The changing epidemiology of malaria elimination: new strategies for new challenges

Chris Cotter, Hugh J W Sturrock, Michelle S Hsiang, Jenny Liu, Allison A Phillips, Jimee Hwang, Cara Smith Gueye, Nancy Fullman, Roly D Gosling, Richard G A Feachem

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The Global Health Group (C Cotter MPH, H J W Sturrock PhD, M S Hsiang MD, J Liu PhD, A A Phillips BA, J Hwang MD, C Smith Gueye MPH, N Fullman MPH, R D Gosling MD, Prof Sir R G A Feachem DSc[Med]) **and Department of Pediatrics** (M S Hsiang), **University of California, San Francisco, CA, USA; and Malaria Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA** (J Hwang)

Correspondence to:
Chris Cotter, Global Health Group, University of California, San Francisco, 50 Beale St, Suite 1200, San Francisco, CA 94105, USA
cotterc@globalhealth.ucsf.edu

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Malaria-eliminating countries achieved remarkable success in reducing their malaria burdens between 2000 and 2010. As a result, the epidemiology of malaria in these settings has become more complex. Malaria is increasingly imported, caused by *Plasmodium vivax* in settings outside sub-Saharan Africa, and clustered in small geographical areas or clustered demographically into subpopulations, which are often predominantly adult men, with shared social, behavioural, and geographical risk characteristics. The shift in the populations most at risk of malaria raises important questions for malaria-eliminating countries, since traditional control interventions are likely to be less effective. Approaches to elimination need to be aligned with these changes through the development and adoption of novel strategies and methods. Knowledge of the changing epidemiological trends of malaria in the eliminating countries will ensure improved targeting of interventions to continue to shrink the malaria map.

Introduction

During the past decade, large increases in funding have supported the scale-up of life-saving interventions for malaria control, contributing to substantial reductions in malaria morbidity and mortality. WHO estimates that between 2000 and 2010, global malaria incidence decreased by 17% and malaria-specific mortality rates by 26%.[1] Although most investments and efforts have been directed towards high-burden countries,[2,3] impressive accomplishments have been made in malaria-eliminating countries (panel 1, figure 1),[4] including in southern Africa,[5–7] Mesoamerica,[8] central Asia,[9] and the Asia-Pacific region.[10–12] In the past 5 years, more countries have been certified as malaria free—Armenia, Morocco, Turkmenistan, and the United Arab Emirates—than in the previous 25 years combined.[1] Following on from the malaria elimination Series published in *The Lancet* in 2010, which described the underlying concepts, definitions, and justifications for malaria elimination,[4,13–18] in this Review we give an update on the status of malaria elimination, particularly the evolving complexity and challenges of the epidemiology of malaria in low-transmission settings.

Key messages

- Over the past decade, 34 malaria-eliminating countries have achieved remarkable success in reducing their malaria burden. Many could eliminate malaria within the next decade.
- Major epidemiological shifts have occurred in malaria-eliminating countries. Malaria cases are increasingly male, adult, clustered geographically, imported, among migrant and other hard-to-reach groups, and caused by *Plasmodium vivax*.
- Present malaria control interventions and strategies are not likely to address this changing malaria epidemiology; novel strategies are urgently needed.
- Development of new equipment and techniques using current and future diagnostics, drugs, and vaccines is needed to support elimination.
- Operational research is driven by malaria control programmes and supported by research institutions and relevant stakeholders.
- Multicountry and regional funding mechanisms and collaborations are pivotal to sustain progress towards malaria elimination.

A decade of progress

Malaria-eliminating countries have contributed substantially to the reduction of the global malaria burden over the past decade. The number of reported annual malaria cases for the 34 malaria-eliminating countries has decreased by 85%, from 1·5 million in 2000, to 232 000 in 2010.[1] In the same period, 25 of 34 malaria-eliminating countries reduced total malaria cases by more than 70%, with 17 countries reporting a greater than 90% reduction. Specifically, malaria-eliminating countries reduced their total caseload by 79% in the Asia-Pacific region, 86% in Latin America, 92% in sub-Saharan Africa, and 96% in the Middle East, Europe, and central Asia (figure 2).

These successes have been driven by several factors, including increased funding, effective vector control, strengthening of health systems, improved case management with more effective treatment regimens, and improved case reporting and surveillance. At the same time, gross domestic product per head in the 34 malaria-eliminating countries increased by an average of 3·5% per year between 2000 and 2010,[19] possibly creating a less favourable environment for transmission through urbanisation and improved housing. These countries have invested heavily in malaria control and do not consider indefinite sustaining of malaria control to be an option. They envision malaria elimination as the

Search strategy and selection criteria

In this review of published and unpublished literature, we searched Google, Google Scholar, and PubMed up to and including Sept 15, 2012, using the terms "malaria" and "epidemiology" and "adults" or "males" or "men" or "migrants" or "migration" or "hard-to-reach" or "marginalised" or "imported" or "importation" or "*Plasmodium vivax*". We searched only for English language results. References were also identified by cross-referencing bibliographies of relevant publications.

long-term goal that would protect their investments from emerging parasite and vector resistance and waning political and financial commitment.[20] In the Greater Mekong subregion (comprising Burma, Cambodia, Laos, Thailand, Vietnam, and the Yunnan Province of China), where artemisinin resistance has been documented,[21] the response has been to move rapidly towards regional elimination.[22] To achieve this aim, these countries need to address the same challenge that all the malaria-eliminating countries face: to attack the remaining parasite reservoirs, albeit with restricted choices of antimalarial drugs.

In malaria-eliminating settings, remaining parasite reservoirs are increasingly clustered in small geographical areas—so-called hotspots.[23] Malaria burdens shift from the traditionally vulnerable populations of young children and pregnant women to older children and men. Cases are more clustered demographically into subpopulations with shared social, behavioural, and geographical risk characteristics, referred to as hot populations or hot-pops. Within eliminating countries, an increasing proportion of cases are imported and, outside sub-Saharan Africa, the proportions of all cases caused by *Plasmodium vivax* are rising.[4] To drive progress towards elimination, strategies need to align with this changing epidemiology. In this Review we present evidence for the changing epidemiology of malaria from different malaria-eliminating settings, and draw attention to adjustments and new strategies that could be adopted to continue shrinking of the malaria map.

Panel 1: **Malaria-eliminating countries**

The term malaria-eliminating country describes a country that is in the process of moving from controlled low-endemic malaria to elimination, and fits into one of two categories: a country that has assessed the feasibility of elimination, declared a national and evidence-based goal, and is pursuing a malaria elimination strategy; or a country that is strongly considering an evidence-based national elimination goal, has already made substantial progress in spatially progressive elimination, and is greatly reducing malaria nationwide.[4]

Malaria-eliminating countries share several important characteristics: they lie at the geographical margins of the disease; they have substantial malaria-free areas; they have greatly reduced their overall malaria burden; and they are experiencing many of the epidemiological shifts described in this Review. Figure 1 shows a world map with countries categorised by their epidemiological status: 111 countries are malaria free, 64 are controlling malaria, and 34 are malaria-eliminating countries.

A changing epidemiology

Adults and men

A striking and common epidemiological shift in malaria-eliminating countries is the increasing proportions of adults and men among all malaria cases.[10,11,24–27] This shift is connected to the increasing importance of occupational and behavioural factors outside the home that put these groups in contact with infective vectors.[24,25,28–30] These so-called hot-pops of adult men act as parasite reservoirs, with many infections carried asymptomatically and with low parasite densities,[31–33] and have been reported as the source of infection for seasonal outbreaks and epidemics.[28]

In Sabah state, Malaysia, although numbers of cases reduced substantially between 1994 and 2011, adult men accounted for an increasing proportion of cases (figure 3A). This trend has been attributed to men engaging in plantation work and forest activities that expose them to outdoor biting vectors.[36] In Bhutan, where confirmed cases decreased by 70% between 2004 and 2007, similar shifts in risk based on occupational behaviours—such as collecting firewood in forests, sleeping in fields overnight to protect crops, and crossing the border to India—have been noted.[10,37,38] In the Philippines, nocturnal visits to the forest associated with occupational activities such as farming, forest clearing, hunting, and wood gathering increased the chances of malaria infection in adult men by six times.[25] In Sri Lanka, where malaria incidence decreased by 99·9% between 1999 and 2011, the proportion of infections in adults increased from 59% to 95%, and the proportion of infections in men increased from 54% to 93% over the same period (figure 3B).[35] The increase in the proportion of adult male cases could be linked to the country's internal conflict between 1983 and 2009;[10] this increase is similar to that in other countries in conflict where combatants are the highest-risk group for malaria.[39,40]

In low-transmission areas in Latin America, such as Peru and Suriname, malaria risk increased substantially for men aged 15 years and older and was occupationally related to charcoal producers, gold miners, and loggers.[24,41] In South Africa and Swaziland, where large reductions in malaria have been supported by the regional Lubombo Spatial Development Initiative (LSDI),[7] the mean incidence in Limpopo (1998–2007) and Mpumalanga provinces (2001–09) was highest in men. This trend is associated with outdoor activities that expose adult men to infective vectors, such as occupation, sleeping outdoors, and social activities.[26,42]

Hard-to-reach populations

Residual transmission in some malaria-eliminating countries is concentrated in a few hard-to-reach populations. Delivery of services to these hot-pops can be challenging because their identities vary by setting and their members often face substantial barriers to healthcare access.[41,43] Hard-to-reach populations, including ethnic or political minority groups, are typically impoverished and mobile, often driven to more remote areas by marginalisation, safety concerns, and economic opportunities.[24,43,44] They might avoid accessing the health systems because of fear of unwanted attention from government authorities, thus making monitoring and treatment of their malaria difficult.[41,45] Equitable access to malaria prevention and treatment should be addressed early in an elimination effort.[33,46]

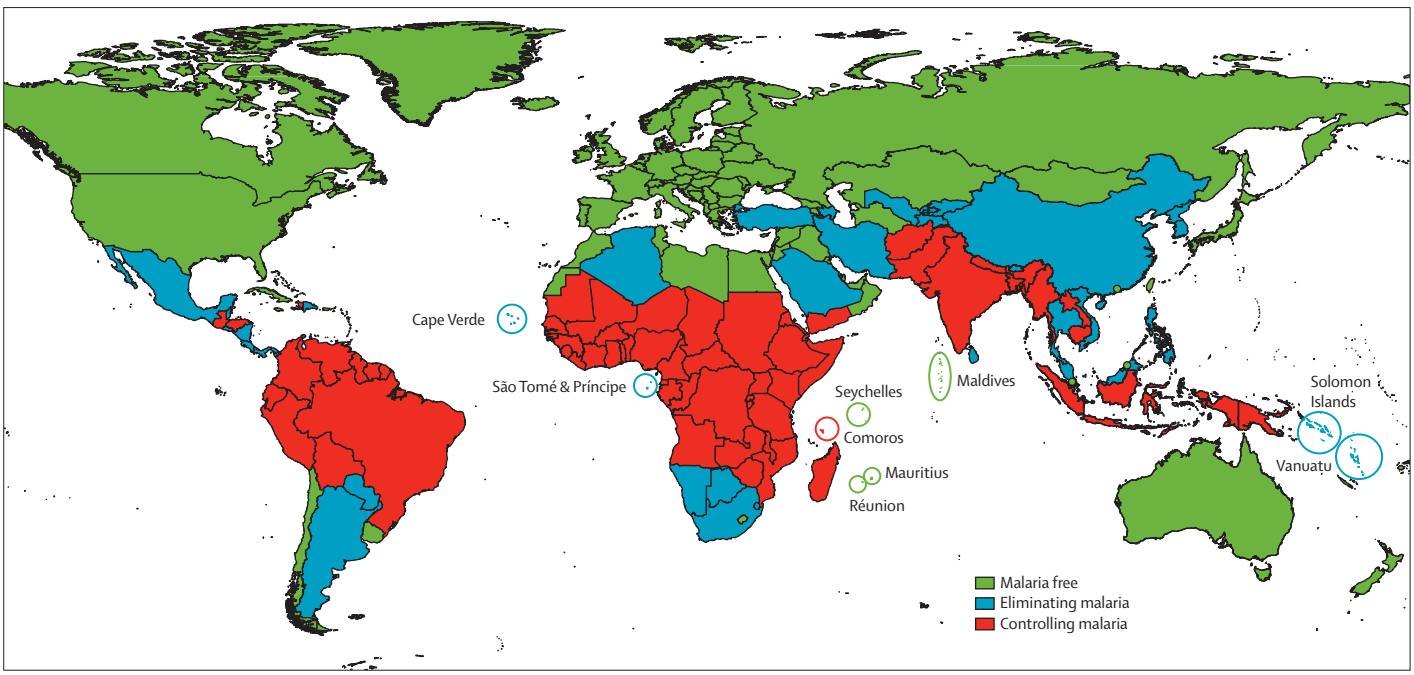

Figure 1: **Categorisation of countries as malaria free, eliminating malaria, or controlling malaria, 2012**
Adapted with permission from authors and publisher.[4] See panel 1 for discussion.

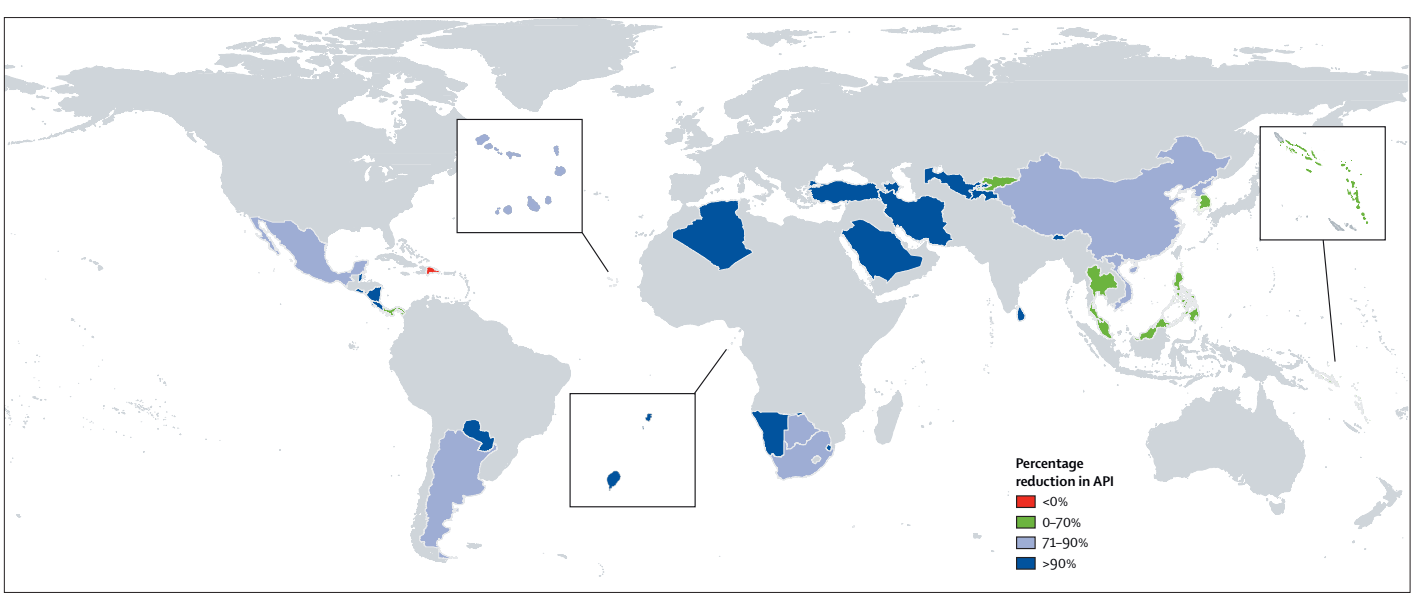

Figure 2: **Percentage reduction in annual parasite incidence (API) in the 34 malaria-eliminating countries, 2000–10**
The Dominican Republic is the only country with increasing malaria incidence during this time.[1]

Migration and imported malaria

In many malaria-eliminating settings, imported malaria is the sole or main threat to achievement and maintenance of elimination, with greatest risk for countries neighbouring high-endemic areas.[24,44,47] In Saudi Arabia, for example, malaria cases decreased substantially between 1999 and 2010, and the proportion that were imported increased from 23% to 99% (figure 4). Movement of people around the world can cause the disease to spread to non-endemic or previously eliminated areas;[43,50] the reintroduction of *P vivax* to Greece is a reminder that malaria is an international threat to health systems worldwide.[51]

With the ever-increasing movement of people around the world, more instances of malaria reintroduction to receptive malaria-free areas have been documented.[50,52,53] For example, China has eliminated *Plasmodium falciparum*

from large parts of the country, but with more Chinese nationals returning from work in sub-Saharan Africa, the country faces increasing rates of imported *P falciparum* malaria.[54]

Despite stringent border controls between neighbouring countries, transmission can be sustained in areas along and across international borders. For example, transmission in South Korea continues to be a challenge in the demilitarised zone along the border with North Korea.[39] Even in island states, such as Sri Lanka, more malaria cases are originating from other countries,[11] a trend that will probably increase as ferry services and small boat traffic with southern India expand in the post-conflict environment. Importation of malaria between islands in the Philippines, Solomon Islands, and Vanuatu is a constant threat as these countries pursue malaria elimination island-by-island.[55–57] Finally, in the aftermath of emergencies, humanitarian workers or UN security personnel from high-transmission settings could introduce malaria into malaria-free areas.[58] Knowledge of the dynamics of population migration, both domestic and international, and cross-border malaria transmission, is crucial for development of appropriate surveillance and response systems.

P vivax infections

In high-endemic countries, particularly in sub-Saharan Africa, the focus of malaria control has understandably been on *P falciparum*. However, outside sub-Saharan Africa, as malaria is controlled, the relative burden due to non-*falciparum* species increases and different challenges arise.

In many countries where *P falciparum* has been successfully eliminated, such as all malaria-endemic countries in Europe and central Asia, Argentina, Belize, Mexico, and large parts of China, *P vivax* is the remaining challenge,[59] with increasing evidence that *P vivax* infection causes substantial morbidity and mortality.[60,61] In countries with both *P falciparum* and *P vivax*, the ultimate challenge for elimination will be *P vivax*.[4,62] 26 of the 34 malaria-eliminating countries (76%) have a malaria burden solely or mainly due to *P vivax*.[4] In the Solomon Islands, the

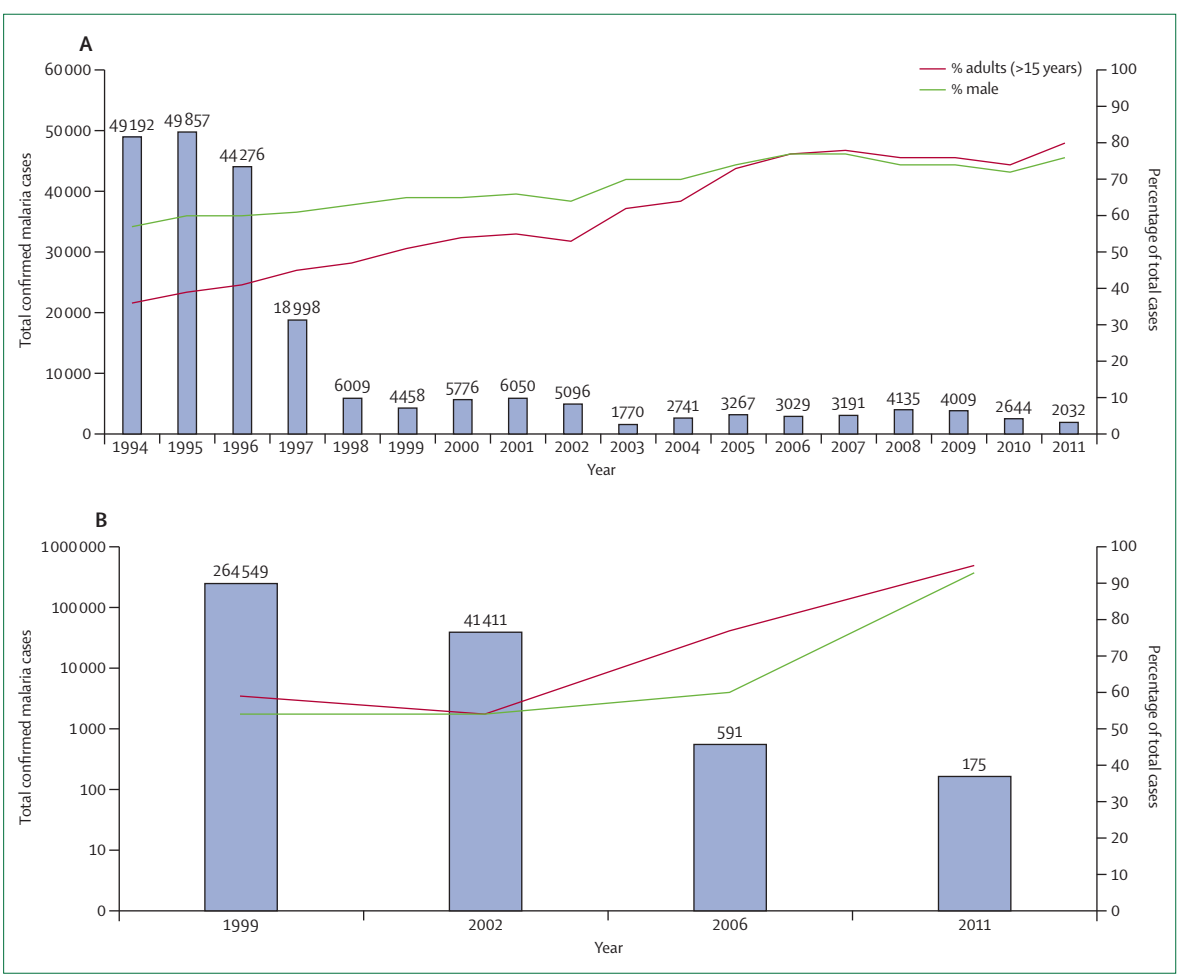

***Figure 3*: The changing epidemiology of malaria in Sabah state, Malaysia, 1994–2011 (A); and in Sri Lanka, 1999–2011 (B)**
Note logarithmic scale for the total confirmed malaria cases in figure 3B. Adapted with permission from the authors.[34,35]

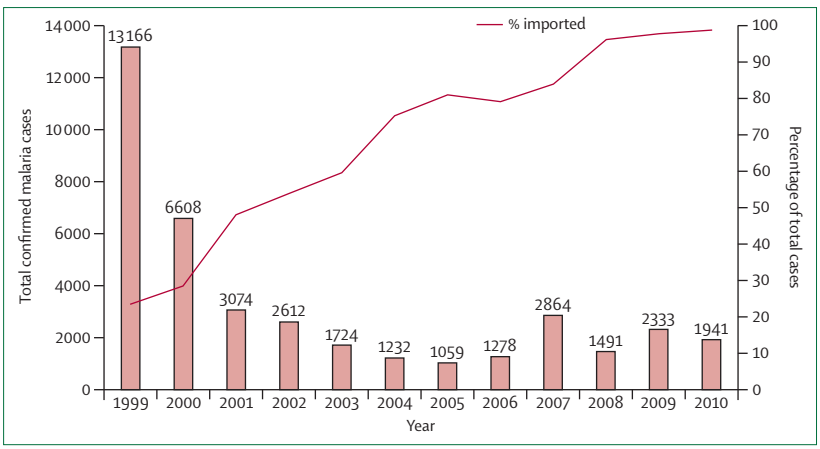

Figure 4: **Imported malaria in Saudi Arabia, 1999–2010**
Imported malaria due to cross-border movement between Saudi Arabia and Yemen, mainly by migrant workers,[48] poses the biggest risk to Saudi Arabia's elimination goal.[49] Saudi Arabia has reduced total malaria cases (indigenous and imported) by 85% from more than 13 000 cases in 1999, to fewer than 2000 in 2010.[1] At the same time, the percentage of imported cases rose sharply, comprising less than 25% of total cases in 1999, and more than 99% in 2010.

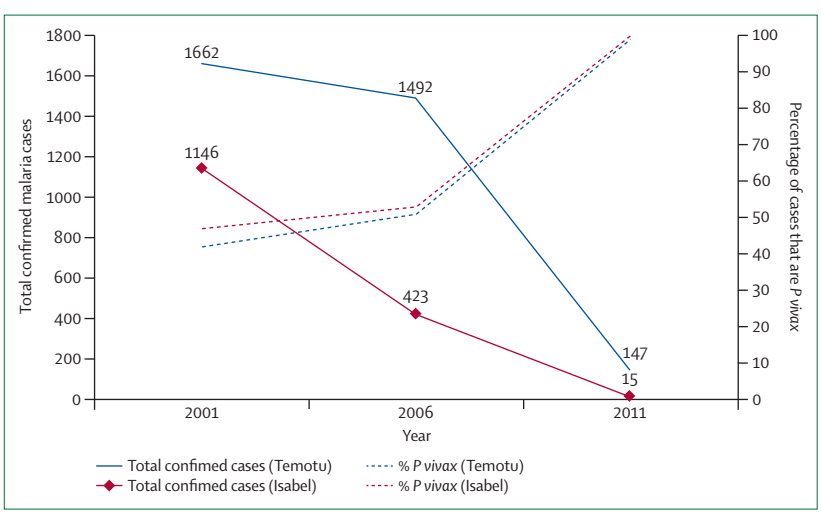

Figure 5: **Increasing importance of *Plasmodium vivax* in the Solomon Islands, 2001–11**
Adapted with permission from authors.[63]

elimination provinces of Isabel and Temotu reduced malaria cases to very low numbers between 2001 and 2011, while the proportion of cases reported as *P vivax* more than doubled (figure 5).[63] Similarly, in Sri Lanka, the percentage of all cases due to *P vivax* increased from 75% to 90% between 1999 and 2011.[35]

P vivax is less responsive to control interventions than *P falciparum* infections because of several unique features: it has a dormant liver stage that can result in relapses even after treatment; it can develop in mosquitoes at lower ambient temperatures than can *P falciparum*, resulting in a greater range of ecological receptivity; unlike *P falciparum* it produces infectious gametocytes soon after parasites emerge from the liver;[64] and parasite densities are often lower than the level of detection by diagnostic tests.[65] Primaquine, the only drug available to treat the dormant liver stage, requires a long treatment course (7–14 days), and poor adherence can result in lower efficacy.[66] Further, the risk of life-threatening haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common inherited blood disorder in malaria-endemic areas, causes health-care providers to hesitate to use the drug. A reliable point-of-care test to detect G6PD deficiency is not available.[64]

Other *Plasmodium* infections

Plasmodium malariae and *Plasmodium ovale* are less prioritised than are *P vivax* and *P falciparum* in malaria control and elimination. Their true burdens are largely unknown because identification by microscopy or rapid diagnostic test (RDT) is not reliable. Similar to *P vivax*, detection of *P ovale* infection is also a challenge because it has a dormant liver stage. PCR-based testing in African and Asian settings shows a higher proportion of both *P malariae* and *P ovale* infections than was previously thought.[67–69]

Plasmodium knowlesi, which has a macaque monkey reservoir and has been reported in Borneo[70] and in other parts of southeast Asia,[71] can cause severe disease in human beings.[72] The burden and distribution of *P knowlesi* is not well defined because it is frequently misdiagnosed by microscopy as other species—most often *P malariae*.[73,74] Surveillance based on molecular testing is limited. The possibilities of human-to-human transmission and strategies for targeting of the reservoir of infection in monkeys is unclear.

As burdens of *P falciparum* decrease, malaria-eliminating countries will need new strategies to diagnose, treat, and interrupt the transmission of non-*falciparum* malaria.

Asymptomatic and low-density infections

Malaria elimination programmes face the challenges of identification and treatment of infections, not only symptomatic cases. For both *P falciparum* and *P vivax*, most infections in a population are likely to be asymptomatic.[75–77] These individuals are missed by passive surveillance, but remain infectious to mosquitoes.[78] Without identification and targeting of this asymptomatic infectious pool, transmission interruption might not be possible. A substantial proportion of infections might be subpatent—ie, of a density lower than the threshold needed for detection by microscopy or RDT. Relative to all infections, the proportion of those that are low density is higher in lower-transmission settings.[79] Although patent infections remain the cause of most malaria transmission, because transmission to mosquitoes correlates positively with the density of sexual and asexual parasites, subpatent infections in low-endemic settings have been estimated to result in 20–50% of all transmission episodes.[80]

Enhancement of present strategies

The epidemiological shift in the populations most at risk of malaria raises important technical, operational, and financial questions for malaria-eliminating countries and those reaching a state of controlled low-endemic malaria.[81] Traditional control interventions are likely to be inadequate to effectively address these changes—novel strategies to tackle such trends need to be systematically explored.

Active and passive surveillance

In countries where malaria is controlled, passive surveillance systems are the cornerstone of detection, providing a standardised way to track progress, gather demographical and epidemiological data, and enable rapid investigation and appropriate response.[82,83] When malaria is eliminated, passive surveillance is the front-line for detection of importation and local transmission. For malaria-eliminating countries, passive surveillance strategies should take into account that malaria cases become increasingly rare, are difficult to diagnose, and affect specific populations. Health workers need continual training to maintain a high clinical suspicion of malaria, particularly for higher-risk groups, such as men who live and work in and around forests or remain outdoors in the evenings, or patients who recently travelled to endemic areas. Innovative strategies to serve high-risk populations—such as those in use in Latin America and the Asia Pacific region via rural community health workers, rural aid posts, and mobile clinics—increase access to malaria diagnosis and treatment in hard-to-reach and conflict areas.[11,41,84,85] When reliable, passive surveillance data can be linked to remote sensing data, including altitude, population, weather, and wetness, to produce risk maps to guide implementation of control and elimination measures.[86,87]

During the elimination phase, active case detection (ACD)—in which malaria programmes are used to seek out infections in high-risk groups—becomes crucial for targeting of the asymptomatic parasite reservoir in hotspots and hot-pops.[88] Although ACD is recommended by WHO[89] and is widely used, several questions remain, such as whether ACD is a cost-effective way to reduce malaria transmission. Methods with standard metrics to assess the operational effectiveness of ACD that include timeliness of actions and coverage need to be developed. For example, in China a standardised system for ACD is being implemented, known as "1-3-7": the system constitutes one day to report the case, three days to investigate it, and seven days to begin a response in the community.[90] Malaria-eliminating countries are increasingly using modified versions of ACD, including so-called reactive case detection and proactive case detection.[16] In reactive case detection, programme staff respond to a single case or a threshold of cases by screening and treating household members and neighbours of a passively detected case—a process sometimes called focal screening and treatment.[91] The most efficient radius for screening and intervention around the home of the passively detected case is unknown, yet has large operational implications.[16] For proactive case detection, high-risk groups and geographical areas are screened and treated without the trigger of a passively detected case—eg, by mass screen and treat campaigns or blood surveys.[88,92] The most effective ways to identify target populations, the best diagnostic tests to use, and the frequency and timing of campaigns have not been established.[93]

Diagnostics

Although microscopy and RDTs are the standard ways to diagnose malaria at health facilities, new and more sensitive methods to screen populations to identify low-density subpatent infections are needed.[31,68] Ideally, these new diagnostic tests will detect all plasmodia species infections at low density and be high throughput, low-cost, and delivered at the point of care.[79] Loop-attenuated isothermal amplification is the method that most closely matches this target profile, since it is lower cost and more field-ready than are other nucleic acid tests.[94] Although microscopy and RDTs continue to be used for screening, use of high throughput nucleic acid tests using pooling techniques[95,96] can assure quality and identify missed infections, albeit on a delayed timescale.[89]

Use of serology to measure past exposure to malaria could be a valuable means to identify at-risk populations, especially in low-transmission settings where the possibility of detection of current infection is low.[96] Although methods have been established, no strategy for the incorporation of serology has been validated for malaria control or elimination. In areas where malaria has been eliminated, serology to detect exposure to the bite of anopheline mosquitoes[97] could be used to indicate potential risk for reintroduction, and support decisions on when to stop or restart vector control measures.

Mass drug administration

Mass drug administration (MDA) is the main method for control and elimination of many parasitic diseases, including lymphatic filariasis, onchocerciasis, and schistosomiasis.[98] Although MDA for malaria has been widely used in China[99] and Russia,[100] little evidence of its effect has been collated, and guidelines for its implementation do not exist. MDA is likely to be most effective during the lowest transmission season, with the aim to reduce or interrupt malaria transmission.[101]

Several key challenges need to be addressed for MDA. The optimum combination of drugs has not yet been determined, but should include those that will affect the sexual (and liver) stages of malaria parasites, a formulation which would probably contain an artemisinin and an 8-aminoquinoline.[101] The optimum timing, the number of rounds per year, and the total duration of MDA also need to be defined, and will depend on the endemicity, seasonality, and rate of importation of

parasites. Clear identification of geographically or demographically defined at-risk populations will affect the design of an MDA strategy. Adequate resources supported by political commitment should be in place to interrupt transmission, because multiple rounds of MDA might be needed over several years in combination with other control measures.[102] Pilot projects with well designed monitoring and evaluation structures measuring adverse events, population acceptability, and transmission reduction would support the progress and adoption of MDA as a more widespread intervention.

Occupation-based vector control

Identification of at-risk populations, and the most effective methods to target them, is crucial in an elimination setting. Traditional vector control interventions, such as insecticide-treated nets and indoor residual spraying, protect the household but are less effective for individuals who are away from their homes during the peak times of vector feeding.[25] In these circumstances, topical repellents, such as N,N-diethyl-3-methylbenzamide (DEET), botanicals, citronella, picaridin, and olfactory binding proteins, could be viable methods to protect these groups.[103] DEET, which has been used for more than 60 years, is effective against mosquitoes, but has shown little effect on malaria prevention.[104,105] Results of evaluations of DEET-based soap in Pakistan[106] and a plant-based repellant in Bolivia[107] showed significant reductions in *P falciparum* and *P vivax*, respectively. Furthermore, decreased malaria infections have been associated with use of longlasting, insecticide-treated hammocks for forest workers in Vietnam,[108] insecticide-treated clothing (eg, chaddars and top sheets) in refugee areas in Afghanistan,[109] and insecticide-treated personal clothes and bedding in Kenya.[110] Textiles treated with longlasting insecticide that retains effectiveness for 70 washes and microencapsulated citronella oils to treat cotton textiles, can be low-cost, simple, adaptable, and scalable approaches to malaria prevention, if proven efficacious.[111] New methods tailored to different occupations and risk groups, especially those affected by outdoor transmission, are needed, as are studies of the efficacy and acceptability of these interventions.

Panel 2: Elimination of malaria in southern Africa

The Elimination 8 (E8) is a collaboration among the eight southernmost countries with malaria in southern Africa to achieve a coordinated regional approach to malaria elimination, and to advance and support a series of cross-border initiatives.[136] The E8 unites the four front-line countries targeted for elimination (Botswana, Namibia, South Africa, and Swaziland) with their higher transmission neighbours to the north, the second-line countries (Angola, Mozambique, Zambia, and Zimbabwe), to strengthen and harmonise malaria elimination efforts in a coordinated way. All eight Ministers of Health have endorsed the E8, and the collaboration was adopted by the Southern African Development Community (SADC) Ministers of Health in 2009.

Imported malaria from the second-line countries to the first-line countries is a constant threat to the four malaria-eliminating countries. Several cross-border initiatives in the region are at different stages of implementation and funding. Cross-border initiatives complement national malaria elimination efforts in several ways:

- Joint mobilisation of financial and technical resources for malaria elimination.
- Increasing of health systems' capacities to effectively implement, sustain, and monitor malaria efforts at national and community levels.
- Coordination of multisectoral efforts between all partners working on malaria.
- Strengthening of programme ownership at district and community levels.
- Sharing of data between national malaria programmes to more effectively target high-risk groups.

Adoption of novel strategies

Case-control studies

To support targeted interventions, improved understanding of the at-risk population is needed. In control settings, such factors can be established through nationally representative cross-sectional surveys, such as malaria indicator surveys. However, in areas where transmission is very low and malaria infections are rare, these surveys are unlikely to adequately detect cases or identify risk factors, and are expensive.[96] Case-control methods are often used to study rare diseases and identify associated behavioural, occupational, and travel risk factors, but have not yet been extensively applied to malaria.[112] Use of methods to support programmes to undertake case-control studies would provide crucial data for malaria risk factors and be of substantial value.

Genotyping

A better understanding of the association between malaria infections and the individuals driving transmission would strengthen intervention targeting. Imported cases are defined on the basis of travel history. Differences between local and imported strains can be identified with use of malaria genotyping. By showing genetic relatedness between parasites,[16] programmes might be able to identify locations or risk groups that seed transmission to others and target them, as is done with HIV and tuberculosis.[113–115] Making an inexpensive field-friendly test would probably involve combination of simple, low-resolution techniques[116,117] with more complex and expensive high-resolution ones,[118] with, for example, low-cost multiple microsatellite markers.[119,120]

Use of networks

Determination of the common risk factors with conventional methods might be difficult in some high-risk groups. Travellers to particular destinations with high-malaria transmission, or high-risk marginalised migrant labourers such as gem miners,[11] are likely to be linked to each other through social networks. These networks can help to reach high-risk groups without definition of risk factors. For example, snowball sampling—a method whereby an initial set of seed subjects refer further subjects in the same risk group—is extensively applied in HIV research to find networks of injection drug users and commercial sex workers.[121–123]

An extension of snowball sampling—respondent-driven sampling—provides representative sampling of hard-to-reach populations[124] and can be used to determine risk factors—eg, in migrants on the Thai–Cambodia border.[125] Time-location sampling is an alternative approach,[126] in which sampling occurs at a set time in locations where the risk groups are likely to gather, such as social clubs, bars, market stalls, or bus stops. With appropriate local adaptation, these methods could be used to efficiently identify, treat, and prevent infections that would otherwise go unaddressed.

Promotion of changes in receptivity

Interventions that reduce the receptivity of an area to transmission could assist in the achievement and maintenance of elimination,[20] as in the southeastern USA in the 1920s and 1930s.[127] The protective effects of housing structure improvements such as house screening, closing of eaves, and ceiling installation have been documented since the 19th century.[128] Installation of ceiling netting has been shown to be cost effective compared with provision of bednets, and reduced transmission by 80% in study areas.[129,130] Entry point screens also reduce vectors for other infectious diseases.[131] Despite potential higher up-front costs of such structural interventions, they are likely to be more cost effective over time because of their permanence and reduced reliance on individual behaviours, which is particularly important since user-driven malaria interventions—such as insecticide-treated bednets—are difficult to sustain when the perceived risk of malaria decreases.[96] More research is needed to ascertain which building improvements are the most effective across different elimination settings, where such improvements should be targeted, whether they are acceptable, and the long-term benefits of permanent reduction of an area's transmission receptivity.

Vaccines in elimination settings

Since the inception of the Malaria Vaccine Initiative in 1999,[132] the goal of a malaria vaccine has been to save lives in the highest risk groups: young children and pregnant women. This goal remains important for high-burden countries. However, in elimination settings, the use of a malaria vaccine that targets at-risk groups should be considered with the objective of transmission interruption. For example, in a seasonal setting, if the vaccine could induce enough immunity to reduce the basic reproductive rate to less than one in the population at risk for the duration of the malaria season, and be administered in conjunction with other control measures, it might interrupt transmission. RTS,S, the only vaccine currently in Phase 3 clinical trials, does have high efficacy over a short duration, and might be useful for this purpose.[133] Generally, vaccines that address transmission are being sought, either through targeting of sporozoites or the sexual stages of both *P falciparum* and *P vivax*. The most promising vaccine candidates are in phase 2a studies.[134] Further investigation is needed of the role of an efficacious vaccine to target at-risk populations in elimination settings, with focus on transmission interruption.

Multicountry and regional efforts

Cooperation between neighbouring countries can further support individual and collective malaria elimination efforts.[43,135] Regional elimination initiatives, such as Elimination 8 (E8) in southern Africa (panel 2) and the Asia Pacific Malaria Elimination Network (APMEN) (panel 3)

Panel 3: Malaria elimination in the Asia Pacific region

Country-led and country-driven, the Asia Pacific Malaria Elimination Network (APMEN) was founded in 2009 to answer calls from endemic countries for a stronger voice and strengthened efforts toward malaria elimination in the Asia Pacific.[137] APMEN includes 14 countries: Bhutan, Cambodia, China, Indonesia, Malaysia, Nepal, North Korea, Philippines, Solomon Islands, South Korea, Sri Lanka, Thailand, Vanuatu, and Vietnam. It provides a unique forum through which countries' malaria programmes work with a broad range of partners, including academic, development, non-governmental, and private sector representatives, in collaboration with WHO, to address the region's malaria challenges, namely *Plasmodium vivax*, a broad range of vector species, importation of malaria and parasite drug resistance.

APMEN works to improve sharing of information, direct operational research, and advocate for malaria elimination through:

- Fellowships that support capacity-building within malaria control programmes.
- Topic-specific working groups, such as the *vivax*, vector, and surveillance working groups.
- Small grants that support capacity-building within local research institutes.
- Annual meetings, in which country partners mix with policy makers, research and training institutes, and funders, among other stakeholders.

Panel 4: The way forward

In this Review we describe many of the strategies and methods needed to address the challenges that the 34 malaria-eliminating countries face. However, additional solutions will be needed to sustain momentum in malaria elimination. Specific proposals include:

- Development of regional and multicountry funding mechanisms to support control and elimination efforts in their own unique ecoepidemiological regions. A funding mechanism for regional elimination efforts can be supported by those who have eliminated in the region, and be a sustainable source of funding. This regional public good will help to reduce importation into malaria-free areas and accelerate the progress of the whole region to elimination.
- Support and expansion of regional technical collaborations, such as the E8 and APMEN. These collaborations are uniquely positioned to maintain high level political support; to monitor continued progress; to tackle cross-border issues; to overcome regional challenges, such as artemisinin resistance, *Plasmodium knowlesi*, and counterfeit drug production in Asia Pacific; to collaborate in research and share research findings; and to collectively address the many operational challenges to regional elimination.
- Increasing of operational research on the requirements for active case detection and surveillance strategies to inform malaria programmes actively engaging in these activities. Standardised metrics for active case detection, such as optimum radius of screening and choice of diagnostic method, will allow countries to assess their own surveillance strategies, identify gaps in performance, and pilot new interventions and technologies.

can stimulate regional elimination efforts by supporting greater collaboration, increased lesson-sharing to tackle common challenges, and direct cooperation with neighbouring countries to address specific border issues.[10,138–142]

With strategies such as active case detection, genotyping, and network identification, countries can better gather information about migration routes and patterns, and develop more targeted border screening techniques for high-risk groups. For island nations, targeting of main entry points, such as airports and ports where travellers arrive, might be easier than in countries with long, passable borders. Many island countries use community vigilance to prevent reintroduction of malaria,[58,143] whereas other countries have implemented employer policies to screen and treat employees for malaria before they can obtain work permits.[144] Innovative strategies to identify and screen individuals at the point of entry could help to achieve and maintain elimination.

Despite the growing importance of imported malaria, the largest international funder for malaria control—the Global Fund to Fight AIDS, Tuberculosis and Malaria—allocates only a small proportion of its malaria funding to multicountry proposals.[145] Further, since the global financial crisis, reliance on funding from international donors is less certain.[2] New regional and cross-border funding mechanisms are needed to support continued progress in the 34 malaria-eliminating countries. A coordinated malaria control effort with endemic neighbours should be a component of all strategic plans implemented by malaria-eliminating countries.

Conclusions

With an 85% reduction in malaria cases between 2000 and 2010, the 34 malaria-eliminating countries have made enormous progress towards their elimination goals.[1] Nonetheless, as countries reduce their malaria burdens, strategies that address the changing epidemiology—specifically, the increasing proportions of infections from non-*falciparum* species, in adult men, from imported transmission and migration, and in hard-to-reach populations—need to be developed, validated, and adopted (panel 4). Regional and multicountry funding mechanisms need to be launched to support malaria elimination and encourage national investment in elimination efforts. In the current climate these mechanisms are more likely to come from regional than global leadership. The new regional collaborations, E8 and APMEN, are showing noteworthy leadership in this arena.

Contributors

RGAF conceived the idea for this Review. All authors participated in the development of the content. The text was drafted by CC, HJWS, MSH, JL, JH, and RDG with contributions from AAP and CSG. AAP, RDG, and RGAF helped to shape the key messages. Data analysis was done by CC and HJWS. NF assisted in the literature review. All authors took part in the preparation, review, and final approval of the paper.

Conflicts of interest

All authors work at the Global Health Group of the University of California, San Francisco, CA, USA. The Global Health Group exists in part to support global, regional, and country efforts to achieve evidence-based malaria elimination. JH works for the Centers for Disease Control and Prevention (CDC) supporting the President's Malaria Initiative. MSH, AAP, JH, RDG, and RGAF serve as members of the Malaria Elimination Group. RGAF cochairs the Asia Pacific Malaria Elimination Network and the Global Health Group is the cosecretariat of the Network. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their employing organisations or of the sources of funding.

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