The enormous decline in the annual morbidity and mortality from malaria is the spectacular global public health success of the past decade. This achievement results largely from increased finance for investment in measures known to prevent malaria: bednets treated with long-lasting insecticides, chemoprophylaxis, and rapid access to effective treatment. Such has been the success of these measures that plans are being put in place to achieve the vision of a malaria-free world within the next three decades. Large financial and political commitments and ongoing research will be required to maintain the gains, overcome known and unknown challenges such as drug and insecticide resistance, and to achieve those goals. Effective vaccines or methods for reducing mosquito vectorial capacity would add enormously to the chance of achieving this goal. The aim of this article is to summarise the current status of malaria control, the recent research successes, the challenges being addressed, and the plan for progress to elimination of malaria in the longer term.

Spectacular progress in reducing the burden of malaria

Funding for major efforts in implementation of known effective preventive measures in the past 15 years has caused an almost 40% reduction in incidence of malaria disease episodes. These measures, together with increased access to effective treatment, have led to a reduction in malaria death rates of 60% globally, and 71% in children under five. It is estimated that between 2001 and 2015, ~6.2 million lives were saved by increasing the provision of these services. Approximately 110 countries are free from malaria, ~40 have committed to an elimination timetable, while 70 focus predominantly on malaria control. Many factors contributed to this success from the many constituencies that make up the Roll Back Malaria Partnership, but most of the progress in Africa is usually attributed to widespread distribution of bednets treated with long-lasting insecticides, combined with increased access to highly-effective drugs.

The current situation

According to the latest information provided by the WHO, ~1.2 billion people are at risk of malaria with the major burden of disease carried by young children and pregnant women living in endemic areas. The burden of malaria is not evenly distributed across the world. About 90% of malaria deaths occur in sub-Saharan Africa and recent estimates suggest that 80% of malaria deaths occur in only 15 countries. The large morbidity resulting from \textit{P. vivax} is seen mainly in the Asia Pacific region. Further general information on malaria is available in the most recent World Malaria Report from WHO. There has been great recent interest in the finding that infections with the simian malaria \textit{P. knowlesi} have become increasingly important in Malaysia and surrounding countries.

The strategy for malaria control leading to elimination

The overall guiding strategy for addressing malaria is summarised in the \textit{Global Technical Strategy for Malaria Elimination 2016–2030}, which was approved and adopted by the World Health Assembly in May 2015. The strategy calls for accelerated action towards malaria elimination in countries and regions, but does not set a time frame for global eradication. Notably this document recognises the continuum of activities from malaria control to elimination, the...
importance of a multi-disciplinary approach, and the need for tailor-made strategies for different situations, even within one country, in other words, ‘One size does not fit all’. One area, for example a mountainous region, may have only the problem of introduced malaria occurring in people of all ages, whereas another highly endemic area may need to focus on children and pregnant women who remain at risk and suffer the consequences all year round.

The Global Malaria Programme of WHO provides support to countries, compiles the Annual Global Malaria Report, and through the Malaria Policy Advisory Committee provides a normative role in reviewing new data or new problems to provide advice for policy implementation at country level.

This WHO strategy is complemented by the Roll Back Malaria advocacy plan, Action and Investment to Defeat Malaria 2016–2030, that was approved in 20155. The publication outlines both the health and economic benefits that would flow from malaria elimination, and like the Global Technical Strategy was the result of extensive consultative processes involving the participation of more than 400 malaria experts from 70 countries. Ambitious but achievable global targets were established, including:

- reducing malaria case incidence by at least 90% by 2030
- reducing malaria mortality rates by at least 90% by 2050
- eliminating malaria in at least 35 countries by 2050
- preventing a resurgence of malaria in all countries that are malaria-free.

The timeline of 2016–2030 is aligned with the 2030 Agenda for Sustainable Development, the new global development framework adopted by all UN Member States in September.

**Malaria elimination**

The major progress already referred to is the result of implementation of known effective preventive measures, including vector control with long-lasting insecticide-treated nets and indoor residual spraying; chemoprophylaxis including intermittent preventive treatment of malaria in pregnancy (IPTp); intermittent preventive treatment of malaria in infants (IPTi) or malaria chemoprevention during the season of malaria transmission (SMC); and provision of ready access to case management with rapidly-effective drugs, primarily artemisinin combination treatments (ACTs).

As countries, or areas within countries, move towards elimination, the emphasis changes from population level data and disease control to intense surveillance for identification of individual infections, followed by planning and, most importantly, implementation of a response. For example, teams might test everyone in a compound or a village surrounding a person presenting with illness, apply control measures locally, and search for the source of introduced cases.

**MalERA (Malaria Eradication Research Agenda)**

Following the call for malaria eradication, the Bill & Melinda Gates Foundation recognised the need for new and better tools for elimination, and new and better systems to guide delivery of services to achieve those goals. Following extensive discussions by working groups, a research agenda was developed (MalERA)6 that included:

- Better and safer drugs for ease of administration to populations. The ‘dream’ product profile is ‘SERCAP’, (Single Encounter Radical Cure And Prophylaxis), i.e. a single dose treatment to kill not only asexual blood-stage parasites but also liver and sexual stages. An intermediate goal would be an alternative and more effective drug to kill hypnozoites, the dormant liver stage responsible for relapse in P. vivax, but without the troublesome side-effects of primaquine, the only drug currently available for that purpose.
- Basic research enabling culture of all life cycle stages of all parasites infecting humans would be required for development of vaccines and for production of better drugs for eradication of hypnozoites. This would entail investment in culture of hepatic stages of P. vivax, and achieving the dream of laboratory culture of sporozoites from gametocytes.
- The emphasis on elimination draws attention to P. vivax, common outside Africa, and with separate challenges such as long-term relapses from hypnozoites, and transmission by vectors biting outdoors and during the daytime, which are therefore not amenable to the standard interventions for vector control.

Many considered that elimination would not be achieved without a major breakthrough such as effective vaccines to reduce morbidity and transmission, or a technology for vast reduction in vectorial capacity of *Anopheles gambiae*, the most efficient and important vector of *P. falciparum* in Africa.

It is a source of optimism that since the MalERA agenda was proposed, funding was directed to address important gaps, a Malaria Eradication Scientific Alliance (MESA) was established, and now through its MESA Track database tool can capture relevant research and development projects. By the end of October 2015, 685 projects from 647 institutions and 84 countries had been documented7. MESA is currently coordinating several expert groups to perform a 5-year ‘refresh’ of the MalERA agenda.

Progress is being made on many other fronts, including conference reports of the *in vitro* culture of sporozoites from gametocytes; successful culture of hepatic stages of plasmodia; and development of new antimalarial drugs, through ‘Medicines for Malaria Venture’ (MMV), a highly successful not-for-profit public-private partnership. The timeframe for initial testing of new drugs (or vaccines) has been dramatically shortened by the development of a blood stage challenge model by Queensland-based researchers.
The challenges for malaria control and elimination

See Table 1 for a more comprehensive list. Some of the biological, societal and economic requirements for elimination are listed in Table 2.

**Artemisinin resistance**
The time and mode of action of artemisinin are not well understood, and *in vitro* tests are not sufficiently developed and standardised to replace the requirement for *in vivo* testing for the presence of resistance. A warning sign, before emergence of clinical resistance, is the detection of delayed parasite clearance from the blood over the first few days of treatment. Because of the fear of emergence of resistance, combination therapy is essential, for example with piperaquine or lumefantrine, so the efficacy of partner drugs is also of great importance to ensure complete parasite clearance. Recently, drug resistance has been associated with some but not all mutations of the *kelch* gene in *P. falciparum* that will probably assist in mapping resistance. Melbourne-based researchers have developed synthetic artemisinin-like compounds, which are probably not susceptible to *kelch*-based resistance.

**Insecticide resistance**
Chemical resistance to insecticides is a well known threat. Strong movements against DDT that is cheap and effective for indoor residual spraying (because of past evidence of harmful environmental effects when very widely distributed in agriculture) mean that there are few suppliers globally, and alternatives are very expensive. Behavioural resistance is another well known complication of the introduction of effective vector control directed at mosquitoes that bite indoors in the evening. Repeated studies have documented the gradual increase in proportion of mosquitoes biting earlier in the evening or later in the morning and resting outdoors where they are not susceptible.

Another huge challenge, particularly for control of *P. vivax* is that the majority of vectors for this parasite bite outdoors and during the daytime. No satisfactory method for long-term control of these vectors is available.

**Elimination as an approach to drug resistance in the Mekong region**
Where artemisinin has been widely used in the Mekong region, delayed parasite clearance has been noted in many countries, and it is felt that in the absence of alternative drugs, the only appropriate approach is to eliminate malaria in the area where resistance has already been detected. Pilot studies have been initiated to test the feasibility of this approach.

Fortunately, delayed parasite clearance due to artemisinin resistance has not yet been seen in parasites from India and Africa, but in the recent past, development of resistance to chloroquine or sulphadoxine/pyrimethamine accompanied by ongoing use of those drugs led to many unnecessary deaths.

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**Table 1. Some of the challenges for malaria control and elimination.**

<table>
<thead>
<tr>
<th>Parasite and vector factors</th>
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<tbody>
<tr>
<td>Artemisinin resistance (and resistance to partner drugs)</td>
</tr>
<tr>
<td><em>P. vivax</em> hypnozoites</td>
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<tr>
<td>Detecting infections at low parasitaemia</td>
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<tr>
<td>Vector resistance (chemical and behavioural)</td>
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<tr>
<td>Substandard and counterfeit drugs</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Societal and economic</th>
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</thead>
<tbody>
<tr>
<td>Inadequate health services to deliver interventions</td>
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<tr>
<td>Lack of financial commitment</td>
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<tr>
<td>Lack of political will</td>
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<tr>
<td>Cross border coordination</td>
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<tr>
<td>Underserved minorities at high risk</td>
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<tr>
<td>Civil unrest</td>
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</tbody>
</table>

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**Table 2. Preparing for elimination.**

<table>
<thead>
<tr>
<th>Biological approaches</th>
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<tbody>
<tr>
<td>SERCAP a drug for ‘Single Encounter Radical Cure And Prophylaxis’</td>
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<tr>
<td>Highly sensitive non-invasive point-of-care tests</td>
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<tr>
<td>Highly effective malaria vaccines</td>
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<tr>
<td>Novel vector control strategies</td>
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<table>
<thead>
<tr>
<th>Societal and economic</th>
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</thead>
<tbody>
<tr>
<td>Political will for a long-term program at high cost per case</td>
</tr>
<tr>
<td>Financial commitment</td>
</tr>
<tr>
<td>Experienced work force</td>
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<tr>
<td>Technical and operational capacity</td>
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<tr>
<td>Ongoing research</td>
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</tbody>
</table>
Funding shortfall

The major advances of the past two decades are at great risk from lack of funding. Not only could progress stall, but major epidemics of malaria could return to cleared areas, as has been seen so often in the past\(^1\), with serious effects on people of all ages whose immunity has declined through lack of boosting by recurrent sub-clinical infections.

The case is now strong for the economic benefits that will follow from the elimination of malaria\(^5\). This message needs to reach the highest levels of government to ensure financial and political commitment and the engagement not just of the health system, but all sectors of society.

Strengthened Health Services

As the malaria map shrinks, the last pockets of transmission are often found in marginalised poor or rural populations with least access to services. As episodes become infrequent, success will depend on a general health service with the capacity to recognise and diagnose infections, then respond with appropriate increased surveillance to detect the origin of the infection and interventions to prevent further spread.

Regional initiatives

APMEN Recognising the need for a partnership across regions and across borders, the Asia Pacific Malaria Elimination Network was established with the support of the Australian government in 2008 to facilitate collaboration amongst nations of the region that had made commitments to achieve elimination within a defined time period. This network enables regional collaboration and facilitates capacity building and knowledge transfer among nations of the region that share similar challenges such as artemisinin resistance, inadequate finance for malaria, or a vast market penetration of counterfeit drugs.

AICEM, the Australian Initiative for Control and Elimination of Malaria, is funded by the Australian government to strengthen malaria control in the Solomon Islands and Vanuatu, and at the same time establish pilot projects for elimination of malaria in certain island populations.

APLMA (www.aplma.org), the Asia Pacific Leaders Malaria Alliance, co-chaired by the Heads of Government of Australia and Vietnam, modelled loosely on the African Leaders Malaria Alliance, aims to bring together Heads of State, politicians, and opinion leaders of civil society to advocate for political and financial commitment to the goals of elimination of malaria. Special task forces are designed to address critical issues that could be barriers to achievement of elimination such as financing, or the safety and quality of medicines (to tackle the problem of counterfeit drugs and ensure that only certified effective products are available in the public and private sectors). Recently, the Alliance endorsed a Malaria Elimination Roadmap towards a malaria-free Asia Pacific by 2030.

Elimination to eradication

The malaria eradication campaign of 50 years ago succeeded in eliminating malaria from many countries but did not achieve its goals in areas of most intense transmission such as heartland Africa. However, many important lessons were learned about the need for community engagement, political will, intensive surveillance as a response, and the need for continued vigilance to prevent return of malaria to a now susceptible entire population that has benefited from a few years of interrupted transmission. As transmission declines and malaria-specific services are phased out, it is critical for awareness of the disease in all its manifestations to be retained at a high level in general services for detection, management, surveillance and response to any new episodes.

Lessons of the eradication campaign are being refreshed, for example on mass drug administration to entire populations (MDA), and comparing this strategy with treatment only of those found with highly sensitive tests to be infected, thus avoiding the unnecessary use of drugs that could have side-effects, so called Mass Screening and Treatment, or MSAT. Research on application of more modern tools such as rapid diagnostic tests, including nucleic acid amplification or data transmission by mobile phones are providing further data to guide strategy. For example, it is important to decide whether the cost of a more sensitive but more expensive and technically difficult nucleic acid detection test adds significant benefit in elimination campaigns, or how PCR-based parasite ‘barcoding’ (genetic epidemiology) can be used to provide rapid analysis of the source of emergent infections, the spread of drug resistance, or the risk of the parasite’s appearance in susceptible areas.

Other major lessons of the eradication campaign were that research must continue throughout the programs to deal with new challenges, and that every country needs to develop the human resource capacity to deal with the multi-disciplinary approach to this grand challenge.

Recent vaccine breakthroughs; progress with \textit{P. falciparum} but little progress with other species

Successful Phase 3 field trials of RTS,S vaccine in African children. Development of the RTS,S vaccine, which provides
35% efficacy against clinical episodes of *P. falciparum* malaria, was an important milestone for the malaria vaccine field. The vaccine includes a fusion protein containing the immunogenic repeat regions of the circumsporozoite protein, T-cell epitopes of the same molecule and the hepatitis B surface antigen that is co-expressed with free hepatitis B virus surface antigen leading to formation of a viral-like particle known as RTS,S. In recent very large trials, participants had good access to malaria prevention and rapid access to treatment, so mortality was low and no effect of vaccination on mortality could be detected. There was a concerning, but unexplained, slight increase in episodes of meningitis in the RTS,S arm, requiring further evaluation. A recent review of RTS,S by WHO recommended that the next step should be to initiate 3–5 pilot implementation studies. Further analysis of trial data showed that the vaccine had higher efficacy against strains homologous to the vaccine, suggesting both a strain-specific as well as a strain-independent mechanism. This vaccine is a very important first step but on its own, is unlikely to be the solution that is required.

**Attenuated sporozoite vaccines**

The most impressive of all malaria vaccine trial results are those achieved with intravenous inoculation of radiation-attenuated whole sporozoites in which up to 100% protection has been achieved in Phase 1 studies using multiple doses of vaccine. Field studies in Mali and Tanzania have also demonstrated efficacy and further trials are planned to optimise dose and delivery schedule.

**Conclusion**

With the spectacular reduction of the burden of malaria in the past 15 years, the time is ripe to re-double efforts both to prevent resurgence and to increase resources with the goal of achieving the health and economic benefits that would result from disease elimination. Major progress is being reported in developing the tools to add to current successful interventions from basic research into biology of hypnozoites and transition of gametocytes to sporozoites, to field trials of vaccines and innovations in surveillance and epidemiology. A multi-disciplinary response coupled with strong community engagement, and ongoing political and financial support will be required to maintain the current rate of decline in malaria, and hopefully achieve the ambitious goal of elimination.

**References**


**Biographies**

**Graham Brown**, AM Professor Emeritus at The University of Melbourne, currently serves as the Deputy Chair of the Board, and Chair of the Executive Committee of Roll Back Malaria. As a clinician-researcher, his interests include malaria vaccine development, antigenic variation and clinical infectious diseases.

**Stephen Rogerson** is a Professor at The University of Melbourne. His research interests include the pathogenesis of malaria in pregnant women and young children, and tools for prevention of malaria in these high-risk groups.

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