

Chapter 13

Malaria Control

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INTRODUCTION

This chapter reviews the strategies for malaria control and empirical evidence on the costs and cost-effectiveness of interventions. It then focuses on a systemic approach to malaria control and elimination, describing the relevance of social and environmental determinants, as well as the health system factors that deliver effective coverage of malaria interventions. Finally, it reviews the tools and technologies being developed for malaria control and their potential contribution to integrated strategies. The chapter uses the terminology endorsed by the World Health Organization (WHO) (see WHO 2016a).

Natural History

The ancient Romans knew that draining swamps could prevent disease. Today we know that malaria, a disease that has afflicted humans since the earliest records, is caused by *Plasmodium spp.* parasites, which, following Nobel Prize-winning studies in 1897 by Sir Ronald Ross, are now known to be transmitted by mosquitoes (Smith and others 2012).

Malaria can be transmitted—with varying degrees of efficiency—by more than 100 species of *Anopheles* mosquitoes, a genus that is abundant worldwide. Gametocytes produced in malaria patients represent the *Plasmodium* stage that infects mosquitoes, when female insects (which need the nutrients in vertebrate blood to produce eggs)

take a blood meal. These gametocytes mate and develop in the insect into motile sporozoites. This *Plasmodium* stage enters the host bloodstream during the next blood meal and migrates to the liver, where sporozoites develop into liver schizonts. These rupture and produce merozoites, which invade red blood cells where they reproduce asexually. When large numbers of parasites are produced, patients experience high fever, anemia, and other symptoms. When capillaries in the brain or other vital organs (lungs) are clogged by red blood cells with altered deformabilities, complications may occur (cerebral and complicated or severe malaria), sometimes resulting in death. During the replication phase in red blood cells, gametocytes are produced as well.

There are two main malaria species in humans: *Plasmodium falciparum* and *P. vivax*. *P. falciparum* is restricted to tropical and subtropical (wet season) regions. The disease was called “quotidian fever” because the fever spikes with synchronized release of parasites from infected red blood cells every 24 hours. The parasites’ escape to higher latitudes is not prevented by a shortage of mosquitoes but by the fact that their development in the insects is highly dependent on ambient temperatures; in temperate climates, this maturation quickly exceeds the average mosquito life span of two to three weeks. *P. falciparum* is also the deadliest form of malaria, because of its propensity to become severe; 92 percent of all malaria deaths occur in Sub-Saharan Africa. *P. vivax* has found a way to avoid this climate trap

by remaining dormant in the liver, as hypnozoites, for months or even years. This form of malaria, called “tertian fever” for its 48-hour periodicity, was spread globally until the middle of the 20th century and had traveled with Renaissance Europeans to the Americas. In Sub-Saharan Africa, *P. vivax* is not widespread because most of the populations are genetically negative for Duffy, a red blood cell receptor that *P. vivax* requires for infection; these populations are therefore resistant. Other genetic variations, mostly affecting red blood cell function, attest to the enormous effect that malaria has had on human evolution.

Plasmodium parasites are eminently adapted to successfully achieve their host-switching lifecycle. The flip side of this specialization is that the parasite species that infect humans appear unable to choose other mammalian hosts. This lack of a wildlife reservoir is clearly an advantage in malaria eradication campaigns.

Burden of Malaria

P. falciparum and *P. vivax* are by far the most prevalent of the five species of parasites that infect humans; *P. knowlesi*, *P. malariae*, and *P. ovale* are less common. Both *P. falciparum* and *P. vivax* can be found in most regions: *P. falciparum* has the highest rates in Sub-Saharan Africa, where *P. vivax* is almost absent, whereas *P. vivax* is the predominant species in the Asia-Pacific region, accounting for 52 percent of infections (Price and others 2007). *P. falciparum* traditionally accounts for the majority of deaths and cases of severe malaria, but the effect of *P. vivax* on severe morbidity is not to be underestimated.

Despite substantial progress, more than 1 billion people still live in areas where malaria can be transmitted (WHO 2014). In 2015, an estimated 212 million cases of malaria occurred worldwide (uncertainty interval [UI]: 148 million–304 million) (WHO 2016c). Most of the cases in 2015 were in the WHO African Region (90 percent), followed by the WHO South-East Asia Region (7 percent), and the WHO Eastern Mediterranean Region (2 percent). About 4 percent of estimated cases globally are due to *P. vivax*; outside of the African continent, the share of *P. vivax* infections is 41 percent. The incidence rate of malaria is estimated to have decreased globally by 41 percent between 2000 and 2015, and by 21 percent between 2010 and 2015 (WHO 2016c). The massive burden in Sub-Saharan Africa is due mainly to *P. falciparum*. The Democratic Republic of Congo and Nigeria are the most populated states with high levels of transmission. Three Asian countries (India, Indonesia, and Pakistan) account for more than 80 percent of *P. vivax* cases (WHO 2014).

In high-burden countries, the most vulnerable populations at risk for malaria tend to be women and children, marginalized populations, and people living in poverty. Young children are especially at risk, because they have not yet built up the partial immune protection that adults acquire from multiple, sustained infections. Pregnant women are at risk because of placental infection; 30 million women living in Sub-Saharan Africa are at risk, leading to 10,000 maternal deaths (Marchesinigi and Crawley 2004) and 200,000 newborn deaths each year (WHO 2016c). Malaria and HIV (human immunodeficiency virus) co-infections occur in more than 3 million cases annually and result in 65,000 additional deaths (Hochman and Kim 2009; WHO 2016c). Economically, countries with a high burden of malaria have growth rates that are 1.3 percent less per person per year than low- and malaria-free countries (Gallup and Sachs 2001; WHO 2016c).

Global Initiatives

Between 1955 and 1970, the WHO led a global initiative to eradicate malaria (Nájera, González-Silva, and Alonso 2011). Control interventions were developed to mitigate the spread of the disease, starting with environmental sanitation measures and the use of dichlorodiphenyltrichloroethane (DDT) in the 1950s and 1960s. Many countries, particularly in North America and Europe, were successful in substantially reducing malaria transmission and even eliminating it. However, DDT was abandoned because of environmental concerns, and the world’s higher-burden countries lacked the necessary tools, approaches, and technical assistance to eliminate the disease without the use of DDT. The goal of worldwide eradication was quietly abandoned around 1970, although many countries continued to drive down the disease rates and some extinguished malaria. The WHO malaria eradication resolution of 1955 was never recalled and formally remains in force.

Decades later, the Millennium Development Goals and Roll Back Malaria (RBM) Partnership’s first Global Malaria Action Plan (GMAP) (RBM Partnership 2008) led to a renewed commitment to the fight against malaria and to a substantial increase in resources. In 2007, while considering the then current state of control as well as the potential of new tools and approaches, the global health community at the Malaria Forum of the Bill & Melinda Gates Foundation officially declared that the new goal was elimination (Roberts and Enserink 2007). Consequently, the RBM Partnership (2008) compiled the GMAP, and national control and elimination strategies were established and began being implemented. As a result of this important shift in

paradigms and approaches and the insight gained from experiences from 2007 to 2015, the two guiding documents for the control, elimination, and, ultimately, eradication of malaria were developed and approved by the WHO member countries at the World Health Assembly 2015: (1) the WHO's (2015a) *Global Technical Strategy for Malaria 2016–2030 (Global Technical Strategy)* and (2) RBM Partnership's (2015) complementary *Action and Investment to Defeat Malaria 2016–2030 (AIM)*. Both documents were approved by WHO member countries in 2015.

Effective interventions, such as insecticide-treated nets (ITNs) (effective because mosquitoes bite almost exclusively between dusk and dawn) and indoor residual spraying (IRS), have been massively scaled up since 2000, using improved insecticides. The proportion of the population at risk in Sub-Saharan Africa sleeping under an ITN for mosquitoes or being protected by IRS rose from an estimated 37 percent in 2010 (UI: 25–48 percent) to 57 percent in 2015 (UI: 44–70 percent) (WHO 2016c). The proportion of the population at risk protected by IRS declined from a peak of 5.7 percent globally in 2010 to 3.1 percent in 2015 and from 10.5 percent in 2010 to 5.7 percent in 2015 in Sub-Saharan Africa (WHO 2016c).

The recent initiatives were made possible mainly by the massive funding increase that began in 2002, particularly by the Global Fund to Fight AIDS, Tuberculosis and Malaria; the U.S. President's Malaria Initiative; the Bill & Melinda Gates Foundation; and other donors (WHO 2016b). As a direct consequence, global malaria mortality rates were nearly halved between 2000 and 2015 (Bhatt and others 2015). Globally, 95 countries report ongoing transmission, and 6 are working to prevent reintroduction (WHO 2016b).

MALARIA CONTROL INTERVENTIONS: EFFECTIVENESS, COSTS, AND COST-EFFECTIVENESS

Effectiveness and Coverage by Geographical Area

In 2008, the first GMAP helped accelerate progress in malaria control and elimination (RBM Partnership 2008). The strategy included three parts, designed to be executed concurrently (RBM Partnership 2008):

- Aggressive control in the malaria heartland, mainly Sub-Saharan Africa, to lower morbidity and mortality rates
- Progressive elimination from the endemic margins to reduce the number of countries that have to invest in fully developed malaria control programs

- Continued research and development to provide new tools.

Vector Control

The development and validation of ITNs was a major breakthrough for vector control. Further developments led to the long-lasting insecticidal nets (LLINs). Current vector control relies largely on either ITNs, especially LLINs, or IRS. The evidence from randomized controlled trials indicates that ITNs reduce cases by an estimated 50 percent, and they reduce all-cause mortality rates in children under age five years in Sub-Saharan Africa by 18 percent (Lengeler 2004).

The WHO recommends that all persons at risk for malaria be protected by ITNs, using roughly one net per two people. As a result of rapidly increasing coverage, LLINs have been responsible for nearly 70 percent of the gains made against malaria over the past 15 years, in combination with IRS. This progress averted an estimated 663 million malaria cases in Sub-Saharan Africa alone (Bhatt and others 2015), emphasizing the central role of vector control in the control and eradication agenda (malERA Consultative Group on Vector Control 2011).

The use of insecticides—such as DDT, pyrethroids, carbamates, and organophosphates in the form of IRS—has been widely adopted around the world. In Sub-Saharan Africa, only countries in Southern Africa and those supported by the U.S. President's Malaria Initiative are conducting IRS activities on a large scale. Unfortunately, insect resistance to pyrethroids has dramatically increased, including among the three major malaria vectors: *Anopheles gambiae* ss, *A. arabiensis*, and *A. funestus* (Badolo and others 2012; Mulamba and others 2014). Resistance to the other main classes of insecticides—carbamates, organochlorines, and organophosphates—is on the rise as well (Quinones and others 2015). The rapid spread of resistance of *Anopheles* mosquitoes to pyrethroids is raising the cost of IRS substantially in many endemic areas. Two problems with surveying resistance—beyond weaknesses in the entomological monitoring capabilities in endemic settings—are the great variability in the resistance mechanisms and the lack of suitable markers and related diagnostic tests. All of these factors seriously hamper effective monitoring.

These concerns have been addressed in a five-point Global Plan for Insecticide Resistance Management in malaria vector control proposed by the WHO (Mnzava and others 2015). Anecdotal evidence suggests control failure is occurring in some parts of Sub-Saharan Africa. This was confirmed recently by a five-year study conducted in five countries by the WHO.¹

Diagnosics

The WHO recommends testing all suspected malaria cases by rapid diagnostic test (RDT) or microscopy. RDTs have substantially changed the individual- and community-based strategies for test-and-treat campaigns, and they form the backbone of the WHO-promoted test-treat-track strategy. The strategy has the following elements:

- Following up and testing every suspected malaria case
- Treating every confirmed case
- Reporting every case in a timely manner through surveillance systems.

The quality of RDTs has continuously improved, mainly because of a quality assurance program developed by the Foundation for Innovative New Diagnostics and the WHO Global Malaria Programme. RDTs for *P. falciparum* are highly sensitive, but their sensitivity for *P. vivax* still needs to be improved. Moreover, health care workers lack the means to diagnose hypnozoite carriers,² which prevents the elimination of *P. vivax*. RDT use, primarily to detect *P. falciparum*, has been scaled up substantially in the public sector, especially in Africa; the testing rate in suspected malaria cases increased from 40 percent to 62 percent from 2010 to 2013. However, testing before prescribing or selling treatments remains a challenge in the private sector throughout the world; in Africa, antimalarials are often sold and used without proper diagnosis (WHO 2014).

Treatments

Access to effective treatments—with WHO-recommended artemisinin-based combination therapies (ACTs) for *P. falciparum* and either chloroquine (where still efficacious) or ACTs plus primaquine for *P. vivax*—is crucial to control efforts. Between 2005 and 2013, the number of ACT treatment courses procured by the public and private sectors increased from 11 million to nearly 1 billion (WHO 2016b). During that timeframe, countries in Sub-Saharan Africa reported treating 50–100 percent of malaria patients with an ACT. Using combination treatments in malaria is essential to prevent losing effective medicines to resistance, as happened repeatedly in the 20th century. The Latin American and Eastern Mediterranean regions reported sufficient distribution of medicines to treat all patients in public health facilities.

Surveillance

Finding and detecting cases are important aspects of a national control program aimed at mitigating the spread of malaria. Surveillance becomes critical when a country moves from control to elimination and even more so

when it has achieved elimination. Surveillance systems need to be closely interlinked with a public health response, namely, the availability of tailored, integrated response packages that interrupt transmission as soon as the surveillance system identifies existing, new, or reemerging pockets of transmission.

The concept of surveillance and response has evolved. Today, surveillance and response more effectively link the activities to detect, report, analyze, and interpret the public health action through integrated packages tailored to specific settings with the primary goal of stopping transmission and treating all infected people. Surveillance response systems focus on what minimal essential data are required to detect pockets of transmission or reintroduction. This approach differs from the classical monitoring and evaluation based on gathering all possible data, which too often leads to information overflow with no feedback and therefore no rapid effective public health action.

Although surveillance was always a cornerstone of the initial GMAP, the *Global Technical Strategy* (WHO 2015a) now builds on surveillance–response as one of its key determinants for elimination and prevention of reintroduction. Currently, all efforts are made to operationalize surveillance–response approaches fully in national control and elimination programs. In 2015, malaria surveillance systems detected an estimated 19 percent of cases that occur globally (UI: 16–21 percent) (WHO 2016c).

Costs and Cost-Effectiveness of Interventions

The costs and cost-effectiveness of malaria control interventions have been extensively evaluated, and a systematic review found that in most settings, malaria interventions are among the best buys in global health based on relevant indicators (White and others 2011). Nevertheless, the literature varies widely in the range of unit costs and cost-effectiveness ratios; these variations are related to differences in the interventions evaluated, the type of costs included, and, most important, the methodologies adopted.

Annexes 13A and 13B tabulate the costs and cost-effectiveness results of studies published between 2010 and 2015, presented in 2012 US\$. The cost of malaria control interventions is relatively low in all countries, but varies widely:

- The financial cost per severe malaria case ranges from US\$30 to US\$200 in most countries; exceptions were observed in two studies in Myanmar and South Africa, which reported much higher costs.

- Various studies estimated only the costs of medicines for uncomplicated malaria, thereby reporting low estimates. For most of the studies that included outpatient services, the costs varied between US\$4.50 and US\$30.00; the costs were higher in the few studies that included services in hospital settings. Most of these cost estimates do not include diagnostic tests, which are rather high—on average, around US\$10.90 per person—again with wide variations.
- The costs of preventive treatments in infants, children, and pregnant women were low (on average US\$2.20, US\$2.90, and US\$2.60, respectively), except in analyses that estimated the full economic costs, including the noncompliant individuals in all population strata.

Most of the studies available indicate rather low cost-effectiveness ratios. The cost per disability-adjusted life year (DALY) averted for intermittent preventive treatment for children ranged from US\$13 to US\$35, and that for preventive treatment in pregnant women was estimated to be less than US\$2. Slightly higher, but still relatively low costs per DALYs averted were reported for case management (from less than US\$2.00 to US\$42.00) and for ITNs (US\$4.50 to US\$128.00). The costs per DALYs averted by IRS were estimated to be higher at US\$163 to US\$183.

Several studies assessed the costs and potential cost-effectiveness of the RTS,S/AS01 vaccine. This agent, which is well tolerated and partially and temporarily effective, is being considered for implementation in endemic Africa. These studies showed that, conditional on assumptions of price and coverage, adding RTS,S to routine malaria control interventions could be highly cost-effective (Galactionova and others 2017; Penny and others 2016).

The costs of vector control interventions were of the same order of magnitude as treatment costs, with wide variations, depending on the setting and the type of study. The economic costs per person protected with ITNs ranged from US\$2.70 to US\$9.20 in low-income countries and up to US\$19.00 in upper-middle-income countries. These costs approximate those for IRS, whereas the costs for insect larval source management are available only per intervention.

Additionally, recent estimates of the costs and potential returns on investments to achieve the 2030 *Global Technical Strategy* goals indicated a global return of up to 40:1. This return is due to averting 3 billion malaria cases and 10 million malaria deaths and to increasing productivity by US\$4 trillion (RBM Partnership 2015; WHO 2015a).

SYSTEMIC APPROACHES TO MALARIA CONTROL AND ELIMINATION

Malaria control and elimination efforts in any setting need to be understood in the context of prevailing ecological and social systems. These highly interconnected systems are the key drivers of control and elimination efforts.

Environmental and Social Determinants of Malaria

Environmental, health, and social system factors affect the transmission intensity, seasonality, and geographical distribution of malaria. Social factors—such as demographics, culture, behavior, migration patterns, socioeconomic characteristics, and politics—affect the uptake and effectiveness of control and elimination interventions. Access to health care and related behavioral factors determine the vulnerability of individuals and communities to infection. These factors have positive and negative effects, which can be modified, depending on how they interact.

In addition, many of these factors adapt to novel local conditions, bringing about additional challenges to control efforts. Relevant examples include the development of drug and insecticide resistance, vector (Awolola and others 2007; Chinery 1984; Sattler and others 2005) and human behavior (Maheu-Giroux and Castro 2013), and environmental changes (Castro and Singer 2011; Gething and others 2010; Hahn and others 2014; Keiser and others 2004; Yamana and Eltahir 2013).

Environmental Determinants

Environmental determinants fall into two broad categories:

- **Natural environment:** temperature, humidity, rainfall, soil quality, elevation and slope, land cover, and hydrography
- **Human environment:** land use, land change, deforestation, housing conditions, infrastructure (water, sanitation, and waste collection), urbanization, development projects (such as roads, railways, dams, irrigation, mining, resettlement projects, and oil pipelines), and disasters abetted by human changes.

Strategies that alter the environmental characteristics associated with malaria transmission were among the earliest interventions tested, validated, and applied at larger scale (Stromquist 1920). Environmental interventions (killing mosquitoes and destroying their habitats)

were crucial for the elimination of malaria in European countries and the United States, and they significantly reduced the burden of the disease elsewhere (Boyd 1926; Neiva 1940; Pomeroy 1920). Case studies documenting sustained success include the construction of the Panama Canal (Gorgas 1915), copper mining in Zambia (Utzinger and others 2002; Watson 1953), and rubber production in Malaysia (Watson 1921). A specific, but enlightening, example is the story of malaria-transmitting *Anopheles* mosquitoes breeding in the small water bodies created in *Bromelia* plants. Bromeliads are epiphytes (plants that grow on trees, mainly in tropical South America) that typically provide space for small reservoirs of water in which frogs and insects, including *Anopheles* species, may breed. Malaria was eliminated from southern Brazil by the removal of bromeliads from urban areas and the introduction of eucalyptus trees on which bromeliads do not grow (Deane 1988; Pinotti 1951).

Housing improvements, first introduced by the Italian hygienist Angelo Celli at the end of the 19th century, were a crucial intervention in Europe and the United States; the screening of barracks during recent wars was a successful intervention (Carter and Mendis 2002; Lindsay, Emerson, and Charlwood 2002). The use of intermittent irrigation strategies for control of malaria around rice paddies continues to be an important strategy in China (Baolin 1988; Singer and Castro 2011). The numerous historical examples of the successful use of environmental management show the crucial nature of designing integrated interventions and tailoring them to given socioecological settings (Keiser, Singer, and Utzinger 2005; Konradsen and others 2004).

Environmental management often has a low priority in endemic areas (Lindsay, Emerson, and Charlwood 2002), although the opportunities for its adoption are excellent. Housing improvements—such as screening doors, windows, and eaves; closing eaves; installing ceilings; improving roofs; sealing cracks in walls; using higher-quality building materials; creating new housing designs; and installing eave tubes (Knudsen and von Seidlein 2014; Lindsay, Emerson, and Charlwood 2002; Ogoma and others 2009; Tusting and others 2015)—are applicable in many endemic areas, especially those experiencing rapid economic development. Construction and maintenance of drainage systems in expanding urban areas that often lack proper infrastructure will improve mosquito control effectiveness, as well as the control of other vector-borne diseases, such as dengue and lymphatic filariasis.

Social Determinants

Key social determinants for local populations include age, economic activity, education, cultural beliefs, population

density, migratory patterns, personal behavior, and knowledge about malaria. Behavior particularly affects the effectiveness of vector control (for example, ITN and LLIN use). Behavior change communication (BCC) strategies are often used to promote malaria prevention and treatment behaviors (RBM Partnership 2012) and can substantially increase the return on investment in malaria control (Koenker and others 2014). Although many malaria-endemic countries have a BCC strategy, a gap in the literature exists with respect to the effectiveness of BCC in promoting behavior change and ultimately reducing malaria transmission. The design, implementation, and evaluation of locally adapted BCC strategies, founded in solid behavior change theory, are especially important in promoting effective and sustainable changes, but they remain challenging for many national malaria control programs.

Health System Factors for Effective Coverage of Malaria Control Interventions

The scale-up of malaria interventions during the past decade highlights the importance of strong health systems (Stratton and others 2008). Effective treatment provides individual benefits by curing infection and preventing progression to severe disease stages. It also provides community-level benefits by reducing the infectious reservoir and averting the emergence and spread of drug resistance (WHO 2012).

Ensuring effective coverage of malaria treatment is particularly problematic and requires simultaneously addressing both supply-side and demand-side challenges in health systems that are often weak. Efficacious therapy is available, but many patients with malaria do not have access to treatment or delay seeking treatment. Providers do not always comply with treatment guidelines, so patients do not necessarily receive the correct regimen or instructions, which may lead to adherence problems. Even when the correct regimen is communicated and administered, some patients will not adhere to it. Others may be treated with counterfeit or otherwise substandard medication. All of these factors lead to treatment failures and potentially to the development and spread of drug resistance.

Recent analyses of the effectiveness of malaria service delivery have assessed supply-side determinants, including diagnosis, staff training, and availability of antimalarial medicines at the health facility level (Berendes and others 2011; McPake and others 1999; Mikkelsen-Lopez and others 2013; Obrist and others 2007; Rao, Schellenberg, and Ghani 2013a, 2013b; Zurovac and others 2008). Other studies assessed patient awareness and perception of illness, affordability of treatment,

and adherence to the treatment regimen (Littrell and others 2013; Mumba and others 2003; Webster and others 2014). These studies estimated the proportion of fever or malaria cases treated in the public sector according to the national guidelines, with estimates generated for the region as a whole (Berendes and others 2011; Zurovac and Rowe 2006) and for given countries (Alonso and others 2011; Khatib and others 2013; Littrell and others 2013; Mikkelsen-Lopez and others 2013; Sumba and others 2008; Webster and others 2014). Consistently, these evaluations revealed substantial inefficiencies in malaria-related service delivery.

A recent comprehensive analysis of available data on effective coverage of malaria case management for 43 countries in Sub-Saharan Africa (Galactionova and others 2015) found considerable international variations. Effective national coverage for malaria case management was found to range from 8 percent to 72 percent in the Sub-Saharan Africa region, for a variety of reasons. Interestingly, the correlation between effective coverage and economic development was weak, indicating that resource constraints play only a limited role. Such patterns of intercountry variation suggest that many system failures are amenable to change. Priority areas for malaria control and eradication policies include identifying the reasons for poor health system performance, intervening to address them, and implementing the respective strategies in program activities.

NEW TOOLS AND TECHNOLOGIES FOR MALARIA CONTROL

Therapies

ACTs have become the mainstay for the case management of uncomplicated malaria over the past decade, and child-friendly versions of most of these agents have become available (Bassat and others 2015). For cases of severe and life-threatening malaria, where oral treatments are not an option, the key data from two pivotal trials in Asia (Dondorp and others 2005) and Africa (Dondorp and others 2013) demonstrated the superiority of injected artesunate over injected quinine. However, the adoption and scale-up of injectable artesunate have been slow. The challenge is to ensure the wide availability of injectable artesunate at affordable prices. The reasons for using parenteral artesunate rather than oral ACTs are, first, that patients are often unconscious and, second, that reduction of the parasitemia quickly and profoundly saves lives in these emergency situations. Where injectable artesunate is not available, particularly where medical facilities are lacking, rectal artesunate suppositories are recommended by the World Health Organization to

achieve a similar rapid reduction in parasitemia as occurs with injected artesunate (WHO 2015b). This recommendation is supported, particularly in children, by a large multisite (including Africa and Asia) randomized trial (Gomes and others 2009). Substantial potential exists to improve access to these treatments for the initial treatment of severe malaria.

New agents are needed for the treatment and prevention of all types of malaria, mainly because of the emergence and spread of drug resistance. Numerous new chemical series and compounds have been identified over the past decade (Wells, van Huijsduijnen, and Van Voorhis 2015). Several key characteristics are important for new molecules, described as target candidate profiles (TCPs) (Burrows and others 2017):

- **Molecules that kill the blood-stage parasites (the cause of clinical symptoms):** In practice, most of the new molecules appear to have killing rates as fast as current or recent drugs and deliver an active plasma concentration from a single dose.
- **New medicines that prevent the relapse of hepatic hypnozoites of *P. vivax* and other recurrent malarialias:** The current standard is a 14-day course of primaquine, an 8-aminoquinoline (8-AQ). A newer 8-AQ, tafenoquine, was shown to be highly active in preventing relapse after single dosing in phase II studies (Llanos-Cuentas and others 2014). However, all drugs in the class carry a risk of hemolysis in G6PD (glucose-6-phosphate dehydrogenase)-deficient individuals. G6PD deficiency is frequent (around 10 percent) in tropical Africa (Carter and others 2011) because it is thought to afford some resistance against malaria. A roadmap for finding new chemical entities without such a risk factor has recently been published (Campo and others 2015).
- **Agents that block transmission:** The other activity of 8-AQs, including primaquine, is blocking transmission of *P. falciparum* by killing gametocytes (TCP3b). In its most recent treatment guidelines, the WHO recommends a reduced single dose of 0.25 mg/kg (WHO 2015b), which is assumed to be safer than its previous recommendation of a single 0.75 mg/kg dose, following a recommendation of the WHO's Malaria Policy Advisory Committee. New agents without potential risks to G6PD-deficient individuals are needed.
- **Chemoprevention:** As the eradication agenda proceeds, it becomes increasingly important to protect against initial infection with agents active against hepatic schizonts. New agents of this type are needed particularly by people entering areas of high transmission from low-transmission areas.

The drug development pipeline is relatively rich in new molecules and targets for the rapid killing of parasites (Wells, van Huijsduijnen, and Van Voorhis 2015) (figure 13.1). The recent availability of efficient controlled human malaria infection (CHMI) models (McCarthy and others 2011) has allowed the assessment of new molecules at an early stage. In these models, volunteers are infected with low (asymptomatic) densities of parasites, whose proliferation is monitored by PCR (polymerase chain reaction). Following administration of experimental drugs, a minimum inhibitory concentration (in blood) and a rate of parasite reduction can be calculated, both of which are highly predictive of the effects in patients.

New medicines that are fully active against emerging resistant strains and that are administered via three-day

regimens can likely be developed. However, among the eradication goals is the availability of a simplified form of therapy, ideally, a single-exposure radical cure (Burrows and others 2017). This ambitious goal makes development of effective new agents more difficult. A new medicine will be a combination of two or more active ingredients; any new molecule that enters a combination must be powerful enough by itself to kill a reasonable number of parasites in the patient, preferably all of them, so that efficacy is ensured even when some parasites are resistant to one of the partner ingredients.

The *Global Technical Strategy* (WHO 2015a) and the *AIM* (RBM Partnership 2015) foresee a 90 percent reduction in case mortality by 2030, underlining the need for new classes of medicines over the next 20 years

Figure 13.1 Current Portfolio of the Global Malaria Medicines Development Effort

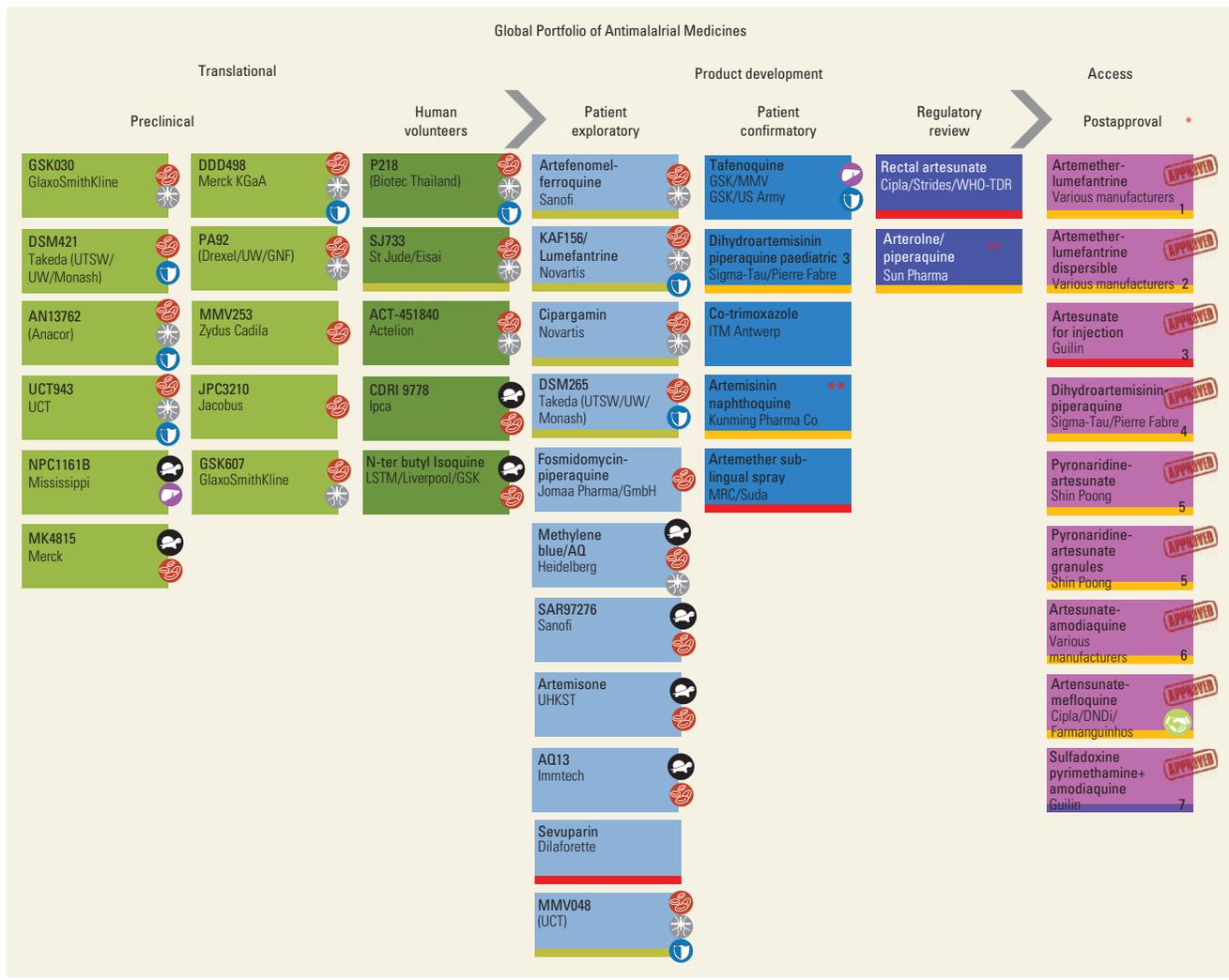
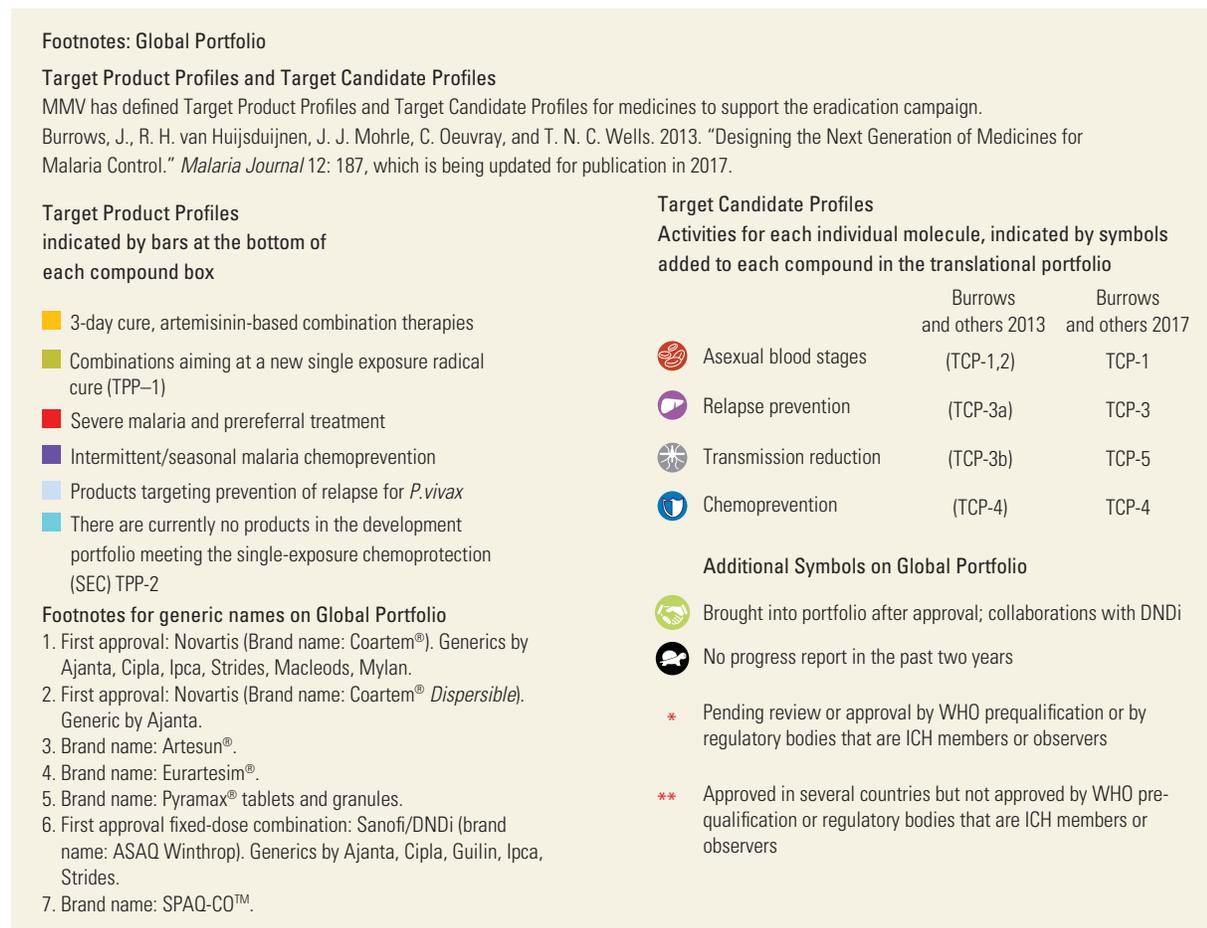


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Figure 13.1 Current Portfolio of the Global Malaria Medicines Development Effort (continued)



Note: This figure is constructed from available information using Internet searches, Thomson Reuters Cortellis database (<http://lifesciences.thomsonreuters.com/products/cortellis>), and searches of the patent and published literature. It represents the portfolio of data as of December 2016. A new version is produced quarterly and is available at Medicines for Malaria Venture, <http://www.mmv.org/research-development/rd-portfolio>. DNDi = Drugs for Neglected Diseases initiative; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MMV = Medicines for Malaria Venture; TCP = target candidate profile; TPP = target product profile; WHO = World Health Organization.

if the precious gains against malaria are not to be lost in the future.

Transmission-Blocking Medicines

The primary drug discovery screens have been conducted against blood-stage forms of the parasite. However, many of the compounds show promising activity against the sexual stages (gametocytes) and in membrane-feeding assays (feeding mosquitoes in special devices with blood from patients) (Bolscher and others 2015; Upton and others 2015). The CHMI model has been modified to also allow the production and characterization of gametocytes (Pasay and others 2016) and hence may provide an effective means of testing transmission-blocking treatments.

P. vivax infections are rising: *P. vivax* develops dormant forms or hypnozoites, which result in multiple

malaria episodes from a single infection. The ideal medicine for treatment would therefore have activity against the asexual and sexual blood stages of the parasite as well as against the hypnozoites where present (*P. vivax* and *P. ovale*) (Hemingway and others 2016).

Medicines for Long-Term Chemoprotection

The goal of providing chemoprotection has long been one of the mainstays of malaria research and development. Historically, chemoprotection has been targeted at tourists and nonimmune military personnel in times of conflict. More recent developments involve medicines to protect children (Wilson and on behalf of the IPTc Taskforce 2011). Studies of intermittent preventive treatment of children (IPTc) show a remarkable effect when used throughout the rainy malaria season; the medicines

reduced the rate of infection by more than 80 percent and the rate of all-cause mortality by 57 percent. The cost of such medicine is relatively low: sulfadoxine-pyrimethamine in combination with amodiaquine costs less than US\$0.70 for one year's treatment. In light of these data, several groups have proposed using ACTs, such as DHA (dihydroartemisinin-piperaquine), for chemoprotection south of the equator, in regions where sulfadoxine-pyrimethamine is ineffective. However, doing so would mean that the same active ingredients would be used for treatment and prevention, which is far from ideal. The WHO recommends against this approach because of the risks of resistance and treatment failure.

Currently available agents are far from ideal. Cycloguanil pamoate (Camolar), for example, was developed by Parke Davis in the 1960s as a long-acting form of cycloguanil. This low-solubility salt was developed for intramuscular use in primates, but it required a slow injection through a 20-gauge needle over a 90-second period because the optimal crystal size was large and the vehicle was oleaginous (viscous) (Schmidt and Rossan 1984). These large particle sizes were needed to achieve a drug release over 200 days. Initial trials in humans provided a duration of protection from nonresistant strains of four to six months (Elslager 1969). This formulation is hardly child friendly, requiring four 1 mL intramuscular injections through a 21-gauge needle.

New medicines for chemoprotection are urgently needed because all drugs currently used in treating malaria suffer from resistance. Two compounds in phase II studies, KAF156 (White and others 2016) (acting against the un-annotated CARL locus, a part of the genome with unknown function), and DSM265 (McCarthy and others 2017; Sulyok and others 2017) (an inhibitor of the enzyme dihydroorotate dehydrogenase, which is essential for the DNA synthesis of the parasites), have also shown good activity against the liver schizont stages and could be used in chemoprevention. Studies in CHMI models with insect challenges are needed to validate whether the preclinical activity can be replicated in human subjects. They are also needed to help decide if these medicines would require daily, weekly, or even less frequent administration.

Malaria Vaccine: The Pace Quickens

The agenda for malaria vaccines was originally presented in the 2006 global malaria technology roadmap. By 2015, the landmark roadmap was to have registered a first-generation vaccine with a protective efficacy of more than 50 percent against severe disease and death and with a duration of protection greater than one year. The current frontrunner is the subunit vaccine RTS,S

in combination with a proprietary adjuvant, AS01 (produced by GlaxoSmithKline and the Malaria Vaccine Initiative). The results for the phase III study involving 15,460 children in 11 centers in 7 countries in Sub-Saharan Africa showed a reduction of 18–28 percent against all malaria episodes without a booster, and a reduction of 26–36 percent with a booster at month 20. The protection was slightly less for severe malaria episodes: a 1.1–10.0 percent reduction without booster and 17.0–32.0 percent reduction with a booster at month 20 (RTS,S/AS01 Clinical Trials Partnership 2012). The vaccine received a positive scientific opinion in July 2015 from the Committee for Medicinal Products for Human Use of the European Medicines Agency.

An analysis of the vaccine's protection and its long-term public health effect for 43 African countries reported a rate of initial protection of 80 percent against infection in children ages 5–17 months and a rate of initial protection of 65 percent in infants ages 6–12 weeks (Olotu and others 2013). Despite observed and predicted protection of the RTS,S vaccine being short lived, when used in combination with other malaria control strategies, such as ITNs, the vaccine has the potential to avert up to 700,000 deaths over a 10-year period. After considering all of the safety data from the clinical trials, the WHO issued a positive policy recommendation for starting to plan a series of large-scale implementation programs (Penny and others 2015; WHO Malaria Policy Advisory Committee and Secretariat 2015).

The WHO, working with the Malaria Vaccine Funders Group, updated the *Malaria Vaccine Technology Roadmap* in 2013 to present the organization's goals until 2030 (Malaria Vaccine Funders Group 2013; Tanner and Alonso 2010). Specifically, by 2030, vaccines will be launched that target *P. falciparum* and *P. vivax*, that have a protective efficacy of at least 75 percent against clinical malaria, that are suitable for administration to appropriate at-risk groups in malaria-endemic areas, that reduce transmission of the parasite, and that thereby substantially reduce the incidence of human malaria infection.

These new goals are in line with the Malaria Elimination/Eradication Roadmap (Tanner and Alonso 2010), which introduced the further concept of vaccines that interrupt malaria transmission (VIMT). These VIMT include classical transmission-blocking vaccines that target the sexual and mosquito stages, as well as pre-erythrocytic and asexual stages that have an effect on transmission. More recently, this terminology has been extended to VIMT through the sexual, sporogonic, or mosquito stages of the parasite (Nunes and others 2014). The current malaria vaccine pipeline from the WHO summary is shown in figure 13.2.

The present challenges to vaccine development are as follows:

- A careful selection of antigens to ensure protection against both *P. vivax* and *P. falciparum* is needed.
- A vaccine that costs around US\$1 per dose would be most attractive. However, if the ideal vaccine may have multiple antigens to target different parasite stages, its production costs may increase. The cost-benefit tradeoffs must be evaluated early to avoid producing a vaccine that might be very effective but is too expensive for widespread adoption.
- Better and more specific adjuvants (which increase antigenicity) are lacking.
- Improved understanding of why acquired immunity to *Plasmodium* is slow to develop, incomplete, and short-lived is needed; this is essential to improve the likelihood of finding a fully protective vaccine.

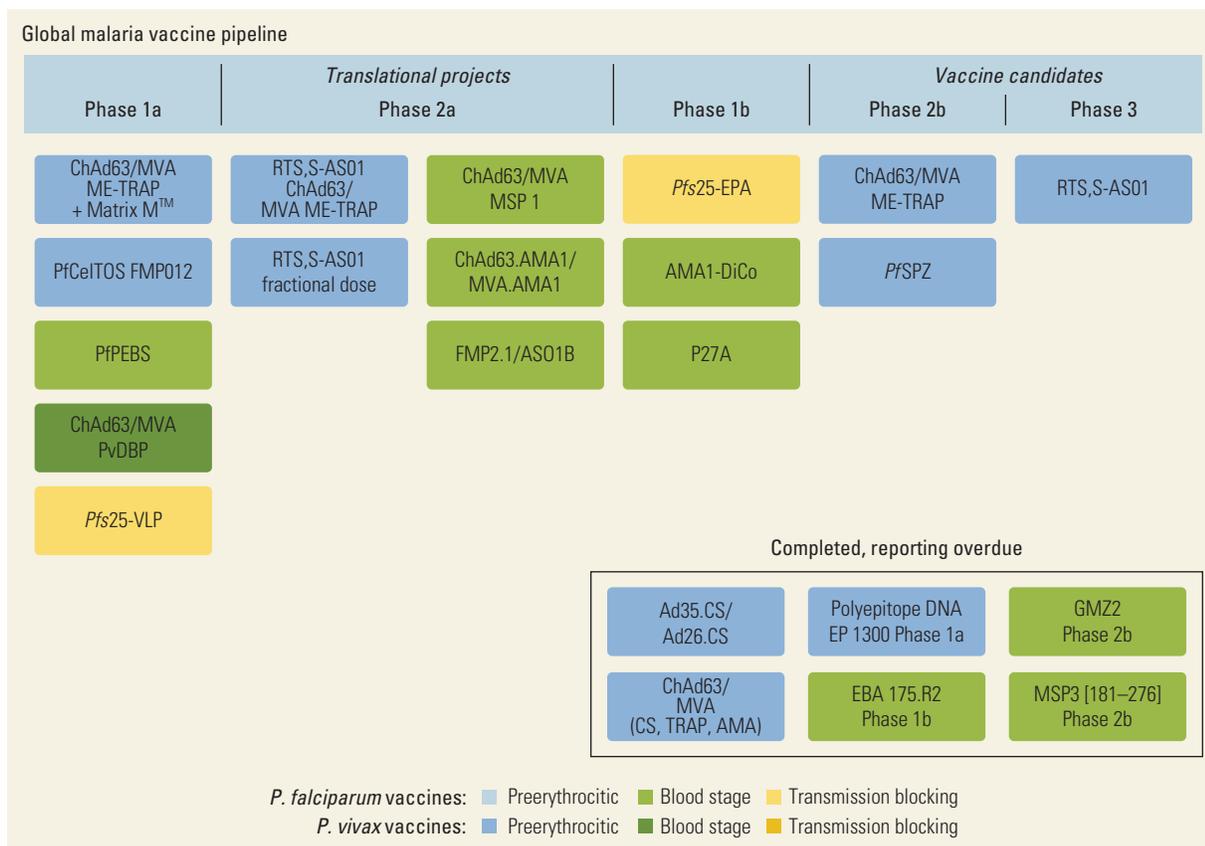
The challenge is considerable, because protozoan parasites have evolved multiple strategies to evade attacks from the mammalian immune system, such as encoding

and switching between dozens of genes that encode different cell surface proteins. Almost all successful vaccines are directed against viruses, very few act against bacteria, and almost none act against protozoans.

Several vaccines are in human volunteer studies or early field trials. The probability of early success in malaria vaccines as a whole at this stage is quite high (Pronker and others 2013). The combination of a wealth of candidates and a poor success rate highlights the importance of having standardized processes for comparing candidates. The Malaria Vaccine Roadmap underscores this point and recommends standardized CHMI models. These same models are being used to benchmark chemoprotective medicines, giving the additional advantage that chemoprotective medicines and vaccines can be compared side by side.

Most of the current vaccine candidates are blood-stage vaccines and specific for one species. Again, community portfolio management is needed to ensure that vaccines with the potential to fulfill the aspirations of the roadmap receive priority. The development of transmission-blocking vaccines has received much attention, because they would

Figure 13.2 Current Portfolio of the Global Malaria Vaccines Development Effort



Source: World Health Organization, http://www.who.int/immunization/research/development/Rainbow_tables/en (March 2016).

substantially affect eradication efforts. The regulatory pathway for such vaccines and drugs, which would protect communities rather than individuals, has been complicated; progress is being made in discussions among members of the vaccine community such as developers, clinical epidemiologists involved in trials, and regulatory agencies (Delrieu and others 2015). There is still a paucity of antigens under study. The major exception and very promising approach is the sporozoite vaccine from Sanaria, Inc., which is being tested in early volunteer studies in Africa (Seder and others 2013). Studies using more than 50,000 attenuated, aseptic, purified, cryopreserved *P. falciparum* sporozoites delivered in four intravenous injections are ongoing in endemic areas and for short-term visitors and travelers (Richie and others 2015).

Finally, the timescales are important. RTS,S/AS01 started phase II (field exploratory) studies over a decade ago; the time to complete the confirmatory studies,

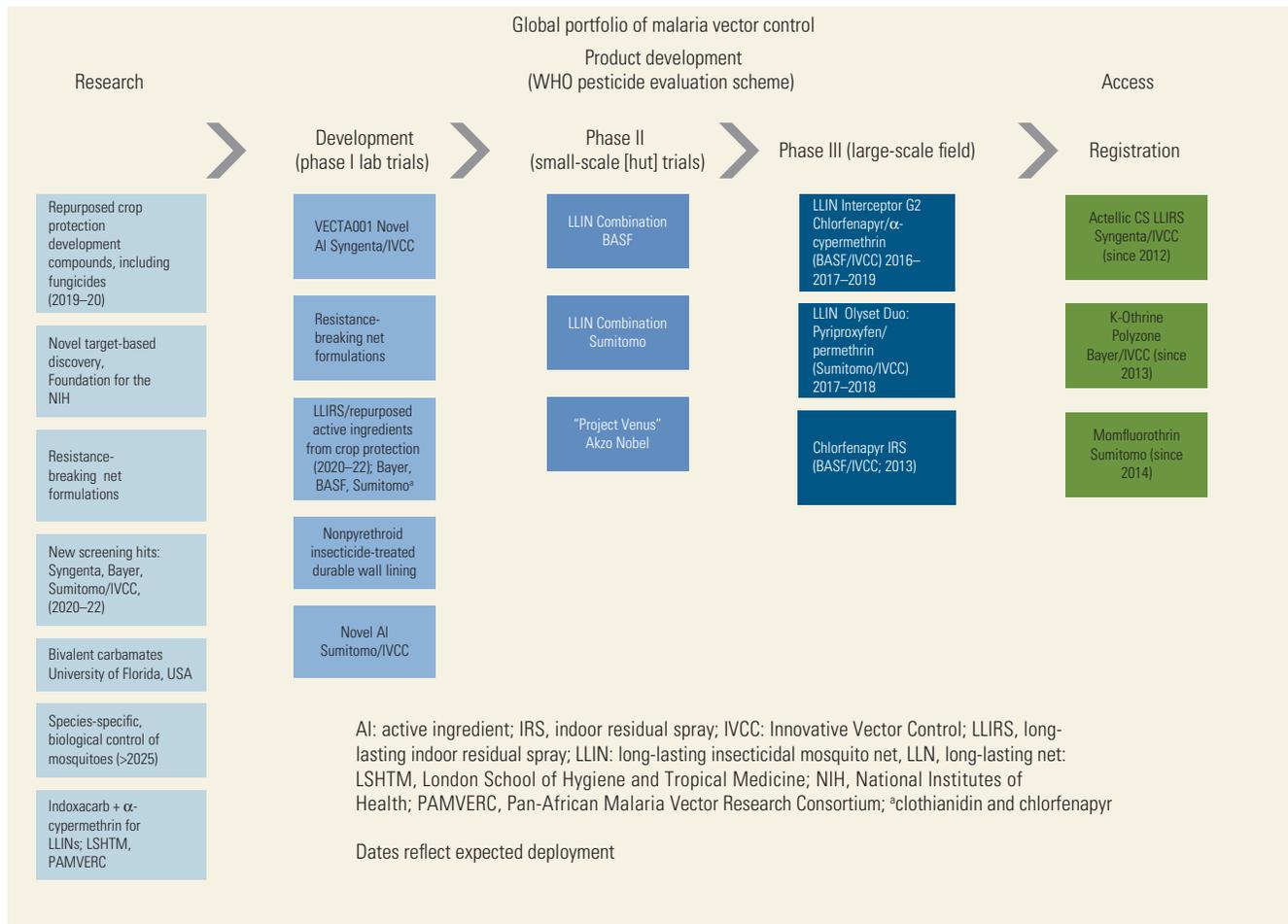
ensure two-year follow up, and submit regulatory documentation was approximately six years. A review of the regulatory lessons from this process is critical to future efforts to shorten some of these timelines.

Vector Control

Success of LLINs under Threat from Insecticide Resistance

An essential requirement for effective resistance management is to speed up the development of new active insecticidal ingredients, as well as alternative vector control approaches. The Innovative Vector Control Consortium, a public-private partnership established in 2005, is managing a portfolio of novel insecticide candidates that are expected to deliver new public health insecticides by 2020–22. In addition to new active ingredients, the current development pipeline of vector control products (figure 13.3) contains repurposed and reformulated

Figure 13.3 Current Portfolio of the Global Malaria Vector Control Development Effort



Source: IVCC 2016.

existing insecticides, such as the microencapsulated organophosphate insecticide pirimiphos-methyl.

Finally, the pipeline also includes noninsecticidal new paradigms for vector control. As a stopgap measure to rapidly address the pyrethroid resistance issue, nets have been designed that combine an insecticide (usually a pyrethroid) with a second chemical (usually piperonyl butoxide), which helps reduce enzymatic resistance in *Anopheles* mosquitoes. These combination nets are being field tested and may prove to be effective in areas with high levels of pyrethroid resistance in malaria vectors. As new insecticides with new modes of action become available, nets should regain their effectiveness. Ideally, future nets should be treated with a combination of insecticides representing various modes of action, thereby reducing the risk of resistance. This combination strategy has worked well for antimalarials and should be chosen for vector control strategies as well.

Mosquito Population Modification Strategies

A promising potential intervention is the use of genetically modified mosquitoes. The recent demonstration that CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 gene-editing technology can be used efficiently to generate genetically modified insects (Gantz and Bier 2015) has raised hopes for future development of malaria-resistant mosquitoes. Another encouraging finding is the recent discovery that genetic modification of certain bacteria (especially *Wolbachia* sp.) from the mosquito microbiota (paratransgenesis) can lead to a dramatic reduction of mosquito vectorial competence (Shaw and others 2016). However, many challenges remain with these approaches, which to date have been largely confined to the laboratory. The issue of driving new genes sustainably into wild mosquito populations remains a major obstacle to widespread implementation, as is testing of the efficacy and the public acceptance of such approaches (WHO/TDR and Foundation for the National Institutes of Health 2014).

Other Noninsecticidal Vector Control Approaches

New vector control tools being developed do not rely on insecticidal action for their effectiveness, thereby providing a welcome alternative at a time of widespread resistance. Spatial repellents have the potential to significantly decrease the entry of malaria vectors into human dwellings (Lambrechts and others 2015; Ogoma and others 2014) and are being tested in large-scale trials around the world. Topical repellents, in contrast, have proven largely disappointing as a malaria control tool, primarily because of compliance problems (Sluydts and others 2016).

Another potential approach is the use of attractive toxic sugar baits, which take advantage of the fact that every female mosquito needs to take one or more sugar meals in addition to blood meals to produce offspring. Such baits attract mosquitoes to artificial sugar sources that are toxic to the mosquito (Qualls and others 2015).

Finally, the careful and evidence-based combination of multiple vector control tools is likely to provide the best avenue to reduce further transmission in currently endemic areas in which either LLINs or IRS is already implemented at high coverage (Okumu and Moore 2011). One such combination, a spatial repellent that protects houses, is associated with attractive traps located at the periphery of villages, using the “push-pull strategy” (Wagman and others 2015).

CONCLUSIONS

Malaria control is one of the great success stories of global public health. Unprecedented success has been and is being achieved for a disease that, by one estimate, may have killed half of all the people who ever lived (Whitfield 2002). Even a high-transmission setting such as the Democratic Republic of Congo has been able to halve the prevalence and incidence rates in the past 15 years (WHO 2016b). These successes have provided the impetus for the world to move forward to attain the goal of eradication. However, substantial threats to these achievements exist. Drug and insecticide resistance top the list of biological and epidemiological problems, while the lack of political will and sustainable financing top the list of external dangers.

In summary, several conclusions emerge:

- Many new malaria control tools are being developed, thanks to product development partnerships for drugs (Medicines for Malaria Venture), diagnostics (Foundation for Innovative New Diagnostics), and vector control tools (Innovative Vector Control Consortium). New strategies are being devised that use existing tools, with countries attempting to become more specific and evidence driven in their strategic plans (WHO 2015a).
- The regulatory landscape for drugs and vaccines is not equipped to evaluate treatments meant to drive low-to-zero malaria transmission. When placing this outlook into the overall context of AIM (RBM Partnership 2015) and the Sustainable Development Goals, one can no longer calculate the payoff of tools introduced to drive elimination from low-to-zero transmission only in terms of present and future

cases averted; a broader economic perspective of productivity gained, as well as the transmission effect, is needed. This enhanced perspective focused on return on investments is essential to evaluate the relative merits of the various tools and to prioritize and select their deployment in multiple settings.

- Consequently, there is a growing need to decide how new control approaches are to be applied in an optimal combination and an integrated way in a world with differing levels of malaria transmission and with contrasting malaria endemicity, even within the same country. Addressing this heterogeneity entails adapting the *Global Technical Strategy* (WHO 2015a) to national and even subnational levels and rigorously implementing surveillance–response strategies and systems.

Given that all activities are based on partnership approaches across the public, private, and charitable sectors, the roles and responsibilities of the partnerships must be well defined at each level. The task of malaria control and elimination calls for more than joint actions. Rather, it requires better, well-defined, and assigned tasks and responsibilities, accompanied by the required power and authority to implement the responsibilities within national strategies and coordinated operational plans.

ANNEXES

The annexes to this chapter are available at <http://www.dcp-3.org/infectiousdiseases>.

- Annex 13A. Dataset of Costs Studies.
- Annex 13B. Dataset of Cost-Effectiveness Studies.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046–US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126–US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

1. For more information on the study, visit <http://www.who.int/malaria/news/2016/llins-effective-tool-malaria-fight/en/>.
2. *P. vivax* and *P. ovale* infections can form hypnozoites that can cause relapses months and even years after the initial infection.

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