well into the prevention of re-establishment phase might also be necessary, for fear of resurgence and loss of gains previously made.

In the low-burden, middle-income countries, the temptation to withdraw development assistance completely is very strong. For some countries, this withdrawal presents little risk given the strength of the health system and the commitment to elimination and prevention of re-establishment. For other countries, a clear international interest exists in ensuring that elimination is achieved and the prevention of re-establishment is sustained. Modest amounts of development assistance allocated to countries in this situation can be valuable for two reasons. First, ongoing development assistance requires substantial co-financing from government and a formal undertaking between the donor and the government that this co-financing will be maintained. Such agreements not only ensure that the resources are available to do the job, but they also make governments less likely to choose to reduce the allocation of funds for malaria as cases decrease. Second, ongoing development assistance helps to maintain political commitment. Continued interactions with a source of international funds, such as the Global Fund, keeps the malaria programme in the eye of policy makers and allows ongoing opportunity to celebrate success and to emphasise the need for continuing vigilance and programmatic effectiveness.

Development assistance for global public goods

Development assistance for malaria does, and should continue to, have an important role beyond the co-financing of national malaria programmes. Development assistance can target particular market failures or areas of special need, through country-specific, regional and global funding. Current examples are investments in fighting artemisinin resistance in the Greater Mekong Subregion and investments on a regional scale in reducing the wide availability and use of counterfeit drugs.[261] Development assistance for malaria also has a crucial role in financing the international coordination and collaboration mechanisms, such as WHO, the RBM Partnership, APLMA, APMEN, and the E8, which are essential for regional and global success. Finally, and perhaps most importantly, development assistance funds malaria research and development, which are essential for eradication (section 5). These examples of use of development assistance beyond financing country programmes are investments in regional and global public goods, an important and growing role for development assistance.[262,263]

Increasing development assistance for malaria

The Commission advocates for an annual increase in development assistance for malaria of $0·5 billion, a 12% increase on current spending. Given that development assistance for health and for malaria has plateaued in the past few years, this goal might appear to be difficult to attain. The Global Fund in its current replenishment round is seeking a total increase of $1·8 billion over 3 years, which would roughly translate into an increased expenditure by the Global Fund on malaria of $0·2 billion per year. Thus, if the Global Fund's replenishment goal is met, the remaining development assistance for the malaria gap is reduced to $0·3 billion. The best prospects for securing these additional funds come from new and smaller donors. China has increased its development assistance for health from $0·1 billion in 2000 to $0·7 billion in 2018.[264] China is preparing to celebrate freedom from malaria in 2020, following 3 years with no local transmission. This situation provides a platform for launching a large-scale programme of financial and technical assistance from China to endemic countries in Africa and Asia. If this initiative were combined with increased investment by malaria-free countries with a clear self-interest in regional elimination, such as Brunei, Malaysia, Japan, Singapore, and South Korea, the target of an additional $0·5 billion could be achieved.

The big funders

Over three-quarters of development assistance for malaria flows through the Global Fund and PMI (panel 8). The investment decisions of these organisations, and coordination between them, have great influence on the pace of progress towards eradication and on whether eradication will be achieved. Although the Global Fund and PMI collaborate at the country level, additional joint strategic planning and policy alignment at the global level could increase effectiveness. New leadership at both the Global Fund and PMI, and a commitment to smart allocation decisions, provide an opportunity to create a more strategic and impactful investment portfolio. Here, we discuss five possibilities.

First, 75% of the Global Fund's 2017–19 country allocations goes to countries in which PMI is also investing. Both organisations spend roughly one-fifth of their country funds in Democratic Republic of the Congo and Nigeria. It is timely to consider whether greater coordination and

complementarity could accelerate global progress, and whether this degree of concentration of investment in two countries is optimal. Arguably, development assistance should be targeted to minimise the timeline to eradication, which does not necessarily mean spending the most money where the most cases occur.

Second, policy alignment with regards to government co-investments in malaria and data sharing could enhance progress in these and possibly other areas.

Third, joint programming and investment in crucial underfunded areas, such as management training and implementation research, could accelerate eradication.

Fourth, the combined investments of the Global Fund and PMI under current arrangements might not necessarily lead to eradication. Although mortality is continuing to decline, annual case numbers are rising and the trajectory towards eradication has stalled since 2015.[1] Modelling different allocation scenarios to explore which leads to eradication in the shortest timeframe would be valuable and would complement the urgent agenda of reducing morbidity and mortality in line with global targets.

Fifth, notwithstanding the creation by the Global Fund of catalytic funds for objectives that cannot be addressed solely by country allocations, over 90% of funds are still allocated on a country-by-country basis. Given the importance of development assistance in funding regional and global public goods, it is worth considering how a proportion of Global Fund and PMI resources should be directed at these broader, non-country-specific goals. These goals could include ensuring the achievement of elimination and the prevention of re-establishment in low-burden and lower-income countries, financing of large-scale demonstration sites in high-burden countries, and supporting implementation research into key operational challenges.

Reducing out-of-pocket spending

The third source of funding for malaria programmes in endemic countries, in addition to development assistance and government spending, is out-of-pocket spending. For health care in general, out-of-pocket spending is a large source of finance in almost all low-income and middle-income countries.[271] In some countries, such as India, this source represents 60% or more of all health-care financing.[271,272] Out-of-pocket spending on this scale is undesirable, forcing families to forego necessary care and causing medical impoverishment. WHO recommends that out-of-pocket spending should not be more than 20% of total health expenditure.[273] Driving down out-of-pocket spending, and reallocating these funds to prepaid social health insurance schemes, is a major goal for universal health coverage (UHC) in all countries. Success to date is minimal and projections show that out-of-pocket spending as a proportion of total health spending will still be 39% in low-income countries, and 51% in lower-middle-income countries, in 2050.[271]

Panel 8: The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) and the President's Malaria Initiative (PMI) investments in malaria

Together, The Global Fund and PMI provide over three-quarters of total development assistance for malaria.

Allocations for malaria from The Global Fund

Since its establishment in 2002, The Global Fund has disbursed US$38 billion, $11·4 billion of which has been for malaria.[265] As of the end of 2017, The Global Fund and its partners had distributed 993 million insecticide-treated nets, treated 776 million malaria cases, and provided finance to more than 100 countries.[266]

In 2014, The Global Fund moved from an allocation model based on country requests to one based on a formula.[267,268] The formula is driven by the country's malaria burden in 2000 and gross national income per capita. As a result, the great majority of investments from The Global Fund are in low-income and lower-middle-income countries with high malaria burdens. In 2017–19, two countries (Democratic Republic of the Congo and Nigeria) received 20% of The Global Fund's malaria country allocations.[269]

Recognising that country-allocated funds would not fully address the emerging biological threats, development of new tools, or elimination efforts, The Global Fund created an $800 million catalytic fund for all three diseases in the 2017–19 allocation period. For malaria, these funds support a new generation of nets ($35 million), introduction of the RTS,S/AS01 vaccine ($15 million), a new regional blended financing mechanism in the Americas ($6 million), regional elimination efforts in southern Africa ($20 million), malaria elimination in 21 low-burden countries ($7 million), and accelerating elimination in the Greater Mekong Subregion, the epicentre for drug resistance ($119 million).

Eligibility for financing by The Global Fund[267]

- All low-income and lower-middle-income countries are eligible, regardless of disease burden
- Upper-middle-income countries are only eligible if they have high disease burden, or if the country is designated under a so-called small island economy exception
- High-income countries are ineligible
- Countries that are malaria free are not eligible, regardless of their income level
- Countries that graduate from eligibility might receive one 3-year transition grant
- In 2018, 99·7% of the global burden of malaria was eligible for financing by The Global Fund

PMI

PMI was created in 2005 and currently provides support to 24 focus countries in sub-Saharan Africa and the Greater Mekong Subregion. PMI's primary objectives are to reduce malaria mortality and morbidity. PMI also supports elimination; seven of PMI's focus countries plus Zanzibar, Tanzania, have adopted national or subnational elimination strategies. PMI is led by the US Agency for International Development and implemented together with the US Centers for Disease Control and Prevention.[270]

Since its inception, PMI has spent over $6·3 billion to support malaria programmes. In 2018, PMI invested $723 million and more than 570 million people at risk of malaria benefited from its support. Roughly 18% of PMI's current investments in countries go to Democratic Republic of the Congo and Nigeria. Country selection and allocations are determined in consultation with other US Government agencies and are based on congressional appropriations for the given fiscal year.[270]

Out-of-pocket spending for malaria is likely to be most problematic in countries that are poor and have high malaria burdens. The mean out-of-pocket malaria spending in the 30 countries with the highest rates of malaria is 20% of total malaria in-country spending (appendix pp 13–15). In some countries, this proportion

is much higher, for example 59% in Niger and 52% in Cameroon. On average, malaria is less dependent on out-of-pocket spending than health in general. In the 30 high-burden countries, out-of-pocket spending comprises 40% of all health spending. However, malaria is a disease affecting mainly very poor households for whom this degree of out-of-pocket spending might cause avoidance of care, which in turn promotes onward transmission. As discussed in section 8, a shared agenda exists between malaria eradication and UHC to drive down out-of-pocket spending and replace it with prepaid and risk-pooled arrangements.

Innovative financing mechanisms

Potential exists for innovative funding mechanisms to supplement development assistance and government spending and help to narrow the malaria financing gap. Work on these innovations over the past two decades can be characterised as high in enthusiasm and ingenuity, and low in money actually generated. However, some innovative financing mechanisms have traction and might have political and advocacy benefits, in addition to financial ones. We discuss four categories here.

First are the private-sector partnerships, exemplified by Product Red (RED) and now joined in Asia-Pacific by M2030.[274,275] These branded, business-led initiatives not only raise additional funds, but also engage businesses and business leaders as important advocates in the achievement of national and regional health goals. Furthermore, the initiatives bring knowledge and engagement to the general population who can contribute to malaria elimination through their purchasing choices. A second category with promise is the regional blended finance initiatives, which bring together resources from regional development banks, the Global Fund, private foundations, and governments to support and incentivise achievement of specific malaria elimination objectives. Leading examples of this model are the Regional Health Fund, created by the Asian Development Bank, and the Regional Malaria Elimination Initiative, led by the Inter-American Development Bank in Mesoamerica.[276,277] Third is the possibility of mobilising social investment bonds to support malaria elimination. These bonds are being increasingly tried in health and other sectors, but are controversial.[278] Social or development investment bonds require an unambiguous and measurable goal, which will trigger repayment to investors. The challenge in establishing such an endpoint is the main reason why the proposed malaria investment bond in Mozambique has stalled.[278] An opportunity exists for bonds focused on malaria elimination. When a country has had zero local transmission for 3 years, it applies for WHO certification of malaria freedom, a formalised and well established process. Whether this unambiguous endpoint could form the basis for investment bonds to finance elimination in countries that are approaching that goal is worth serious exploration. Lastly, some countries are establishing special funds for malaria elimination. In 2018, King Mswati III of eSwatini announced a fund to attract additional financing, particularly from the private sector, to eliminate malaria. Initiated with a $350 000 donation from the King, the Malaria Fund will mobilise resources to finance priority activities, including IRS coverage in high-risk areas, surveillance, and maintaining health sector infrastructure.[279] The Global Fund is exploring the creation of a new financing facility explicitly for elimination and prevention of re-establishment, which would incorporate a number of the innovative approaches we have discussed.

Financing the endgame

Commitment to malaria eradication is tempered by a concern that it will be very expensive in the last remaining, most challenging countries. Per country and per case, this is true, with the cost per case averted approaching infinity. However, given the overwhelming global public good nature of eliminating malaria in the last few countries, the costs might reasonably be borne by development assistance primarily. While recognising the need for continued investment in prevention of re-establishment in poorer countries that have eliminated, the bulk of development assistance for malaria will be concentrated in fewer and fewer countries, plausibly providing sufficient funds for eradication. Imagine malaria in 2040 persisting in some Nigerian states and five other countries with a total population of 300 million. Development assistance for malaria, at the current level of $2·4 billion, would provide $8 per capita per year for eradication. Ongoing domestic allocations of around $4 per capita per year would bring that number up to $12 per capita of total population in the still-endemic countries, and a much higher expenditure per person at risk. These numbers are higher than is likely to be necessary. This optimistic scenario is contingent on donors agreeing to maintain their current levels of expenditure even as investment becomes concentrated in fewer countries and the global malaria burden diminishes.

Malaria eradication as an investment

When arguments are raised to support major investment in some area of global health, they are accompanied by spectacular claims about the return on investment or the benefit–cost ratio. For each dollar spent, it is argued, much larger sums will be returned. However, the methods used to monetise economic and social benefits, the appropriate discount rate, the choice of benefits included, to whom the benefits will accrue, the timescale for reaping the benefits, and the exact value of the benefit–cost ratio, are all matters of great uncertainty.

A systematic review published in 2016 identified ten benefit–cost analyses of malaria control and elimination.[280] Three of the analyses were done during the GMEP era and five focused on elimination specifically.[280]

All but one of these studies showed a positive benefit–cost ratio and the main economic benefit identified was increased labour productivity due to reduced morbidity and absenteeism. The benefit–cost ratios ranged from 2·4 to 146 and the large span of results was attributed to poor study design and the wide range of methods and assumptions used.

The WHO Strategic Advisory Group on Malaria Eradication has commissioned new modelling of the effect on GDP of both malaria eradication during 2000–15, and increased malaria investment between now and 2030. These results are eagerly awaited. Little doubt can exist that the costs of malaria eradication will be far exceeded by the broad welfare and economic benefits derived, and the value of eradication to UHC, other SDGs, and global health security, which we discuss in section 8.

Section 7: leadership, governance, and accountability

Malaria eradication is an ambitious, high-stakes endeavour that requires the full engagement of political, financial, technical, operational, and community leaders, collaborating at all levels.

A brief history of malaria leadership

WHO has been the longstanding leader in global health, directing and coordinating international work in disease control and health promotion since 1948. WHO led the first malaria eradication effort and continues to provide technical leadership to countries and generate global policies and normative guidance for malaria control and elimination.[281] Since the time of the GMEP, leadership has diversified. Global organisations, including the RBM Partnership, the Global Fund, PMI, the UK Department for International Development, and the Gates Foundation, have crucial roles in their areas of specialisation. There is now a healthy range of perspectives and productive debate on technical and policy issues.

A seminal change since the GMEP era has been the rise of country and regional competence and confidence. Progress in reducing malaria morbidity and mortality and achieving elimination is increasingly driven from the bottom up, rather than from the top down.[120] Over the past decade, countries such as China, eSwatini, Malaysia, and Sri Lanka have set more ambitious targets for themselves than those recommended by global organisations.[45,282–284] Similarly, since 2008, countries have come together under the umbrella of regional initiatives, committing to bold regional elimination goals and establishing new platforms for coordination and collaboration (figure 2, panel 1).[285,286] Notwithstanding the persistence of management and operational challenges noted in section 3, ambition and leadership now come strongly from the front line.

Building on this diversification, leadership and accountability can be further strengthened and shaped to support a renewed, time-bound commitment to global eradication.

Country leadership, governance, and accountability

Leadership and governance structures

Perhaps the most important leadership requirement for malaria eradication is unambiguous and energetic commitment by national and subnational leaders in every endemic country.[48,262] The past decade has shown great progress in this area, but too many national and subnational leaders are still unfamiliar with and uncommitted to malaria elimination in their country, province, or district. Well informed leadership by heads of state sets a national vision for malaria and can mitigate fluctuating commitment caused by political turnover, particularly in the ministry of health. Furthermore, leadership by the head of state is advantageous in institutionalising a whole-of-government approach to malaria, including diplomacy, fiscal policy, infrastructure, and trade—instruments that can be leveraged to accelerate malaria elimination.

In some countries, including Uganda, parliamentary groups have been established to raise malaria and other health priorities to national importance.[263] Such groups can be influential in garnering support during national budget negotiations, mobilising constituencies for improved community engagement, and strengthening the visibility of malaria in the media. Positioning malaria as a legacy issue can incentivise decision makers who operate on short political cycles to act across sectors and political parties. As elimination approaches, ownership of the malaria agenda by political leaders will become both more attractive and necessary.

A growing number of countries are establishing leadership platforms to connect high-level political leadership and multisectoral stakeholders with malaria operations and management. Although the nomenclature differs—national malaria elimination taskforces, national end malaria councils, national steering committees—the functions are mainly the same: mounting a high-level, multisectoral response to drive accountability and generate political, technical, and financial support for malaria elimination. A number of African countries, including Zambia, are establishing councils to end malaria with support from the African Leaders Malaria Alliance (ALMA), the RBM Partnership, and others. In Asia-Pacific, the APLMA Malaria Elimination Roadmap calls for endemic and postelimination countries to establish national malaria elimination taskforces (or similar), chaired by a senior central agency official. One such body was established in Thailand by the Office of the Prime Minister to facilitate multiagency action and drive progress towards ambitious national elimination targets.[287] Working with WHO country offices that can provide essential support in developing and deploying sound technical strategies, malaria programmes benefit from these leadership platforms because of their role in mobilising resources, ensuring accountability, overcoming obstacles, and increasing ambition and coordination. Leadership platforms can also link to national

centres for disease control and emergency operation centres to enhance outbreak response and elevate malaria among other disease priorities.

Leadership at the subnational level is increasingly important,[49] especially in countries with federal structures, such as India, Indonesia, and Nigeria, where health is largely a state or provincial responsibility.[288–290] Every state leader must be fully committed in order to achieve national malaria elimination.[48,291] Empowering subnational leaders, particularly at district level, to respond to the technical, financial, and operational needs of malaria programmes, can have powerful effects on community engagement and domestic financing.[74] Leadership development programmes are underway in the Philippines and Thailand to motivate provincial governors and mayors to allocate provincial health budgets and UHC funds for malaria—an approach that will strengthen sustainability in anticipation of transition from donor financing or programme integration. These efforts to increase the capacity of subnational leaders to deploy concrete political and financial assets in response to the operational needs of the programme is of growing strategic importance, especially considering the heterogeneity of malaria transmission in many countries. Broader movements are seeking to bolster community leadership, including the RBM Partnership-supported campaign Zero Malaria Starts with Me, which was endorsed at the 2018 African Union Summit and has been launched in several countries.[292]

Commitment frameworks and accountability tools

Various country-level accountability tools are available to monitor malaria progress. With the support of ALMA, some countries in Africa have adopted national scorecards to track subnational progress, identify challenges, and drive action. Linking national scorecards and related data with high-level political leadership can enhance rapid action to address gaps. These actions should support, enable, and reward malaria programmes to push harder and go further, thereby incentivising greater data transparency on progress or setbacks. A few countries, including China, have established a process for subnational verification of elimination to not only prepare subnational units for national certification, but also recognise local success.[293]

As with the HIV/AIDS movement, a robust civil society can strengthen accountability. Greater support from the global community to enhance capacity and tools for country-level civil society can promote responsiveness by leaders and decision makers to the communities they serve.

As noted in section 3, data availability and transparency are prerequisites for an effective response and accountability. Increasing data availability and transparency on malaria epidemiology, financing, and health services quality and access emboldens civil society and community leadership to hold governments and their partners accountable for the achievement of health goals.

Regional leadership, governance, and accountability

Leadership and governance structures

Although countries are driving progress and action, regional bodies must promote and be accountable for regional elimination, a precursor to global eradication. WHO regional offices have had an important role in enhancing uptake of normative guidance and facilitating greater commitment from countries. In addition, regional initiatives for malaria now cover almost all endemic countries (figure 2, panel 1). These regional initiatives should be strengthened and empowered to be the main mechanism linking regional political and economic bodies, such as the East Asia Summit or African Union, with the priority actions required from member countries to eliminate malaria.[285] Regional malaria initiatives should also link with country-level leadership and global malaria platforms to ensure alignment with country and global accountability and monitoring mechanisms.

In collaboration with WHO regional offices, the secretariat and technical teams of regional and subregional malaria alliances, such as ALMA, APLMA, the E8, and the Sahel Malaria Elimination Initiative, support action and accountability in member countries. As accountability managers, these alliances have a vital role in maintaining political commitment at the highest level, identifying regional barriers to progress and best practices, actively promoting collaboration among neighbouring countries, and ensuring progress is reviewed by the political and economic bodies that can incentivise action by member states. Regional alliances can help accomplish these goals by supporting mobilisation campaigns (such as M2030) or providing malaria programme networks, such as APMEN, with the necessary channels to address obstacles of a political nature.

Regional malaria alliances can work with regional economic bodies, including the Southern African Development Community and the Economic Community of West African States, to leverage diplomacy and regulatory, migration, or trade policies to harmonise regional elimination activity and incentivise country action. In some regions, malaria alliances could be broken down into more manageable subregions that share similar malaria landscapes or political interests; for instance, APLMA is developing concerted subregional efforts in the Greater Mekong Subregion, Melanesia, and south Asia.

Commitment frameworks and accountability tools

Several regional initiatives for malaria elimination, including ALMA, APLMA, and the E8, have developed regional scorecards to monitor and review progress across a standard set of indicators. Indicators are selected in collaboration with national malaria programmes, WHO,

and the RBM Partnership and represent consensus on shared metrics and priorities. Scorecards have also served as useful advocacy tools, especially among heads of state, that remind leaders of national commitments and provide a high-level and visual overview of country-level progress in comparison to their peers. Regional scorecards can identify areas for technical and implementation support, apply collegial pressure, and support peer-to-peer problem solving during review processes which occur during regional high-level meetings at the African Union and the East Asia Summit. Although these scorecards have led to additional resource commitments, accelerated commodity delivery, and policy change,[294] a shift will soon be required to move from an annual review of scorecards to a sophisticated platform built on timely, quality data that enhances the speed of political and financial actions.

At a subregional level, disease monitoring platforms have emerged to rapidly respond to outbreaks and other operational challenges. In the Greater Mekong Subregion, an independent regional monitoring and support team has been newly established to monitor progress on targets within the Regional Artemisinin-resistance Initiative. This monitoring panel provides national leaders, programme managers, and the Global Fund's Regional Steering Committee with an independent assessment of progress towards elimination of multidrug resistant malaria in this important subregion.

Civil society is also organising at the regional level to ensure accountability, strengthen community engagement, and improve access to services. For example, Malaria Free Mekong is a civil society platform in the Greater Mekong Subregion where a complicated, multi-stakeholder response is underway. In a formal review in 2017, this platform was recognised as vital for ensuring transparency and accountability, especially in relation to the most vulnerable and at-risk populations.[295]

Global leadership, governance, and accountability

Leadership and governance structures

Global organisations should view their primary role as supporting countries and regional bodies in driving country and regional elimination until global eradication is achieved. Greater clarity on roles, improved collaboration, and increased leadership of global platforms by those who represent progressive and successful endemic countries will enable global actors to align with the growing expectations from countries, particularly those with increasing geopolitical power.

Unlike 50 years ago, plurality in leadership is now the reality, as welcomed by the WHO Director-General.[296] WHO has a unique role in setting global targets, updating technical strategies, and issuing normative guidance. WHO can strengthen this essential contribution by being flexible and in tune with innovation and ambition coming from the front line. In formulating its guidance, WHO depends heavily on committees of international experts. Rebalancing these committees to have a mixed representation of implementers, researchers, and stakeholders from endemic countries will ensure that new guidance is relevant to those who rely on it. As the leader in setting normative guidance, WHO is often the technical arbiter of what can and cannot be supported by the Global Fund. Because normative guidance aims to support the collective, it must keep pace with the needs in more ambitious countries for innovation, flexibility, and a learning-by-doing approach. The road to eradication requires more nimble guidance on emerging issues, rapid approvals and streamlined regulatory pathways for new commodities and tools, and faster, more transparent data collection and reporting. The establishment of the WHO Malaria Elimination Oversight Committee to provide independent advice and monitoring of malaria elimination is welcome. WHO also has a crucial role in the certification of countries as malaria free, a task of rising importance as the pace of elimination quickens.

In 2016, WHO convened the Strategic Advisory Group on Malaria Eradication to examine whether a renewed effort to eradicate malaria should be recommended to the WHO Director-General. The Strategic Advisory Group is expected to publish its findings in late 2019.

The RBM Partnership is a central collaborative platform for malaria comprised of over 500 organisations. Having emerged from the reform process in 2017, the RBM Partnership is positioned to take advantage of the geopolitical shifts and become a truly global partnership that can effectively coordinate the malaria community. Given the multitude of health and development priorities on the global agenda, the RBM Partnership has a comparative advantage in providing a cohesive voice for malaria within broader agendas, including the SDGs, health financing, global health security, and UHC.

The End Malaria Council provides high-level engagement by influential world leaders from both the public and private sectors. Although a separate entity from the RBM Partnership, the End Malaria Council takes strategic guidance from the RBM Partnership, particularly in identifying actionable priorities that would benefit from leadership at the highest levels. The Commission encourages the malaria community and the RBM Partnership to leverage the End Malaria Council to resolve high-level obstacles. The Commission also recommends that the End Malaria Council establish an independent monitoring board for malaria eradication that can hold WHO, the RBM Partnership, regions, countries, and all other malaria partners accountable for achieving milestones on the road to eradication. An independent monitoring board has been essential for polio eradication (panel 9) and could similarly drive accountability in ensuring sufficient progress against the globally agreed-upon trajectory for eradication.

Finally, at the global level, plenty of space exists for greater policy coordination and strategic alignment between the major global malaria organisations. For example, as discussed in section 6, the Global Fund and

Panel 9: The Independent Monitoring Board (IMB) of the Global Polio Eradication Initiative (GPEI)

In 1988, the World Health Assembly called for the eradication of polio by 2000.[297] However, by 2001, progress had stalled after over a decade of falling incidence. The World Health Assembly requested the establishment of the IMB for polio eradication in 2010, the first body of its kind in global health.[298]

Representing a range of expertise, the IMB meets twice a year to hear from countries and core GPEI partners (WHO, UNICEF, the US Centers for Disease Control and Prevention, Rotary International, and the Bill & Melinda Gates Foundation) on progress, risk mitigation strategies, and actions on previous IMB recommendations. The IMB holds all actors accountable to programme weaknesses and management failures, and demands viable solutions.[299] Importantly, the IMB provides a firm reminder that a business-as-usual approach will not achieve the ultimate goal of polio eradication. As described by Rutter and Donaldson,[298] IMB's first report pointed out the failure of GPEI "to fundamentally alter its approach despite a decade-long stagnation of progress" and that this "burning platform" put polio eradication at risk.

The IMB has been successful in (1) elevating polio as a priority by instigating a 2012 World Health Assembly resolution that declared polio eradication a programmatic emergency; (2) initiating important leadership platforms, including taskforces led by heads of state in endemic countries; (3) advancing a targeted approach that focused attention and resources on so-called poliovirus sanctuaries at district level; and (4) encouraging innovation and evaluation of new tools.[298]

Characteristics of success

The success of the IMB has been attributed to its strong leadership, clearly defined milestones against which to assess progress, and willingness to speak boldly and accept constructive criticism.[299] Additionally, the IMB:

- Embraces a network model: initial polio efforts were vertically managed by WHO, an approach that relied on a single actor with little accountability; the GPEI then introduced a partnership network model with the IMB as its accountability mechanism; the IMB has not been shy in addressing issues such as reluctance to share data, power dynamics, and territorialism[298]
- Maintains fierce independence and transparency: unlike WHO, the IMB is not governed by member states, and unlike global partners and donors who rely on positive relationships with countries, the IMB can directly challenge national polio programmes;[299] controversial recommendations are made public
- Adapts to shifting context: the IMB has adapted its approach to address emerging issues, including the establishment of the Transition IMB to guide the transition of polio assets

Application to other global health areas

Although the IMB for polio arguably could have been established earlier, it has successfully served as an honest broker of accountability since its inception. The IMB's focus on a definitive goal, paired with its ability to adapt to changing epidemiology and context, make such a mechanism attractive to other disease efforts that have eradication in sight but have yet to establish a global accountability platform.

PMI could work together more closely on investment strategies, data-sharing efforts, and domestic financing incentives. Similarly, greater role clarity between WHO and the RBM Partnership, of which WHO is a founding member, would further enable countries to draw on support from the appropriate platform, particularly in relation to technical assistance—a term that is often and unhelpfully defined differently among various organisations.

Commitment frameworks and accountability tools

The key requirement for accountability at the global level is data. Throughout this report, we emphasise the need for increasingly rapid and transparent reporting, by both countries and their partners. The major funders, the Global Fund and PMI, could do more to ensure that this occurs. In addition, strong accountability will require universal access to all data. This access will require the establishment of a global data hub or warehouse, as proposed in section 5, which will be helpful now but essential in the final stages of eradication, particularly as a key asset for the proposed independent monitoring board for malaria eradication.

Most importantly, the world needs a roadmap for eradication. Figure 5 shows how the world might be in 2030 and 2050 if previous relationships among key variables are maintained. Maps and other data are required depicting where the world needs to be at 5-year intervals between now and 2050, in order to eradicate malaria by 2050 or sooner. These predictions are engineered futures rather than modelled futures; purposefully driven and not passive. The engineered futures should be ambitious but feasible, based on a wide array of technical and socioeconomic data. Emphasising the importance of country ownership in eradication, the starting point is for each country, with external support as necessary, to develop and commit to its own roadmap to elimination. These roadmaps would then be aggregated to the regional level, enabling regional bodies to endorse and support the regional journey to malaria freedom. Finally, these regional roadmaps would be combined into a global plan for eradication by 2050 or sooner, which would be endorsed by the World Health Assembly and UN General Assembly, and which would ensure that all countries, donors, and implementing partners are

accountable to the milestones and, ultimately, the goal of eradication.

Section 8: alignment with broader health and development goals

A drive to eradicate malaria supports and reinforces several priority health and development goals, and vice versa. Chief among these goals are the Millennium Development Goals (MDGs) which concluded in 2015, the 2016–30 SDGs—including UHC, equity promotion, and poverty reduction—and global health security.

The MDGs and the SDGs

From 2000 to 2015, global and national development policies were guided by the MDGs. Policies and priorities for the period 2016–30 are now steered by the SDGs. Here, we briefly review the association between malaria and the MDGs and the role that malaria eradication will have in achieving relevant SDGs.

Malaria and the MDGs

When the MDGs were established in 2000, malaria was rampant. Between 2000 and 2015, global incidence decreased by 37% and the mortality rate by 60%.[2] Despite the uncertainty of success at the outset, MDG Target 6C, to halt and reverse the incidence of malaria and other major diseases by 2015, was met.[300] Because a high malaria burden can negatively affect poverty, education, productivity, and child and maternal health, progress in reducing malaria during this period also contributed to accomplishments related to MDG 1 (poverty reduction), MDG 2 (universal primary education), and MDG 5 (improving maternal health).[300,301]

Most notably, reductions in malaria contributed to MDG 4 (child mortality reduction). In 2000, malaria directly accounted for an estimated 12% of all deaths in children younger than 5 years and 22% of all child deaths in sub-Saharan Africa, where it was the leading cause of death in that age group.[300] The 65% decrease in the global malaria mortality rate in individuals younger than 5 years between 2000 and 2015 greatly facilitated progress against MDG Target 4A, which aimed to reduce the mortality rate in this age group by two-thirds.[300] It can be reasonably assumed that benefits have flowed in both directions and that broader improvements in child and adult health and advances in education, particularly among girls and women, substantially contributed to reductions in both childhood and adult malaria.

Malaria and the SDGs

The SDGs were adopted by the UN in 2015 to succeed the MDGs.[302] As with the MDGs, progress towards malaria eradication is expected to have a positive effect on many of the SDG goals and targets. SDG 3, good health and wellbeing, includes two targets with direct links to malaria: Target 3.3 aims to end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases, and Target 3.2 aims to end preventable deaths and reduce mortality rates of neonates and children younger than 5 years.[302] In 2017, the global mortality rate for children younger than 5 years was 39 per 1000 livebirths, with malaria causing 3% of all deaths in this age group.[303] In sub-Saharan Africa, the mortality rate was 74 per 1000 livebirths and malaria was responsible for 10% of deaths in this group.[303] Reversing the increase in cases and deaths in high-burden countries described in section 1 is essential both for malaria eradication and to achieve the broader child mortality targets in SDG 3. Additional SDGs that will probably accelerate, and be accelerated by, progress toward malaria eradication are Target 3.8 (achievement of UHC), SDG 1 (end poverty), and SDG 10 (reduce inequalities), all discussed here.[302]

UHC

UHC requires that all people have access to the health services they need, of sufficient quality to be effective, while also ensuring that the use of those services does not expose them to financial hardship.[304] The world has committed to achieving UHC by 2030 under SDG Target 3.8.[302] Taken together, the goals of UHC and malaria eradication perfectly capture the power of a so-called diagonal approach to health, in which a horizontal focus on strengthening health systems is combined with an aggressive vertical focus on controlling and eliminating specific diseases.[305,306] Both approaches depend on a similar set of health system capacities and similar infrastructure, and progress towards one goal makes achievement of the other easier and less costly.[307,308]

Two important caveats must be mentioned. First, the synergies between malaria eradication and UHC do not occur passively; they require active effort and constant attention. The Global Fund has led the way in promoting UHC benefits by offering additional financing explicitly for health system strengthening that supports and complements its disease-specific funding portfolios.[309] PMI similarly prioritises health system strengthening as a core strategic focus area.[310] Second, achieving malaria eradication is not contingent on achieving UHC. History indicates that, regardless of income level, malaria elimination can be achieved well before UHC, as shown by Jamaica, Sri Lanka, Tajikistan, and the USA, among many other countries.[311,312] The journey to UHC in wealthy countries has taken 100 years and some have yet to achieve it.[311] Similarly, many lower-income countries will still be working towards UHC in 2050, despite the global goal of 2030, although investments in malaria eradication can accelerate progress.

Here, we discuss four elements of malaria eradication and UHC that reinforce each other and present opportunities for action to accelerate progress towards both goals: service integration, private provider oversight, quality of services and interventions, and financial protection for vulnerable populations.

Service integration

Unlike eradication of diseases such as smallpox or polio, which rely primarily on vaccination, malaria eradication requires a diverse package of interventions, the successful implementation of which relies on health system capacities and infrastructure that are also essential for UHC. In section 3, we briefly describe the risks and challenges associated with integration and emphasise the important role of good management. When done correctly, integration of malaria operations into the general health system can create efficiencies and opportunities for multidisease, multisectoral approaches that do not exist in vertically managed disease control programmes and can also serve to strengthen UHC. The value of integration is well illustrated in the areas of case management, vector control, and surveillance.

In malaria-endemic countries, community health workers commonly diagnose and treat malaria at the local level, and they often serve as the primary points of contact with the health system for rural and remote communities.[13,73] Expanding the number of community health workers, and the breadth of their responsibilities to include non-malaria services, will increase coverage and access to both malaria interventions and basic health care.[313] Combining the delivery of primary health care with disease control interventions at the community level can also strengthen community participation, essential for achieving both UHC and malaria eradication.[74,314] An example of an integrated, community-level approach to malaria case management implemented in Burma/Myanmar is described in panel 2.

In the field of vector control, standalone programmes focused on *Anopheles* mosquitoes struggle to attract funding as malaria rates fall and other diseases, particularly dengue, rise in relative importance. This situation calls for integrated vector-borne disease control approaches that, notwithstanding the key differences between *Anopheles* and other vectors, share human resources, infrastructure, and capacity to intervene.[315] Finally, standalone surveillance systems for malaria are inefficient and unattractive to health system planners and funders. What countries need, and are increasingly creating, are multivalent surveillance systems that concentrate initially on a shortlist of key health problems and are gradually expanded to embrace a wider array of health challenges.[316,317] Malaria eradication can pioneer the development of more efficient, integrated approaches to health care.

Private provider oversight

All countries have mixed public and private delivery systems for their health-care needs, including infectious diseases such as malaria. The proportion of care delivered by the private sector varies widely, and is generally higher across low-income and middle-income countries where public sector infrastructure and human resources are frequently insufficient to meet the needs of the population, particularly in poor, rural, and remote areas.[318,319] The existence of a large private health-care delivery sector within a country is not in itself a problem. What is important—and too often absent—is effective government oversight and stewardship of both formal and informal private health-care providers.[320] The large private sector that operates in many low-income and lower-middle-income countries is typically unregulated, and the national policies that apply to the public sector are either disregarded or not effectively enforced across private sector providers.[321] In countries such as India and Nigeria, this situation can cause a substantial proportion of malaria cases to be poorly diagnosed, inappropriately treated, and unreported.[322]

Countries with large, unregulated private health-care sectors will have great difficulty achieving malaria elimination or UHC. Countries that have successfully eliminated malaria in the past decade have either a relatively small private health-care sector, such as Sri Lanka, or effective government oversight of all providers, as in China.[296,323] This issue needs to be tackled urgently in India, Nigeria, and many other high-burden countries. Experience has shown that private providers are willing to be convened and conscripted, but are seldom asked.[321] Approaches include working at the national level to create formal agreements between representatives of private providers and the government; working at the district level to informally co-opt and collaborate with local private doctors, clinics, and hospitals; and using social health insurance programmes to link treatment and reporting requirements to eligibility for reimbursement, for example as in the Philippines.[321,324]

Service quality

Achieving UHC requires that health-care services be of sufficient quality to diagnose and treat the most common diseases.[304] Regrettably, major deficiencies in health-care quality exist in all countries, especially those with low or middle income. Two reports published in 2018 thoroughly reviewed the alarming quality deficit and attribute more than 8 million deaths per year in low-income and middle-income countries to poor quality of health services.[325,326]

Poor quality is widespread in both the public and private sectors. In India, quality concerns were prominently cited as reasons for bypassing public facilities in order to seek care from private providers.[325] Under these conditions, malaria and other diseases are commonly misdiagnosed, incorrectly treated, and unreported. Preventive programmes, such as IRS and LLIN distribution, might not have the precision required to be effective. The implications of poor-quality health services are self-evident: malaria eradication efforts are undermined and UHC is weakened, particularly among the most vulnerable populations.[327,328] In section 3 we identified priority management and operational issues

that, when addressed, will undoubtedly strengthen the quality of malaria programme activities as well as those of the broader health system.

Financial protection

Providing financial protection is an essential pillar of UHC, and achieving both UHC and malaria eradication will require that lower-income countries implement a variety of subsidy, prepayment, and insurance programmes to limit the burden of out-of-pocket health spending on individuals and households.[304] The *Lancet* Commission on Investing in Health outlined a path to UHC called progressive universalism, which prioritises coverage for diseases that disproportionately affect poor and rural populations, including malaria.[329]

The enemy of financial protection is out-of-pocket spending. As discussed in section 6, malaria is much less reliant on out-of-pocket expenditure than health-care spending in general, although the extent of out-of-pocket spending varies widely. In countries with high malaria burdens, where out-of-pocket expenditure as a share of total health-care spending tends to be high, out-of-pocket malaria spending might also comprise a substantial percentage of total malaria spending; for example, over 50% in Cameroon and Niger (appendix pp 13–15).[259] In countries that are nearing elimination, out-of-pocket malaria expenditures are very low as a result of reduced spending on patient care, the main driver of out-of-pocket malaria costs. Overall, out-of-pocket spending is still too high in many low-income and middle-income countries, causing financial hardship or the avoidance or deferment of treatment. Common cause exists between supporters of UHC and malaria eradication to prioritise increased total spending on health and to drive out-of-pocket spending into prepaid and risk-pooled insurance schemes to avoid financial hardship for vulnerable populations.

Promoting equity and reducing poverty

The promotion of equity (SDG 10) and reduction of poverty (SDG 1), strongly affect public policy and resource allocation at national and global levels. The links between poverty, equity, and health are well established.[330,331] Malaria represents an extreme manifestation of these associations.

Equity

Malaria is not distributed equally. Pregnant women and children younger than 5 years bear the greatest burden of malaria in high-transmission settings, with multiple negative effects that are further magnified by poverty. Repeated exposure to malaria during childhood is associated with poor cognitive development and increased absenteeism from school, putting children in endemic areas at a disadvantage from a very young age.[332] Globally, poor and vulnerable people are more likely to contract malaria and are at a higher risk of severe disease and death.[333,334] These groups are also underserved by the health system and do not have equitable access to malaria prevention, diagnosis, and treatment.[335]

In health and other sectors, the benefits of public investments are primarily captured by the middle class.[329,331] Because of the extreme concentration of malaria in poor and vulnerable communities, investments in malaria are highly equity enhancing. This is true in high-transmission settings, where the benefits from malaria control in poor communities will be large—and increasingly so as elimination approaches and malaria becomes more concentrated in the most disadvantaged communities.[335] The equity benefits of investments in malaria elimination and eradication should be championed.

Poverty

Poverty is a cause and a consequence of malaria.[336,337] Children from low socioeconomic groups are much more likely to contract malaria compared with children from higher socioeconomic groups.[338] Within poor communities, people in the poorest households have a higher burden of malaria compared with individuals from less poor households.[339,340] In addition, these groups often do not have the financial resources to cover health-care expenses. The costs associated with malaria vary across settings but can be substantial, especially among low-income households in highly endemic countries.[341,342] In Malawi, estimates indicate that the direct and indirect costs of each malaria episode consume more than a week's worth of income for most families.[343] These catastrophic health expenses trap families and communities in a cycle of poverty.

Malaria also impedes development at the national level. A strong negative association exists between malaria incidence and national economic growth. In 1995, the income levels of countries with intense malaria transmission were one-third of countries without malaria, and there was a 1·3% difference in annual economic growth between the two groups over the period 1965–90.[336] The economic benefits of eliminating malaria arise from increases in trade, tourism, and foreign direct investment, and improved productivity and increases in human capital.[301] We briefly review the economic returns from investment in malaria eradication in section 6. Malaria eradication will not only help alleviate poverty at the household level, but also can be expected to have much broader positive effects on the economic fabric and social capital of the world's poorest countries.

Global health security

Over the past two decades, global health security has emerged as a major priority in global health and development,[344,345] and a key motivation for the financing of global health programmes by wealthy nations.[346–348] Initially viewed as protection from the pandemic spread of infectious diseases, the definition of global health security has expanded to include protection from biological

weapons and the spread of antimicrobial resistance; access to safe and effective health services, products, and technologies; and the defeat of major endemic diseases such as malaria.[349,350] The Global Health Security Agenda was launched in early 2014 and is a growing partnership of over 64 nations, international organisations, and NGOs.[351] We describe three areas of synergy between the Global Health Security Agenda and a commitment to eradicate malaria: capacity, the effect on malaria of other disease outbreaks, and malaria's potential for resurgence.

Capacity

A country that has built strong global health security infrastructure is better equipped to achieve malaria elimination, while a country that has achieved malaria elimination is well positioned to expand that capacity to protect against future epidemics or pandemics. The capacity requirements to achieve and sustain malaria elimination and protect against global health threats overlap, and must be in place at the country and regional levels.[13,47,349,352] At the country level, overlapping capacity requirements include strong surveillance, laboratory, and reporting systems, multisectoral communication and collaboration, and a trained workforce able to rapidly respond to the emergence and spread of new pathogens and drug-resistant versions of existing pathogens. At the regional level, capacity is required for cross-border collaboration, sharing of surveillance and laboratory data in real time, and regional early warning systems.[13,47,349,352]

Multiple examples of capacity overlaps between global health security and disease eradication can be found in the polio eradication programme, particularly the EOC model. During the 2014–16 Ebola epidemic in west Africa, Nigeria had two local outbreaks, one of which occurred in Lagos. Despite the potential for rapid spread in such a densely populated area, health officials were able to limit ongoing transmission and bring the outbreaks under control within weeks, mainly because of the EOC infrastructure, coordination mechanisms, and expertise borrowed from the local polio programme.[353] Since then, front-line polio workers have helped support the Lassa fever outbreak response in Nigeria, and a measles immunisation campaign in Pakistan.[354,355] In India, which has been polio-free since 2011, polio EOC infrastructure and human resources have been transitioned to improve routine immunisation coverage rates, strengthen surveillance of vaccine-preventable diseases, and support elimination programmes for a range of infectious diseases, including malaria.[356]

Evidence from polio eradication efforts shows that EOCs provide a platform for government ministries and external partners to coordinate emergency responses, mobilise resources, and bypass cumbersome national and subnational bureaucratic processes. EOCs also present an opportunity to maintain surge capacity for outbreak management and to complete elimination operations in otherwise neglected or hard-to-reach populations, while allowing for integration of standard malaria interventions into the broader health system and overall strengthening of global health security.[357]

Effect of disease epidemics on malaria

When malaria-endemic countries have other infectious disease outbreaks, malaria risk can increase, particularly when health systems are overwhelmed and disrupted. This happened when the west Africa Ebola epidemic occurred during peak malaria transmission season in 2014. For much of that year, routine malaria services were halted and malaria case detection and treatment dropped precipitously as health facilities closed, health workers were diverted to Ebola response, and the public avoided seeking health care out of fear.[358] Modelling the effect of decreased health system capacity on malaria morbidity and mortality in 2014 suggests that 3·5 million untreated malaria cases and 10 900 additional malaria-attributable deaths occurred across Guinea, Liberia, and Sierra Leone as a result of disrupted services during the Ebola epidemic.[359]

An additional challenge arose due to the similarities in clinical symptoms between Ebola and malaria. Estimates suggest that 33% to 54% of patients admitted to Ebola treatment units did not have the disease, putting these patients at risk for exposure to Ebola and increasing the burden on the units.[360] Similarly, in eastern Democratic Republic of the Congo in late 2018, up to 50% of people screened in the Ebola treatment units were found to have malaria only, and there was an eight-fold increase in reported malaria cases compared with the same period in 2017.[361] High rates of malaria might also mask other common causes of febrile illness besides Ebola. Eliminating malaria in areas at high risk for epidemic or pandemic outbreaks of febrile disease will prevent malaria surges, relieve the competition for scarce resources, and allow more focused and effective responses to acute emergencies.

Resurgence potential of malaria

Until malaria is eradicated, countries in the prevention of re-establishment phase will remain at risk from outbreaks triggered by importation of cases from endemic countries. Although most countries that have already achieved malaria elimination have strong health systems capable of rapidly detecting and treating imported cases, this will increasingly not be the situation in the future.[362] After 2025, most countries that eliminate will be low-income or lower-middle-income countries with relatively weak health-care systems. The risk of resurgence is higher in areas where the population retains partial immunity and infections are more likely to be minimally symptomatic or asymptomatic, and thus might not come to the attention of the health system.[138] Since population immunity wanes quickly once regular exposure to infection ceases, the risk of undetected cases leading to resurgence is higher in areas that have

substantially reduced transmission but not yet achieved elimination. Historically, malaria resurgence following complete elimination has been rare, but this situation is highly dependent on ongoing investment in surveillance and response, and cross-border and regional collaboration with endemic neighbours.[363,364] Once malaria eradication is achieved, the risk of resurgence no longer exists—a direct benefit to global health security.

Section 9: conclusions and recommended actions

Following 2 years of discussion, important new analyses on the epidemiological and financial dimensions of malaria eradication, a comprehensive examination of the literature, and drawing upon the deep and expansive expertise of the Commissioners and the other authors, the Commission has reached four seminal conclusions.

First, that malaria can be eradicated by 2050. Second, that the social and economic benefits of eradication, and the value to global health security, UHC, and other SDGs will greatly exceed the costs. Third, that a combination of plausibly available domestic and international resources is sufficient to pay for malaria eradication. And fourth, that the alternative options—including ongoing investment in control and prevention of re-establishment, the persistence of malaria foci indefinitely in Africa, the risk of resurgence, and and a losing battle against resistance—are extremely unattractive. For each of these conclusions, we identify opportunities for action that will accelerate the path to eradication.

Central to the Commission's conclusion on the feasibility of eradication is the projected future effect on malaria endemicity of global trends and enhanced malaria control (figure 5). We project a world in 2050 with scattered pockets of low-level malaria, brought about by the combined effect of global trends and scale-up of current interventions. The key question is whether that modelled trajectory can be deliberately accelerated to create a world with no malaria by 2050 or sooner. The answer in this report is strongly affirmative. By enhancing the software of eradication (sections 3 and 7), by developing and deploying innovative hardware (section 5), and by spending an additional $2 billion per year (section 6), it is highly probable that this modelled future can be transformed into a malaria-free, purposefully driven, engineered future.

Conclusion 1: malaria eradication is possible within a generation

The feasibility of eradication by 2050 is an assertion based on the balance of evidence and on the probability that particular challenges will be overcome. This assertion cannot be proven in a rigorous or formal sense but is supported by evidence presented in this report. The Commission notes that the degree of certainty concerning malaria eradication is at least as strong as it was when the eradication campaigns against smallpox, polio, and Guinea worm were launched. The evidence also makes clear that malaria will not be eradicated under a so-called business-as-usual scenario and that specific actions are required at country, regional, and global levels to ensure that eradication is achieved. These actions will be reinforced by a global commitment to pursue malaria eradication as a defined, time-limited goal. The evidence also shows that malaria eradication will not be achieved with current tools alone, and that research, development, innovation, and the rapid deployment of new tools are essential for regional elimination and global eradication. Here, we discuss essential actions for eradication.

Strengthen leadership and accountability at national, regional, and global levels

A complex network of national, regional, and global stakeholders currently provides technical, operational, advocacy, and financial leadership on malaria. Building on this network approach, leadership and accountability can be further enhanced and shaped to support a renewed, time-bound commitment to global eradication. The driving force behind global eradication is regional elimination. Regional platforms should be supported by global partners to strengthen regional commitment and motivate unambiguous and energetic commitment by national and subnational leaders in every endemic country.

Specific recommendations in this report include the creation of country-level malaria elimination task forces; the strengthening of regional and subregional organisations such as ALMA, APLMA, the E8, and the Sahel Malaria Elimination Initiative; further clarification of roles and sharpening the focus of the global apex institutions, WHO and the RBM Partnership; the development of greater policy alignment and complementarity between major funders, especially the Global Fund and PMI; and the creation of an independent monitoring board for malaria eradication, modelled on the equivalent structure for polio, to serve as a bold and honest guardian of the milestones along the eradication pathway.

Strengthen management at all levels

Weak management might be the single largest constraint to national and regional elimination and global eradication, and addressing this issue should be prioritised. This will require the development of training opportunities and the availability of both international and domestic funds to support them. At the global level, merit exists in creating an elite training programme suitable for senior malaria managers at national and subnational levels. Such training could be offered by a consortium of southern and northern universities, with an emphasis on practical management skills with strong contributions from business schools and the private sector. Elite training programmes of this kind not only strengthen the management capacity

and skills of key individuals, but also create a cadre of well trained malaria managers worldwide, who speak a common language and form an active professional network. To encourage this, the programme should develop ongoing mentorship of and interaction among alumni.

Of equal or greater importance is the proliferation of local approaches to management training with a focus on the district level. District-level malaria managers and staff, together with community leaders and representatives of the national or state level, need to come together regularly for management training, iterative problem solving, and team building. In some settings, including private health-care providers and any contractors to whom malaria services have been outsourced will be important. Different models for these activities will need to be tried, assessed, modified, and expanded. Major funders should strongly encourage and support management training at all levels.

Implement programmes that are smarter, more nimble, and driven by data

A national malaria programme that implements a single, country-wide strategy, uninformed by real-time data, unresponsive to changing circumstances, and awaiting generic policy guidance issued periodically by WHO before modifying its approach is unlikely to achieve malaria elimination. What is required is nimble, flexible, data-driven management, highly responsive to local circumstances, and constantly adjusting in the light of new evidence. Active community participation and the incorporation of community-generated ideas into the design and implementation of interventions will further strengthen programme effectiveness. Such arrangements require enhanced managerial autonomy at the district level, necessitating more flexible administrative procedures both by national authorities and by global funders. The smarter and more targeted use of interventions will probably reduce programme costs, freeing up resources to be spent elsewhere. The quality and effectiveness of programme implementation will continue to be stronger predictors of success than epidemiological trends or how much money is being spent.

Share and use data

The ability to collect, analyse, and use data is being transformed by the ongoing revolution in information technology. The Commission predicts that these trends will be transformative over the next 5–10 years. This data revolution will affect programme management at the subnational and national level, will strengthen coordination and South–South cooperation at the regional level, and will be essential to track progress towards eradication at the global level. For this revolution to happen, data need to be generated and shared more rapidly and universal access to data should be the norm. The Commission recommends a move towards quarterly reporting of national data and the creation of data hubs that facilitate universal access to this information.

Address the most challenging areas now

Using current data and future projections of malaria rates and R_C, we predict countries in which malaria elimination will be hardest and where the final elimination efforts will be focused (figure 5). To engage strongly with these countries now is important for two main reasons. First, to drive down deaths and cases to modest levels to prepare for elimination. Second, in some of these countries or some parts of these countries, to create large-scale demonstration sites to explore the limits of the possible with optimal use of current tools, strong management, and sufficient finance. New tools and techniques can be rapidly tested and rolled out in these demonstration sites.

Position surveillance and response as a central strategy

In all countries, at all stages of the elimination continuum through to the prevention of re-establishment, strong surveillance systems, and strong response to the data which they produce, are the core of any malaria programme. Particularly as control efforts succeed and malaria becomes less common, cases must be reported, investigated, and acted on promptly. New molecular technology will increasingly enhance the usefulness and effectiveness of surveillance. Several regions are leading the way in the design and implementation of effective surveillance and response systems, including China, eSwatini, Malaysia, Thailand, and Zanzibar, Tanzania. Surveillance is also crucial in monitoring insecticide and drug resistance. South-South technical collaboration, facilitated by regional bodies such as APMEN and the E8, can promote the adaptation and implementation of these models in other countries.

Co-opt private sector health-care providers

The Commission concludes that countries with large and unregulated private health-care sectors will have great difficulty achieving either malaria elimination or UHC. Following the need for strong management, this challenge is perhaps the greatest barrier to both malaria elimination and UHC. India and Nigeria are strong exemplars of this problem. Solutions are complex and highly country specific. In both India and Nigeria, the situation might be best managed at the state level, with supporting legislation, policies, and interventions at the national level. Government needs to embrace its stewardship role for all health-care providers and ensure that malaria cases are correctly diagnosed, treated, and reported, irrespective of whether they present at a public or private facility. This issue is domestic and involves strong, local, vested interests. External advice might add little value or even be counterproductive. Countries have to solve this problem for themselves.

Leverage the private sector and the market for service delivery

The national malaria programmes of most countries try to do everything themselves; provide all commodities, employ all malaria workers, and deliver all malaria interventions. This approach is certainly not necessary and, depending on the capacities of the government and especially the ministry of health, it might not be desirable. The Commission recommends active engagement with the private sector in the delivery of services with the expectation that this will relieve government of burdensome tasks and improve service delivery and efficiency. Two salient opportunities exist. The first is re-establishing the private market for LLINs, with close government oversight and adequate public subsidies, including free distribution for households who cannot afford to purchase nets from private outlets. This move from a supply-driven to a demand-driven approach to LLIN distribution might be especially appropriate in countries that are transitioning out of eligibility for Global Fund support. A second opportunity is outsourcing certain malaria services. This approach is already used with donor funds: PMI contracts with international NGOs to support IRS, and the Global Fund has many private sector Principal Recipients, which greatly expand access to malaria diagnosis, treatment, and prevention. Countries might benefit from adapting this model to embrace government contracting with both for-profit and not-for-profit private entities to provide specified services. These initiatives should be closely monitored for quality and cost, and successful models scaled up and replicated in other countries.

Proceed cautiously with transition, integration and decentralisation

Some countries are facing, and most countries will eventually face, the transition from reliance on development assistance to sustained programme support from domestic sources. Financial transition is often accompanied by broader country initiatives to integrate previously vertical disease programmes into the mainstream health system. In parallel, decentralisation in many large federal countries and in some smaller non-federal countries is devolving responsibility for financing and delivering health services, including malaria, to subnational and local government structures. The consequent restructuring of financing, operations, and delivery are complex challenges which countries can best navigate through careful planning and a realistic implementation timeframe. In the longer term, positive outcomes from a responsive and sustainably resourced health system might be anticipated. In the short term, these processes pose dangers to the continued success of a country throughout its malaria elimination continuum. Unless managed carefully, simultaneous transition, integration, and decentralisation places countries at grave risk of malaria resurgence and the loss of gains hard-won over the past decades.

Prioritise research and development investments

Although substantial progress can be made by improving management and optimising the use of tools available now, new tools and strategies are essential for eradication by 2050. The Commission identifies four areas in which enhanced investment is likely to have the greatest effect in overcoming operational and biological impediments to eradication. First, the Commission is enthusiastic about the potential to harness the data and information technology revolution to develop new generations of tools and techniques for collecting, analysing, and using data for decision making at local, national, regional, and global levels. These efforts should include research and development to optimise the value of new molecular surveillance technology. Second, the Commission recognises the need for substantial investment in diagnostics, drugs, and vector control technologies. Progress in these areas will be essential for elimination in the hardest places and global eradication. Third, gene drive technologies have a truly game-changing potential, and could address the challenges posed by efficient vectors in high-transmission areas and the high cost and operational difficulties inherent in the current dependence on LLINs and IRS. Fourth, the Commission emphasises the importance of implementation research to find practical solutions to local operational problems. The Commission cautions against the use of randomised or other formalised trials to answer operational questions and recommends a pragmatic and iterative learning-while-doing approach.

Several outcomes from this research—improved targeting of interventions, simplified drug regimens, longer-lasting insecticides, and more—have the potential to reduce programme costs. Well before a new product becomes available, initiating policy discussions to clarify regulatory pathways, use-scenarios, and financing options is essential to shorten the time between product launch and widespread use.

Develop, commit to, and manage an eradication roadmap

Eradication by 2050 requires both rapid elimination in low-burden countries and accelerated malaria reduction in high-burden countries. These targets must be considered together and are dual requirements for success. More specifically, to be on track for eradication by 2050, the world outside Africa needs to be malaria-free, or almost so, by 2030. This goal is achievable, but only with accelerated progress in the Americas and, particularly, the Asia-Pacific region. In parallel, great progress is required across Africa, including the achievement of a 90% reduction in cases by 2030, as called for by the *WHO Global Technical Strategy for Malaria 2016–2030*.[6] Intense subnational efforts in very high-transmission areas of Africa will establish what is possible when strong management, optimal use of technology, and adequate funding are combined.

A crucial next step towards eradication is the development of a detailed roadmap showing the required

progress of all countries and regions in 5-year increments between now and 2050. This roadmap should build on information from multiple sources, including the current situation (figures 1, 3); future projections based on a variety of scenarios and incorporating new data and modelling techniques as they become available (such as in figures 4 and 5); and country-based judgments concerning what is likely to be achieved given the social, political, and economic circumstances. These views of the world at future dates will be a balance between likelihood of success and aspiration. Emphasising the importance of country ownership of eradication, the creation of a global eradication roadmap would begin with each country developing and committing to an elimination plan. These country commitments and plans would then be aggregated into subregional and regional plans, which would then be assembled and endorsed as a global eradication roadmap. The global eradication roadmap and its 5-year incremental targets—and the corresponding regional and country elimination plans—will need to be proactively managed and used, particularly by the proposed independent monitoring board for malaria eradication, to hold all countries, donors, and malaria partners accountable to eradication by 2050. Constant updating and incorporation of new data, and frequent presentation and discussion at national, regional and global fora, will be essential.

Conclusion 2: malaria eradication is a good investment with large social and economic rewards

Malaria is not just another infectious disease, it is a disease that has had a devastating effect on people and communities over tens of thousands of years. During most of the past century, malaria was the number-one killer across the tropics. Currently, the disease is still a leading cause of death in children younger than 5 years in Africa, and in a dozen African countries, it is responsible for over a fifth of all postneonatal childhood deaths. Allowing this situation to continue is socially and economically indefensible.

The benefits for countries, regions, and the world from elimination and eradication are substantial, including the avoidance of large numbers of cases and deaths, and substantial gains in education, productivity, and the economy. Most of these benefits would be realised by a high level of control, a scenario under which malaria is eliminated from many countries but persists among poor communities across much of Africa and also in Papua New Guinea and parts of the Amazonian region (figure 5). So why eradicate?

The answer is the eradication dividend. In the control scenario, the risk of importation and resurgence in countries or parts of countries that are malaria free is constant, requiring ongoing investment in surveillance and periodical, intense efforts to deal with outbreaks that will inevitably take place. If a major resurgence occurred, the consequences—including substantial mortality in non-immune populations—could be devastating. In countries that still have active malaria transmission in poor and isolated communities, the infrastructure and resources required for national malaria programmes would have to be sustained. Eradication allows all these investments to stop and brings the risk of resurgence to zero. Substantial resources will be freed up and can be reallocated to other health priorities. The once-and-for-all nature of malaria eradication is a benefit to every country, every region, and the world, for all time.

In addition, the development community nowadays is rightly focused on poverty alleviation, promotion of equity, the achievement of UHC, and the strengthening of global health security. As this report shows, malaria eradication contributes strongly to all of these goals, and vice versa. Eradication is a truly win-win proposition. However, this win-win scenario will not occur passively. Deliberate efforts are essential to ensure that malaria investments promote UHC and global health security and the other way around.

Conclusion 3: malaria eradication can be afforded

Effective programme management, design, and implementation are essential for success. Without these elements, large amounts of money can be spent and eradication will still not be achieved. However, well managed and effective programmes need adequate resources to ensure that they get the job done. Arguably, a combined strategy of increasing total spend and emphasising management and efficiency on the ground will be the recipe for success. Consensus is needed on how much money is required, where it should come from, and to what purposes it should be allocated. These matters are taken up in the action steps proposed below.

Spend an additional $2 billion per year

Malaria eradication is likely to cost over $6 billion per year. The world is already spending around $4·3 billion. Additional funds in the order of $2 billion a year can make a big difference. To reduce donor dependence, extra money will come preferably from a modest increase in development assistance for malaria (we propose $0·5 billion) and a substantial increase in government malaria spending, especially in the most affected countries (we propose $1·5 billion).

Mobilising an additional $1·5 billion from government health spending will be challenging, especially in the short term. On average, in the high-burden countries, malaria spending has been rising faster than either GDP or total health spending. This situation is encouraging and shows the commitment of individual countries and regions. The wide range of government spending on malaria among high-burden countries provides opportunities. If Nigeria chose to spend the same proportion of its GDP on malaria as the average high-burden country (0·07%),[259] an additional $0·3 billion per year would be generated. In practice, the level of reasonable government malaria expenditure must be

addressed country by country in the light of GDP growth, tax collection, overall public spend on the health sector, and the priority of malaria. We recommend detailed work in each high-burden country to determine reasonable objectives to increase public expenditure on malaria. These commitments can then be embodied in agreements between the countries and donors, and should be generously incentivised.

Generating additional development assistance for malaria will also be challenging, given that development assistance for health in general has barely changed since 2011. The Global Fund is seeking an additional $1·8 billion in its current replenishment. This sum is for three diseases over 3 years and implies an increase in malaria spending of $0·2 billion per year. In addition, new donors and smaller donors could readily do more. China has become a major source of development assistance for health, now ranking tenth, ahead of Australia and 13 other traditional donor countries. China's role in malaria internationally is growing, and opportunity exists for the country to be among the leading donors for malaria eradication, with a focus on both Africa and Asia-Pacific. The expected celebrations of its malaria freedom in 2020 could offer an attractive venue for China to announce a greatly expanded role in malaria eradication. Other Asian countries, such as Brunei, Malaysia, Singapore, and South Korea could do more, especially focusing on their neighbours and noting their strong self-interest in a malaria-free region. In addition, opportunities exist for wealthier states in the Middle East, some European countries, and the larger economies of the Americas to increase their role in supporting malaria eradication. Taking these opportunities together, the target of an additional $0·5 billion of development assistance for malaria could be achievable. In addition, the current major donors must maintain the real value of their investments over the next decades and not reduce them as the number of endemic countries and the global burden of malaria decline.

Allocate development assistance for malaria more smartly

In addition to maintaining current spending, major contributors of development assistance for malaria need to carefully consider how they are allocating their resources. The two main channels of development assistance for malaria, the Global Fund and PMI, both spend most of their funds in the same ten high-burden countries. That this allocation of resources will lead to eradication is uncertain. We propose several actions. First, modelling should determine what pattern of development assistance from all sources is most likely to lead to eradication in the shortest timeframe. Second, these insights should guide a joint investment strategy by the Global Fund and PMI to ensure that all elements that are essential to eradication are supported. In parallel, the crucial investment in innovation and technology development must continue, supported particularly by the Gates Foundation, the US National Institutes of Health, and private industry.

Invest in the prevention of re-establishment

No one assumes that low-income countries that have eliminated polio or measles, for example, should be cut off from development assistance to maintain the child vaccination programmes against these diseases. Yet, that policy appears to prevail for malaria, whether implicit or explicit. The Global Fund formally excludes countries with no malaria from eligibility. Countries such as China and Malaysia can be expected to maintain elimination and prevent re-establishment without development assistance. However, for tropical, low-income countries that have recently eliminated, a requirement might exist for continued development assistance to maintain the national malaria programme at the capacity required to rapidly identify and treat imported cases and to deal effectively with outbreaks that occur. Without these measures, malaria will surely resurge in highly receptive geographies with an abundance of anopheline vectors. Preventing this from occurring is as important for global eradication as the next wave of elimination or accelerated progress in high-burden countries.

Conclusion 4: alternatives to eradication are untenable

The alternative to a commitment to malaria eradication is business as usual, perhaps with some enhancements. This situation will probably lead to the persistence of malaria in poor countries and poor communities in Asia-Pacific and the Americas, up to mid-century and beyond. In Africa, although a few countries on the southern and northern margins of the endemic zone might eliminate, malaria will persist for decades in many countries, with major social and economic consequences. Countries that have eliminated will face the constant threat of importation and re-establishment and therefore will have to maintain substantial malaria surveillance and response capacity. Finally, parasites and mosquitoes will become increasingly resistant to more drugs and insecticides. The evolutionary arms race against drug and insecticide resistance is ongoing and *Plasmodium* and *Anopheles* might win. Nowadays, although close to catastrophe with artemisinin resistance, the malaria community seems to be keeping one step ahead but this might not always be the case. The ability of parasite and mosquito populations to select for resistance to any and all pressures that are applied is probably infinite, but the ability to discover and deliver new drugs and insecticides is not. The only way to end this arms race for good is eradication.

Additionally, the issue of equity is central. If the international community decides not to push for eradication by 2050 or sooner, it consigns poor communities in many African countries and a few places elsewhere to ongoing sickness and death that could be prevented.

The road ahead

The malaria map has shrunk dramatically since the discovery by Sir Ronald Ross in India in 1897 that malaria was transmitted by *Anopheles* mosquitoes. Back then, all countries in the world (roughly 200) had endemic malaria. By the year 2000, only 106 countries still had malaria transmission, and by 2017, this number had declined to 86. Malaria has been declining for over a century, and the pace of this reduction has accelerated since 2000. Most countries still affected have low levels of malaria compared with the past, while roughly 30 countries continue to have stubbornly high burdens. The world is at an important decision point. The malaria community can continue current efforts and anticipate gradual reductions in most countries, persistent transmission in some parts of Africa, an ongoing and increasingly difficult struggle against drug and insecticide resistance, and the constant threat of resurgence, or it can commit to eradication by 2050 at the latest and be done with malaria once and for all.

During the work of the Commission, people have asked whether eradication is merely conscientious elimination. Although eradication is achieved by elimination, country by country and region by region, a global commitment to eradicate by 2050 brings purpose, urgency, and dedication to the task, well beyond a policy of simply eliminating where possible as soon as possible. An eradication goal provides a rationale for countries to eliminate, knowing that their neighbours and regions are also committed. An eradication goal encourages investment and innovation in high-burden countries to accelerate the endgame, and it motivates a prioritised and aggressive research agenda to rapidly develop and deploy the new tools required to achieve eradication within three decades. The Commission concludes that a time-bound commitment to eradicate is essential to bend the curve and create a world with no malaria by 2050.

As with HIV, vanquishing malaria is associated with bold exceptionalism where the historical nature of the goal drives energy and investment well beyond those mobilised for other health goals. This exceptionalism should be seen as an asset to the health sector rather than a problem to be corrected. The international health community should vigorously embrace malaria exceptionalism and use the substantial investments on offer to help countries achieve the goals of UHC, protect global health security, enhance equity, reduce poverty, and promote multiple objectives within other SDGs.

The Commission has delivered its manifesto. We urge that the relevant organisations at country, regional, and global levels consider the manifesto carefully and commit to it. At present, both the Gates Foundation and WHO have committed to malaria eradication, although the WHO commitment thus far does not have a specific timeline. The Global Fund, PMI, and the RBM Partnership have yet to formally commit to a time-bound eradication goal. In addition, the major malaria organisations should come together to agree on a collaborative and collective way of working, with mutual acceptance of the role of others. This occasion would also provide an opportunity to revisit an enhanced role for the End Malaria Council and the possible creation of an independent monitoring board. Following these developments, the urgent task of constructing a detailed roadmap must commence. This roadmap would delineate precise goals for malaria epidemiology, finance, operations, and research and development at 5-year intervals from 2020 to 2050. To ensure that malaria eradication remains driven by countries and regions, the goals for epidemiology, operations, and domestic finance must be set by countries and aggregated up to regions and the world. Meanwhile, the Commission will contribute by tracking progress, and updating recommendations concerning the operational, technical, and financial building blocks of eradication laid out in this report.

Malaria eradication will save many lives in perpetuity; it will promote equity and reduce poverty; it will deliver broad benefits to the human welfare and the economy of Africa and many parts of Asia and the Americas; and it will contribute to UHC, global health security, and the achievement of the SDGs. These are compelling reasons to eradicate. However, these arguments are not sufficient to motivate and sustain the necessary degree of global commitment and cooperation. A higher ambition and vision are required. Malaria eradication is a goal of epic proportions that represents the best of human ingenuity and requires an extraordinary degree of trust and collaboration among all nations. It is this bigger vision that will propel and sustain the community in the long and sometimes difficult road to a malaria-free world.

Contributors

The first draft and subsequent iterations of this report were written by a core team led by RGAF, and comprising IC, GN, KH, EL, JW, and HJW. All Commissioners contributed intellectual content to the overall report structure and concepts, the writing and editing of subsequent drafts, and the conclusions. The report was prepared under the general direction of the Commission Co-chairs RGAF and WM-S. All authors approved the final version for publication and agree to be accountable for resolving any future questions related to the integrity or accuracy of the report. The views expressed in this publication are those of the authors and do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated or the funding source.

Declaration of interests

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