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# Eradicating malaria

*JOEL G. BREMAN*

## ABSTRACT

*The renewed interest in malaria research and control is based on the intolerable toll this disease takes on young children and pregnant women in Africa and other vulnerable populations; 150 to 300 children die each hour from malaria amounting to 1 to 2 million deaths yearly. Malaria-induced neurologic impairment, anemia, hypoglycemia, and low birth weight imperil normal development and survival. Resistance of* Plasmodium falciparum *to drugs and* Anopheles *mosquitoes to insecticides has stimulated discovery and development of artemisinin-based combination treatments (ACTs) and other drugs, long-lasting insecticide-treated bednets (with synthetic pyrethroids) and a search for non-toxic, long-lasting, affordable insecticides for indoor residual spraying (IRS). Malaria vaccine development and testing are progressing rapidly and a recombinant protein (RTS,S/AS02A) directed against the circumsporozoite protein is soon to be in Phase 3 trials. Support for malaria control, research, and advocacy through the Global Fund for HIV/AIDS, Tuberculosis and Malaria, the U.S. President's Malaria Initiative, the Bill & Melinda Gates Foundation, WHO and other organizations is resulting in decreasing morbidity and mortality in many malarious countries. Sustainability of effective programs through training and institution strengthening will be the key to malaria elimination coupled with improved surveillance and targeted research.*

**Keywords**: *malaria eradication, disease control, health programs*

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## Glossary

| Abbreviation | Name |
|---|---|
| ACT | Artemisinin combination treatment |
| DDT | Dichlorodiphenyltrichloroethane |
| EIR | Entomologic inoculation rate |
| GFATM | Global Fund for HIV/AIDS, Tuberculosis, and Malaria |
| IPT | Intermittent preventive treatment |
| IRS | Indoor residual spreaying |
| LLINs | Long-lasting insecticide treated bed nets |
| MEG | Malaria Elimination Group |
| MIM | Multilateral Initiative on Malaria |
| MVI | Malaria Vaccine Initiative |
| PMI | President's Malaria Initiative |
| RBM | Roll Back Malaria |
| $R_o$ | Reproduction rate |
| VSA | Variable surface antigen |
| WHO | World Health Organization |

## Background

The ''first'' global malaria eradication program was initiated in 1955 by the World Health Organization (WHO) and was based mainly on household spraying with dichlorodiphenyltrichloroethane (DDT). While progress was made in many countries in southern Europe, north Africa, and the Middle East with low to moderate seasonal transmission, the program stopped about 1971; this was due to mosquito resistance to DDT, lack of inclusion of Africa in the global program, and numerous administrative and strategic inadequacies, including poor insecticide supplies, among other reasons (Table 1)[1,2]. The good news is that several promising malaria control, elimination, and research initiatives have begun over the past decade. Field activities have followed breakthroughs in drug discovery, personal protection, vector control and immunology (with real hope for a vaccine), and in unprecedented resource allocation to fight this perennial scourge[3,4]. This paper will review the recent progress in understanding the manifestations of malaria, and discoveries and experiences in control and prevention that will lead, ultimately, to the demise of this disease before 2050.

***Table 1*** *Reasons why countries failed to eliminate malaria during the WHO Global Malaria Eradication Program, 1955–1971*

| | |
|---|---|
| 1. | Failure in keeping the plan of operations current |
| 2. | Weak monitoring of operational activities and epidemiological situations |
| 3. | Inadequate surveillance of morbidity, mortality, and incidence |
| 4. | Inadequate training |
| 5. | Imprecise diagnostics |
| 6. | Poor supervision |
| 7. | Inadequate human resources and poor quality of staff and operations |
| 8. | Lack of DDT supplies |
| 9. | Pulling staff out of the program |
| 10. | Weak health systems |
| 11. | Research agendas given low priority |
| 12. | Malaria transmission originally stable or of intermediate stability |
| 13. | Major population movements from adjacent malarious countries |
| 14. | Political instability |
| 15. | Lacking or fluctuating political and financial commitment |
| 16. | Internal and/or external armed conflicts |
| 17. | Donor fatigue |
| 18. | Poor public understanding and support of the programme |

Malaria is a protozoan disease transmitted by the bite of infected female *Anopheles* mosquitoes. It is the most important of the parasitic diseases of humans, with transmission in 107 countries affecting close to three billion people and causing one to two million deaths each year, mainly young African children[1,3,4]. There are tens of thousands of imported cases of malaria annually into countries where malaria has been eliminated; in addition, local transmission following importation occurs periodically in North America and in Europe, indicating the continual danger to non-malarious countries. Major treatment and prevention challenges remain closely linked to increasing resistance of the parasite to drugs and the vectors to insecticides.

## Etiology and natural cycle

Five species of the genus *Plasmodium* cause malarial infections in humans. These are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesei* (a newly confirmed human species). Almost all deaths are caused by falciparum malaria. Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from her salivary gland during a blood meal (Figure 1)[5]. These are carried rapidly via the bloodstream to the liver, where they begin a period of asexual reproduction as liver schizonts. The swollen infected liver cell eventually bursts, discharging motile *merozoites* into the blood-stream. These then invade the red blood cells (RBCs) and multiply

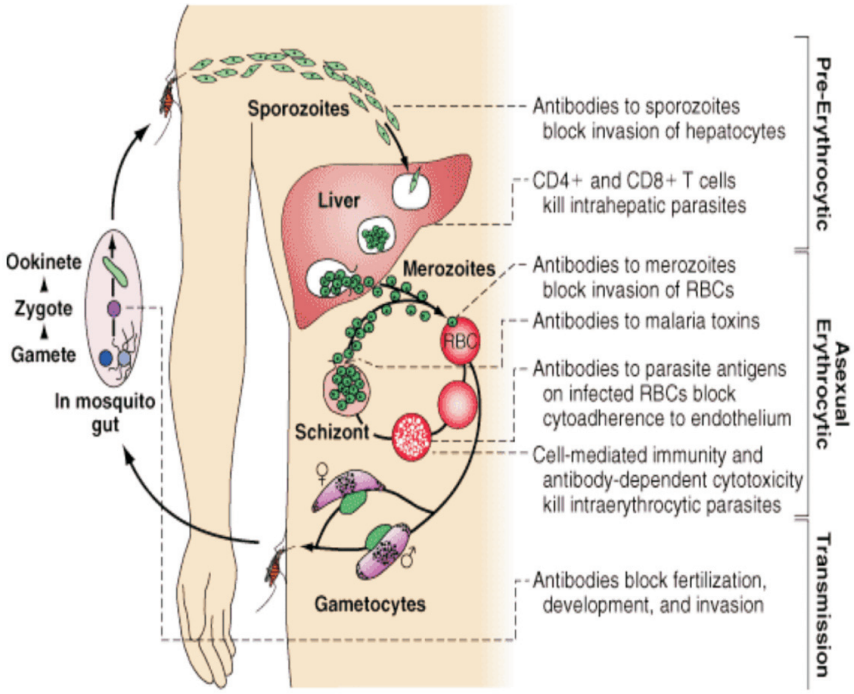



***Fig. 1.*** *The malaria cycle. Data from ref 5.*

as trophozoites, 6- to 20-fold every 48 to 72 h. When the parasites reach densities of $\sim 50/\mu L$ of blood, the symptomatic stage of the infection begins depending upon the immune status of the patient. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain dormant for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or *hypnozoites*, are the cause of the relapses that characterize infection with these two species.

During the early stage of intraerythrocytic development, the small ''ring forms'' of the four parasitic species appear similar under light microscopy. As the *trophozoites* enlarge, species-specific characteristics become evident, pigment becomes visible, and the parasite assumes an irregular or ameboid shape[6]. The disease in humans is caused by the direct effects of RBC invasion and destruction by the asexual parasite and the host's reaction. After a series of asexual cycles (*P. falciparum*) or immediately after release from the liver (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesei*), some of the parasites

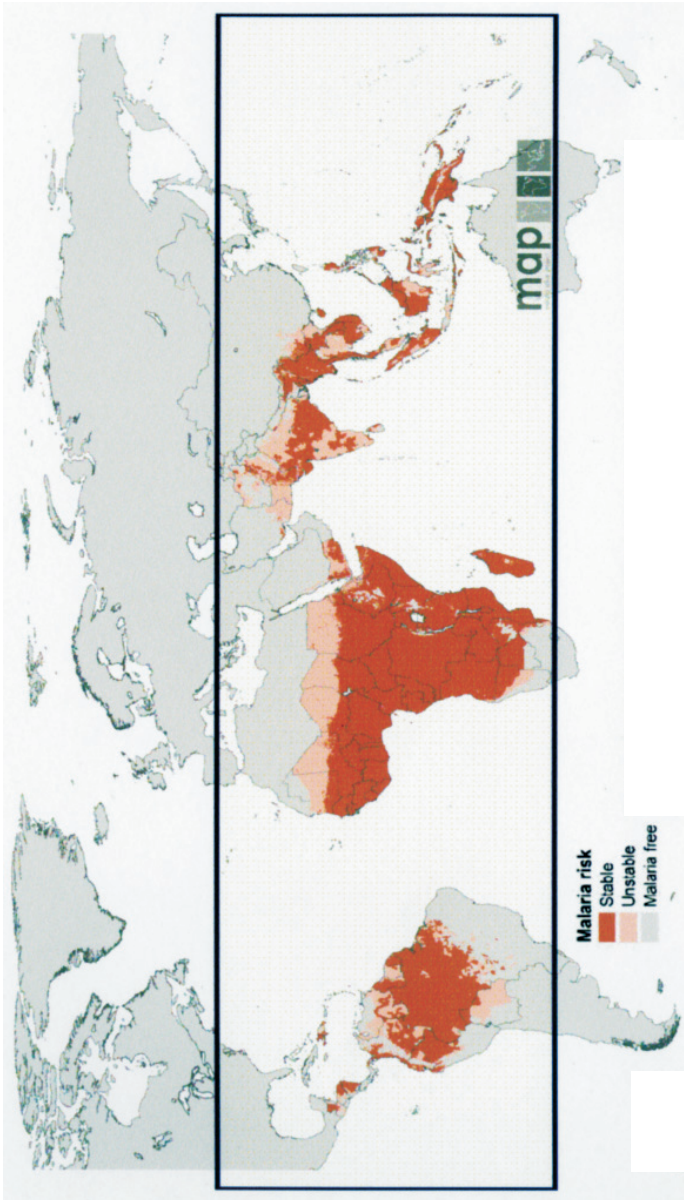



***Fig. 2.*** *Malaria: epidemiology, 2008. Data from refs 43–45.* © Licensed to the Malaria Atlas Project. (MAP: www.map.ox.ac.uk) under a creative commons. Attribution 3.0 license (http//creative common. org).

develop into morphologically distinct, longer-lived sexual forms (male and female *gametocytes*). These are ingested by the female mosquito during feeding; maturation of the parasite occurs within the mosquito gut during pregnancy and sporozoites migrate to the anopheles' salivary glands (Figure 1).

## Epidemiology

While the malaria map has shrunk since the 1950s, the disease remains endemic throughout most of the tropical regions of the world (Figure 2)[7]. *P. falciparum* predominates in Africa, New Guinea, and Haiti (Hispaniola and the Dominican Republic); *P. vivax* is more common in Central America. The prevalence of these two species is approximately equal in South America, the Indian subcontinent, eastern Asia, and Oceania. Over one billion attacks of malaria occur yearly, about evenly divided between *P. falciparum* and *P. vivax* (Table 2)[7,8,9,10]. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common. *P. ovale* is relatively unusual outside of Africa and, where it is found, comprises $<1\%$ of isolates. *P. knowlesei*, similar morphologically to *P. malariae*, has been identified recently in patients in Malaysia, the Philippines, Thailand, and Myanmar by molecular methods[11]. Proof of transmission from human-to-human via mosquito is still awaited.

The epidemiology of malaria may vary considerably even within relatively small geographic areas. Endemicity traditionally has been defined in terms of parasitemia rates or palpable-spleen rates in children 2 to 9 years of age as hypoendemic ($<10\%$), mesoendemic (11 to 50%), hyperendemic (51 to 75%), and holoendemic ($>75\%$). In holo- and hyperendemic areas – *e.g.*, certain regions of tropical Africa or coastal New Guinea where there is intense *P. falciparum* transmission, people may receive more than one infectious mosquito bite per day, and are infected repeatedly throughout their lives. In such settings with intense perennial transmission morbidity and mortality due to malaria are considerable during early childhood.

The entomologic inoculation rate – number of infectious (sporozoite carrying) female anopheline bites per year (EIR) – is a term used to indicate transmission intensity. While there are seasonal and geographic differences, an EIR of $<10$/year is low transmission, $10-49$/year intermediate transmission, and $\geq 50$/year is high transmission. Recent studies have shown that risk measured by EIRs is related to transmission, seasonal length, climate suitability, altitude, population density, and other factors[12]. In general, the higher the EIR the greater the burden of malaria, particularly on young children[13].

Constant, frequent, year-round infection is termed *stable transmission*, generally in areas with EIRs of $>100$/yearly; in such areas, by adulthood most malarial infections are asymptomatic. In

***Table 2*** *Global malaria burden, 2005*

| Region | *Plasmodium falciparum*, 2005 | | | | *P. vivax*, 2004 | | | *P. falciparum* and *P. vivax* |
|---|---|---|---|---|---|---|---|---|
| | Population at risk (millions) | Cases (million) (%) | | | Population at risk (millions) | Cases (millions) (%) | | Cases (millions) |
| Africa | 521 | 365 | (215–374) | (57%) | 50 | <1 | | 215–374 |
| Southeast Africa | 1,314 | 119 | (66–224) | (34%) | 1,347 | 90–248 | (63%) | 156–472 |
| Western Pacific | 142 | 15 | (9–26) | (4%) | 890 | 20–77 | (20%) | 29–103 |
| Eastern Mediterranean | 176 | 12 | (5–25) | (4%) | 211 | 11–34 | (9%) | 16–59 |
| Americas | 55 | 4 | (2–8) | (1%) | 78 | 10–28 | (7%) | 12–36 |
| Europe | 4 | 1 | (0–1) | (<1%) | 20 | 1–4 | (1%) | 1–5 |
| Total | 2,212 | 516 | (297–658) | (100%) | 2,596 | (132–391 | (100%) | 429–1,049 |

Data from ref. 9. (range; % based on highest estimate)

Data from ref 10.
Data from ref. 8.

areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. Malaria behaves like an epidemic disease in some areas, particularly those with seasonal - unstable malaria, such as northern India (Rajasthan), Sri Lanka, Afghanistan, Iraq, Turkey, Ethiopia, Eritrea, Burundi, southern Africa (Zimbabwe, Botswana, Mozambique, Swaziland, South Africa), Madagascar, and south-eastern Europe (Azerbaijan, Georgia, Tajikistan). An epidemic can develop when there are changes in environmental, economic, or social conditions, such as heavy rains following drought or migrations (usually of refugees or workers) from a non-malarious region to an area of high transmission; a breakdown in malaria control and prevention services can intensify epidemic conditions. This situation usually results in considerable morbidity and mortality among all age groups[14].

The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity of the anopheline mosquito vectors. More specifically, the transmission of malaria is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the tenth power of the probability of the mosquito's surviving for 1 day[3,15]. Mosquito longevity is particularly important, because the portion of the parasite's life cycle that takes place within the mosquito (sporogony)–from gametocyte ingestion to subsequent inoculation–lasts for 8 to 30 days, depending on ambient temperature; thus, to transmit malaria, the mosquito must survive for $>7$ days. The most effective mosquito vectors of malaria are those such as *A. gambiae* in Africa, which are long-lived, occur in high densities in tropical climates, breed readily, rest within dwellings, and bite humans in preference to other animals.

The basic reproduction rate ($R_o$) – the number of infections that one person can transmit to others varies greatly in malaria; $R_o$ is dependent greatly on the length of gametocytemia in infected persons, population densities, as well as geographic distribution of the vector and parasites, mosquito lifespan, biting habits, and other ecological factors. The range of $R_o$ has been estimated recently to be wide, from one to $>3{,}000$[16].

## Manifestations

Malaria is a very common cause of fever in tropical countries, but the diagnosis can be enigmatic in non-endemic areas. The first symptoms of malaria are nonspecific; the lack of a sense of well-

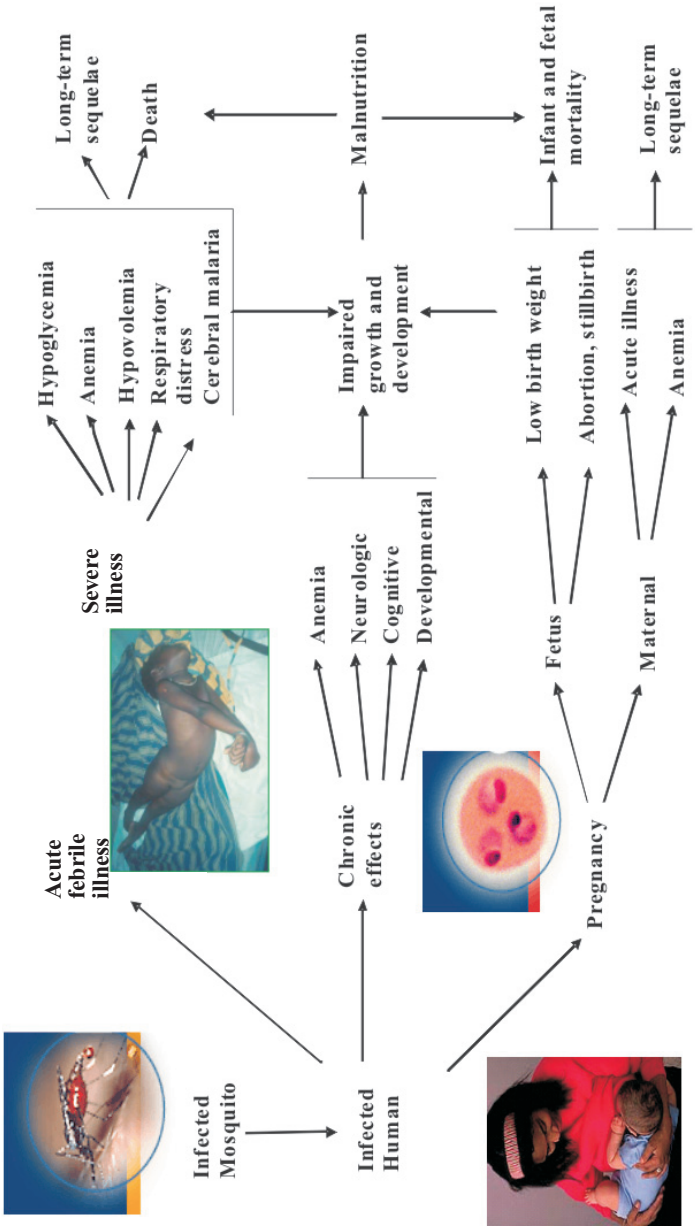



***Fig. 3.*** *Manifestations of the malaria burden. Data from ref. 17.*

being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia, or diarrhea may suggest

another diagnosis. Although headache may be severe in malaria, there is no neck stiffness or photophobia resembling that in meningitis. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection with *P. vivax* or *P. ovale*. The fever is irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40°C in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of cerebral disease. Most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anemia, and (in some cases) a palpable spleen. Anemia is very common among young children living in areas with stable transmission, particularly where drug resistance has compromised antimalarial efficacy. In nonimmune individuals with acute malaria the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise-healthy individuals in malaria-endemic areas and reflects repeated infections. Mild jaundice is common among adults; it may develop in patients with otherwise-uncomplicated falciparum malaria and usually resolves over 1 to 3 weeks. Malaria is not associated with a rash like those seen in meningococcal septicemia, typhus, enteric fever, viral exanthems, and drug reactions. Petechial hemorrhages in the skin or mucous membranes – features of viral hemorrhagic fevers and leptospirosis – develop only rarely in severe falciparum malaria.

## Severe falciparum malaria

Appropriately and promptly treated, uncomplicated falciparum malaria carries a mortality rate of $\sim 0.1\%$. However, once vital-organ dysfunction occurs or the total proportion of erythrocytes infected increases to $> 2\%$ (which corresponds to more than $10^{12}$ parasites in an adult), mortality rises steeply. The major manifestations of severe falciparum malaria, particularly in vulnerable African children, are shown in Figure 3[17]; the clinical features indicating a poor prognosis are listed in Table 3[5].

***Table 3*** *Features indicating a poor prognosis in severe falciparum malaria*

| |
|---|
| Clinical |
| Marked agitation |
| Hyperventilation (respiratory distress) |
| Hypothermia ($<36.5°C$) |
| Bleeding |
| Deep coma |
| Repeated convulsions |
| Anuria |
| Shock |
| Laboratory |
| Biochemistry |
| Hypoglycemia ($<2.2$ mmol/l) |
| Hyperlactatemia ($>5$ mmol/l) |
| Acidosis (arterial pH $<7.3$, serum $HCO_3$ $<15$ mmol/l) |
| Elevated serum creatinine ($>265$ μmol/l) |
| Elevated total bilirubin $>50$ μmol/l) |
| Elevated liver enzymes (sGOT (AST) and sGPT (ALT) $\times 3$ upper limit of normal, 5-nucleotidase ↑) |
| Elevated muscle enzymes (CPK ↑, myoglobin ↑) |
| Elevated urate ($>600$ μmol/l) |
| Hematology |
| Leucocytosis ($>12{,}000/\mu l$) |
| Severe anemia (PCV $<15\%$) |
| Coagulopathy |
| Decreased platelet count ($<50{,}000/\mu l$) |
| Prolonged prothrombin time ($>3$ s) |
| Prolonged partial thromboplastin time |
| Decreased fibrinogen: ($<200$ mg/dl) |
| Parasitology |
| Hyperparasitemia |
| Increased mortality at $>100{,}000/\mu l$ |
| High mortality at $500{,}000/\mu l$ |
| $>20\%$ of parasites identified as pigment-containing trophozoites and schizonts |
| $>5\%$ of neutrophils contain visible pigment |

Data from ref. 6.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; PCV, packed cell volume.

## *Cerebral malaria*

Coma is a characteristic and ominous feature of falciparum malaria and, despite treatment, is associated with death rates of $\sim 20\%$ among adults and 15% among children[18]. Any obtundation, delirium, or abnormal behavior should be taken very seriously. The onset may be gradual or sudden following a convulsion.

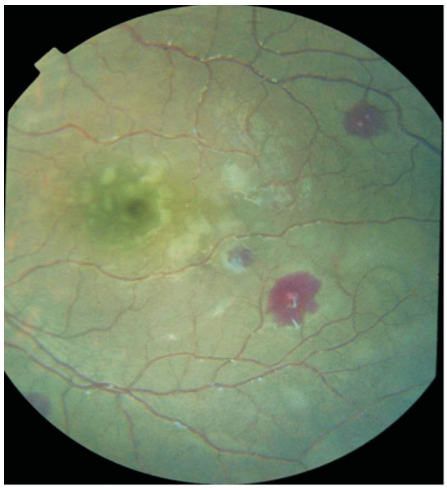


***Fig. 4.*** *Funduscopic findings in cerebral malaria. Data from ref. 5.*

Cerebral malaria manifests as diffuse symmetric encephalopathy; focal neurologic signs are unusual. Approximately 15% of patients have retinal hemorrhages; with pupillary dilatation and indirect ophthalmoscopy, this Figure increases to 30 to 40%. Other funduscopic abnormalities include discrete spots of retinal opacification (30 to 60%), papilledema (8% among children, rare among adults), cotton wool spots ($<5\%$), and decolorization of a retinal vessel or segment of vessel (occasional) (Figure 4)[19,20]. Convulsions, usually generalized and often repeated, occur in up to 50% of children with cerebral malaria. Whereas adults rarely (*i.e.*, in $<3\%$ of cases) suffer neurologic sequelae, $\sim 15\%$ of children surviving cerebral malaria – especially those with hypoglycemia, severe anemia, repeated seizures, and deep coma – have some residual neurologic deficit when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition and learning – all of varying duration – have been reported. Approximately 10% of children surviving cerebral malaria have persistent language deficit. There is also an increased incidence of epilepsy[21,22].

## *Hypoglycemia*

An important and common complication of severe malaria, hypoglycemia, is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both host and – to a much

lesser extent – the malaria parasites. To compound the situation, quinine and quinidine – drugs used for the treatment of severe chloroquine-resistant malaria – are powerful stimulants of pancreatic insulin secretion. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. The usual physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria.

### *Acidosis*

Acidosis is an important cause of death from severe malaria. Hyperlactatemia commonly coexists with hypoglycemia. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, hypovolemia, lactate production by the parasites, and a failure of hepatic and renal lactate clearance. The prognosis of severe acidosis is poor.

### *Noncardiogenic pulmonary edema*

Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. The pathogenesis of this variant of the adult respiratory distress syndrome is unclear. The mortality rate is $>80\%$. This condition can be aggravated by overly vigorous administration of intravenous fluid. Noncardiogenic pulmonary edema can also develop in otherwise-uncomplicated vivax malaria, where recovery is usual.

### *Renal impairment*

Renal impairment is common among adults with severe falciparum malaria but rare among children. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis, although renal cortical necrosis never develops.

### *Hematologic abnormalities*

In severe malaria, both infected and uninfected RBCs show reduced deformability, which correlates with prognosis and development of anemia. Splenic clearance of all RBCs is increased. In nonimmune

individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. As a consequence of repeated malarial infections, children in many areas of Africa may develop severe anemia resulting from both shortened RBC survival and marked dyserythropoiesis. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual. Less than 5% of patients with severe malaria have significant bleeding with evidence of disseminated intravascularcoagulation. Recent findings show that there are several erythrocyte and variant hemoglobin mutations (hemoglobin F, E, and C, sickle cell, the thalassemias, hereditary ovalocytosis, glucose 6 phosphatase deficiency) that are linked to malaria; they have an important role in susceptibility to infection and protect against severe malaria by a common mechanism that inhibits cytoadherence of parasitized RBCs to microvascular endothelium[23].

### *Liver dysfunction*

Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections, is more common among adults than among children, and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis.

## Other complications

Septicemia may complicate severe malaria, particularly in children. In endemic areas, Salmonella bacteremia has been associated specifically with *P. falciparum* infections[24,25]. Chest infections and catheter-induced urinary tract infections are common among patients who are unconscious for $>3$ days. Aspiration pneumonia may follow generalized convulsions.

### *Malaria in pregnancy*

In hyper- and holoendemic areas, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, $\sim 170$ g) and consequently increased infant and childhood mortality. In general, infected mothers in areas of stable

transmission remain asymptomatic despite intense accumulation of parasitized erythrocytes in the placental microcirculation[26]. Recent studies have shown the importance of interactions between *P. falciparum* variable surface antigen (VSA) and chondroitin sulfate A as a placental receptor site for sequestration of infected erythrocytes and subsequent pathology leading to low birth weight[27]. Maternal HIV infection predisposes pregnant women to malaria and their newborns to congenital malaria infection and exacerbates the reduction in birth weight associated with malaria.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections, and vulnerable to high-level parasitemia with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 110 g), but, in contrast to the situation in falciparum malaria, this effect is more pronounced in multigravid than in primigravid women[26].

### *Malaria in children*

Up to 90% of the estimated 1 to 2 million persons who die of falciparum malaria each year are young African children[4]. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, acute renal failure, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past has been attributed incorrectly to ''anemic congestive cardiac failure'' but is usually caused by metabolic acidosis, often compounded by hypovolemia. Evidence is accruing that severe malaria can result in long term neurocognitive and developmental deficits[21,22].

## Definitions: control, elimination and eradication

Control is reduction of malaria (or other diseases) to a level that is no longer a public health problem or that is acceptable to the community. Elimination is reduction of disease transmission in humans to zero in a defined geographic area. Eradication is global elimination of human disease. Countries and areas achieving elimination will have importations of cases from endemic areas; imported cases require prompt detection and containment to prevent reestablishment of endemicity. For countries achieving disease elimination and eradication, a sensitive surveillance system that

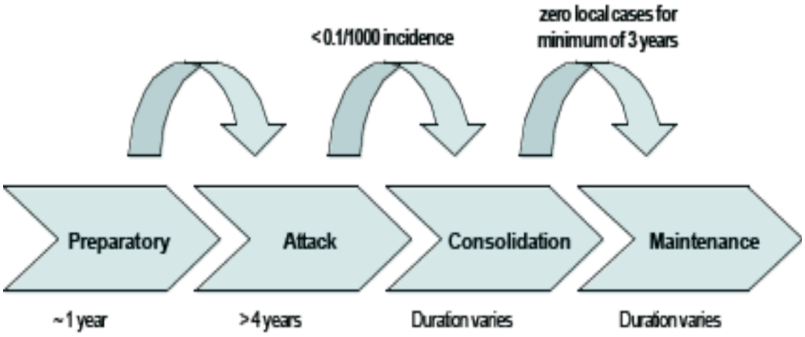



***Fig. 5A.*** *Phases of maleria eradication. Data from World Health Organization, 2008.*

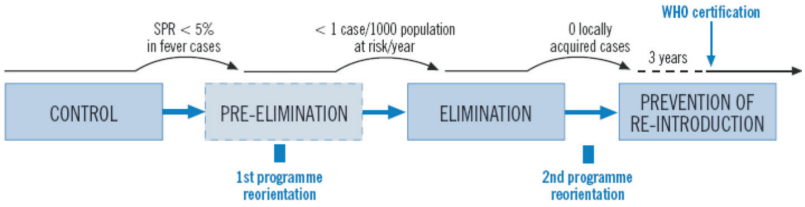



***Fig. 5B.*** *Steps from malaria control to elimination. SPR, slide or rapid diagnostic test positivity rate. Data from World Malaria Report, 2008*

could detect and respond to cases if they existed is required: likewise, surveillance is the key to disease control[28].

A scheme showing the various phases of malaria eradication is shown in Figure 5A and 5B[1,3]. WHO has based the movement from the attack to consolidation to maintenance phases on incidence of parasitemia in the population at risk[3]. The preparation and other phases depend on firm national commitment, adequate human and material resources, training and sustained international support and cooperation.

## *Malaria research and elimination initiatives*

Much progress has been made in research and control of malaria since 1997 when the Multilateral Initiative on Malaria (MIM) began as an international alliance of organizations and individuals concerned about the state of malaria research. This coalition has been responsible for developing scientific expertise and strengthening institutions in over two dozen African countries[29,30]. In 1998, Roll Back Malaria (RBM) began at the World Health Organization: this initiative has divided into the Roll Back

***Table 4*** *Malaria control goals, strategies and targets. Goal: halve the burden by 2010 (roll back malaria partnership)*

| Strategy | Targets for 2010 (Abuja Malaria Summit, 2000, revised 2007) |
|---|---|
| • Prompt access to effective treatment | • 80% of patients having access to and using correct and affordable treatment within 24 hours of symptom onset |
| • Provision of insecticide treated nets (ITNs) | • 80% of children $<5$ years and pregnant women benefiting from personal and community protection, such as ITNs |
| • Prevention and control of malaria in pregnant women | • 80% of pregnant women at risk accessing intermittent preventive treatment[a] |
| • Epidemic and emergency response | • 60% of epidemics detected within two weeks of onset |
| | • 60% of epidemics responded to within two weeks of detection |

Data from ref. 28.

Malaria Partnership (www.rollbackmalaria.org), a high-profile advocacy and consensus building coalition, and the Global Malaria Program, directed toward strengthening national programs by establishing business plans, updating treatment and prevention guidelines, and developing training materials. In 2000, the Abuja (Nigeria) Summit on Malaria was held at which African heads of state established control objectives by 2010 focusing on access to and delivery of services: these were further refined by RBM and, as part of the Millennium Development Goals (Table 4)[31]. Many organizations and countries quantify ''control'' as reduction of malaria morbidity and mortality by 50% by 2010 and by 75% by 2015, in accordance with the Abuja Declaration, WHO, and the Millennium Development Goals[3,31,32]. In October 2007, in a dramatic moment, Bill and Melinda Gates committed their Foundation to malaria eradication at which time Margaret Chan, Director General of WHO, supported this goal. Although a long term (2050) timeline is now being mentioned (and is reasonable), this declaration has energized greatly the malaria control and research communities.

## *Strategies and tactics*

Malaria, its control, and ultimate eradication depend on relationships of human, parasite, and mosquito (intrinsic factors) and the environment, socio-economic milieu, and control initiatives (extri-

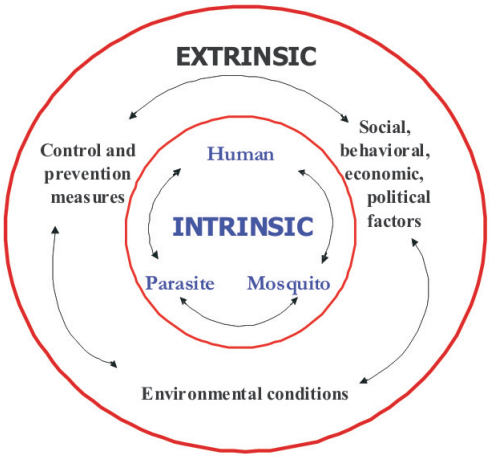



***Fig. 6.*** *Intrinsic and extrinsic factors linked to the malaria burden. Data from ref. 33.*

nisic factors) (Figure 6)[33]. The strategies used in malaria control and elimination rely on antimalarial drugs, personal protection, vector control, and research[3]. The drug use strategy with artemisinin-based combination treatments (ACTs) or other drugs includes: management of acutely ill patients and intermittent preventive treatment (IPT) of persons at high risk – currently pregnant women (with sulfadoxine-pyrimethamine) but infants and children are being considered for IPT (Table 5)[34]; personal protection involves use by individuals, families and communities of long-lasting insecticide (with synthetic pyrethroids) treated bed nets (LLINs), repellents, or other materials within dwellings; classical vector control methods include insecticide residual spraying (IRS) of households with DDT or other compounds, larviciding of mosquito breeding sites, drainage and filling of water collection areas and environmental improvements to prevent mosquito multiplication (Table 6)[35]. More attention to urban malaria will be required as such centers increase even more in the near future. Antimalaria interventions are among the most cost-effective tools in medicine and public health (Table 7)[36]. Detection and response to malaria epidemics is another control strategy defined by WHO[14].

The research themes in support of malaria control and elimination follow the same strategies – newer and improved drugs, vaccines, diagnostics, vector control methods, modeling of malaria spread, monitoring and evaluation, surveillance, integration strategies, and

***Table 5*** *WHO recommended drugs for malaria treatment and control, 2009*

| Drugs | Primary indications |
|---|---|
| Artemether-lumefantrine<br>Artesunate + amodiaquine<br>Artesunate + mefloquine<br>Artesunate + sulfadoxine-pyrimethamine | ACTs recommended by the WHO for treatment of uncomplicated malaria |
| Dihydroartesinin-piperaquine<br>Artesunate + chlorproguanil-dapsone | ACTs currently under evaluation |
| Quinine<br>Artesunate, artemether | Recommended treatments for severe and complicated malaria |
| Chloroquine | Treatment for non-*falciparum* malaria |
| Sulfadoxine-pyrimethamine | IPT in pregnant women and children |
| Primaquine | Prevent relapses and/or radical cure with *P. vivax* |

ACTs = artemisinin-based combination treatments; IPT, intermittent preventive treatment; WHO, World Health Organization.

***Table 6*** *Insecticides recommended by the WHO for indoor residual spraying*

| Insecticide | Class | Recommended dosage of active ingredient ($g/m^2$) | Duration of effective action (months) |
|---|---|---|---|
| DDT | Organochlorine | 1–2 | >6 |
| Fenitrothion | Organophosphate | 2 | 3–6 |
| Malathion | Organophosphate | 2 | 2–3 |
| Pirimiphosmethyl | Organophosphate | 1–2 | 2–3 |
| Propoxur | Carbamate | 1–2 | 3–6 |
| Bendiocarb | Carbamate | 0.1–0.4 | 2–6 |
| Alpha-cypermethrin | Pyrethroid | 0.02–0.03 | 4–6 |
| Cyfluthrin | Pyrethroid | 0.02–0.05 | 3–6 |
| Deltamethrin | Pyrethroid | 0.02–0.025 | 3–6 |
| Etofenprox | Pyrethroid | 0.1–0.3 | 3–6 |
| Lambda-cyhalothrin | Pyrethroid | 0.02–0.03 | 3–6 |
| Bifenthrin | Pyrethroid | 0.025–0.05 | 3–6 |

Data from ref. 35.
DDT, dichlorodiphenyltrichloroethane; WHO, World Health Organization.

***Table 7*** *Malaria interventions are highly cost effective*

| Category | Sub-Saharan Africa | |
|---|---|---|
| | Cost per DALY averted ($) | Burden (in M of DALYs) |
| Childhood immunization | 1–5 | Not assessed |
| Malaria prevention | 2–24 | 35.4 |
| Surgical services & emergency care | 7–215 | 25.0–134.2 |
| Childhood illnesses | 9–218 | 9.6–45.1 |
| Cardiovascular disease | 9–273 | 4.6 |
| HIV/AIDS (prevention) | 6–377 | 56.8 |
| Maternal/neonatal care | 82–409 | 29.8–37.7 |
| HIV/AIDS (treatment) | 673–1,494 | 56.8 |
| Tuberculois (treatment) | 4,129–5,506 | 8.1 |

Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.
DALY, disability adjusted life year.

health systems/implementation research (Table 8)[3]. Development of malaria vaccines is one of the highest priorities in malaria research; much recent progress has been made with a preerythrocytic (RTS, S/AS01A) stage recombinant vaccine, which has shown up to 60% protection for 6 months in children; this vaccine is soon to go into a phase 3 trial in Africa[37,38,39]. It is essential that vaccines, drugs, and other new tools interrupt transmission. Development and an assessment of the safety and effectiveness of gametocytocidal drugs (*i.e.* 8-aminoquinolines and artemisinins) and transmission blocking vaccines must receive the highest priority if eradication is to be achieved; some of the experimental vaccines in the Gates supported Malaria Vaccine Initiative (MVI) pipeline are shown in Figure 7[40,41].

WHO has divided malarious countries into four groups: those that never had malaria or eliminated the disease; those that have recently qualified for certification of elimination or with conditions amenable to elimination (25 countries); countries with generally unstable malaria which are amenable to sustained control and ultimately, elimination with current tools (32 countries); and, countries with intense stable transmission and relatively poor health infrastructure (47 countries). The latter countries are in the ''scale up for impact'' category needing more time to reap the benefits of research to assure interruption of disease transmission (Table 9)[3]; Figure 8 shows countries in various phases of control or elimination[1].

***Table 8*** *Research themes and tools required in support of malaria control and elimination*

1. Improved mosquito control
   - New classes of rapid, long-acting insecticides which do not induce excito-repellancy, for indoor residual spraying and long-lasting insecticidal nets
   - Longer-lasting insecticidal nets
   - Strategies to delay the onset of insecticide resistance, such as
     - mosaic treatment or combination treatment of long-lasting insecticidal nets and for indoor residual spraying
     - combination of tools, for example long-lasting insecticidal nets and indoor residual spraying combined with other approaches such as larviciding
   - Insecticide-treated material for use by forest workers and dwellers, such as for hammocks, clothes and blankets
   - New tools for the control of mosquito vector species that are not amenable to indoor residual spraying and long-lasting insecticidal nets; and
   - Transgenic vectors refractory to maturation of parasite or female *Anopheles*

2. Better treatment
   - New classes of antimalarial medicines with the following characteristics
     - provide $>95\%$ cure rates, with highly effective infectivity blocking efficacy ($>99\%$ gametocytocidal activity) for both *P. vivax* and *P. falciparum*
     - fixed-dose combinations with three medicines, each with a different mode of action and matched pharmacokinetic properties
     - single-dose treatment regimen
     - high safety profile, including children, infants and pregnant women
   - A new class of safe, effective antimalarials for radical treatment of *P.vivax*

3. Robust and sensitive diagnostic tools to enable detection of parasite carriers (latent infections, asymptomatic infections and hypnozoites)

4. Vaccines, especially those that block transmission and reduce infection rates

5. Improvements to existing delivery, use, and evaluation strategies are needed, especially:
   - Encouraging behavioral change so that people comply fully with medication and use long-lasting insecticidal nets correctly
   - Monitoring and evaluation, specifically
     - improved tools to assess entomological parameters
     - new tools to monitor malaria infections, as substitutes for serological surveys
     - methods to allow targeting of interventions to high-risk areas and groups

6. Improved surveillance methods
   - Clinical and epidemiological definitions of malaria and endemicity
   - Assessment of contribution of multiple pathologies in patients and malaria attributable fractions to overall burden
   - Use of modern electronic reporting systems with feedback

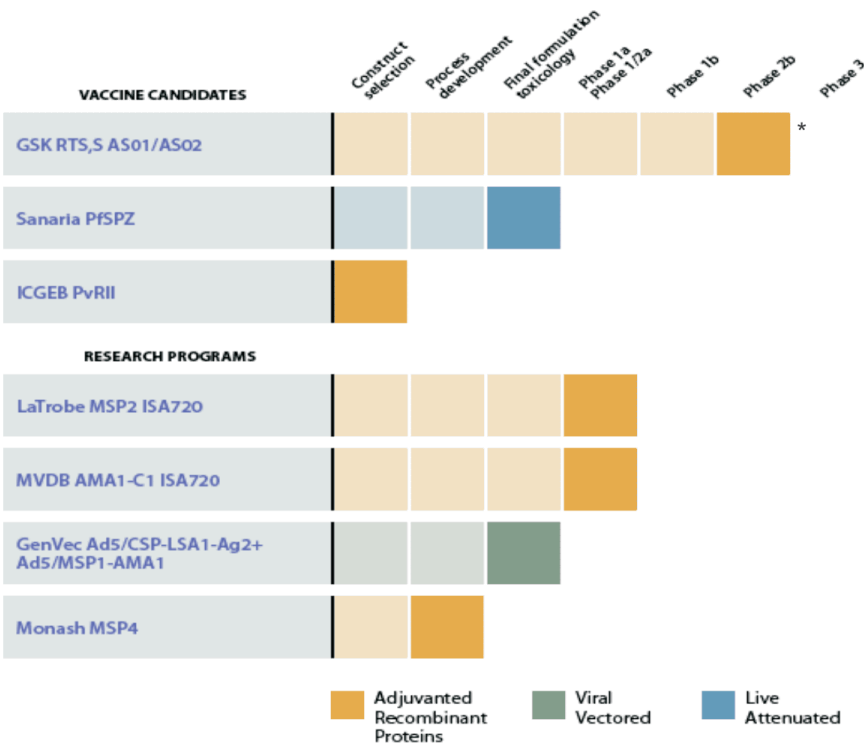



***Fig. 7.*** *Current malaria vaccines in PATH Malaria Vaccine Initiative (MVI) pipeline. PATH Malaria Vaccine Initiative, 2009, http://www.malariavaccine.org/rd-portfolio.php *Soon to advance to Phase 3.*

## *Supporting organizations*

Major organizations that have had influence on control and elimination of malaria over the past decade have been the Global Fund for HIV/AIDS, Tuberculosis, and Malaria (GFATM), the U.S. President's Malaria Initiative (PMI), the Malaria Control Booster Program at the World Bank, and the new Malaria Elimination Group (MEG), the latter focusing on ''shrinking the malaria map'' by working with a few countries having unstable, low-transmission infection, good control programs, health infrastructure, political stability and political will. Since the GFATM began in 2002, over 70 million nets have been distributed, 74 million drug treatments given and over $3 billion devoted to malaria of which $1.568 billion was granted to 28 countries in November 2008.

***Table 9*** *WHO categorization of malarious countries*

| Scale-Up for Impact (SUFI) | Sustained control | Elimination |
|---|---|---|
| SSA<br>Angola, Benin, Burkina Faso, Burundi, Cameroon, CAR, Chad, Comoros, Congo, Cote d'Ivoire, Djibouti, DRC, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe | SSA<br>Botswana, Cape Verde, South Africa, Swaziland | SSA<br>Mauritius |
| SEA<br>Bangladesh, India, Indonesia, Myanmar | SEA<br>Bhutan, Negal, Thailand, Timor-Leste | SEA<br>Korea DPR, Sri Lanka |
| Other regions<br>Haiti, Papua New Guinea | Other regions<br>Afghanistan, Belize, Bolivia, Brazil, Cambodia, China, Colombia, Costa Rica, Dominican Republic, Ecuador, French Guiana, Guatemala, Guyana, Honduras, Laos, Paraguay, Peru, Phillippines, Solomon Islands, Suriname, Vanuatu, Venezuela, Vietnam, Yemen | Other regions<br>Algeria, Argentina, Armenia, Azerbaijan, Egypt, El Salvador, Georgia, Iran, Iraq, Krygyz Republic, Malaysia, Mexico, Morocco, Oman, Republic of Korea, Russian Federation, Saudi Arabia, Syrian Arab Republic, Tajikistan, Turkey, Turkmenistan, Uzbekistan |

Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.
SSA, Sub-Saharan Africa; SEA, South East Asia; CAR, Central African Republic; DRC, Democratic Republic of the Congo; DPR, Korea Democratic People's Republic.

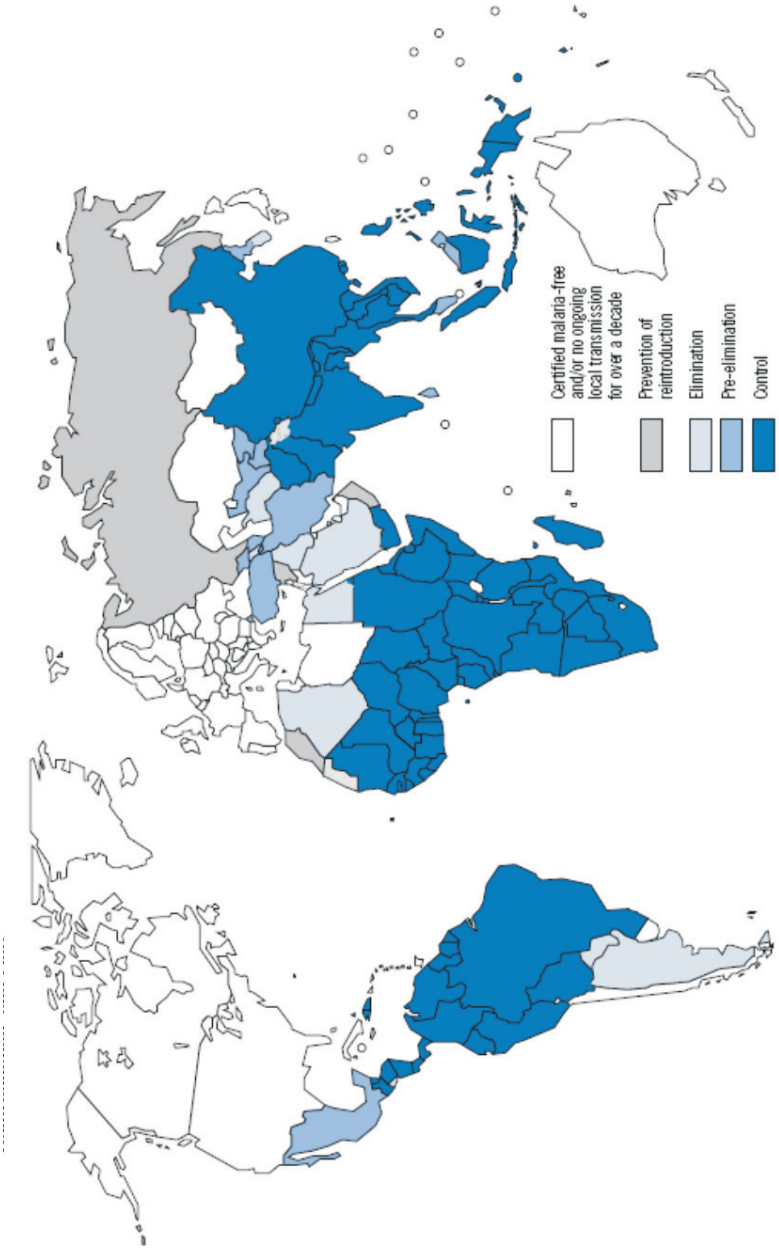



***Fig. 8.*** *Malaria-free countries and malaria-endemic countries in phases of control, pre-elimination, elimination and prevention of reintroduction, end 2007. China, Indonesia, Philippines, Solomon Islands, Sudan, Vanuatu and Yemen have subnational elimination programs. Data from the World Malaria Report, 2008.*

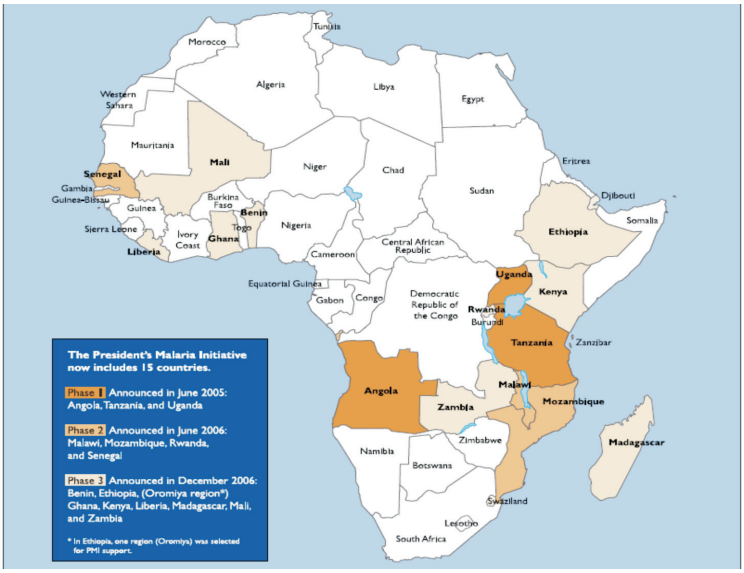



***Fig. 9.*** *Map of Africa showing countries supported by PMI in years 1, 2, and 3. Data from the President's Malaria Initiative Report, March 2008.*

***Table 10*** *US funding for malaria activities, 2007–2008*

| | 2007 (million $U.S.) | 2008 (million $U.S.) |
|---|---|---|
| Foundations | 214.4 (Gates 194.2) | 230.9 (Gates 210.8) |
| Corporate | 9.5 (ExxonMobil 9.0) | 10.4 (ExxonMobil 10.0) |
| USAID bilateral | 248.0 (PMI, 172) | 350.0 (PMI 300) |
| CDC | 9.0 | 9.0 |
| DoD | 24.6 | 23.1 |
| NIH | 90.2 | 90.2[a] |
| USG to GFATM | 181.0 | 212.5 |
| Total | 776.7 | 926.1 |

Data from the Global Health Council, 2008.
[a]Provisional.
USAID, United States Agency for International Development; CDC, Centers for Disease Control and Prevention; DoD, Department of Defense; NIH, National Institutes of Health; USG, United States Government; GFATM, Global Fund to fight AIDS, Tuberculosis, and Malaria.

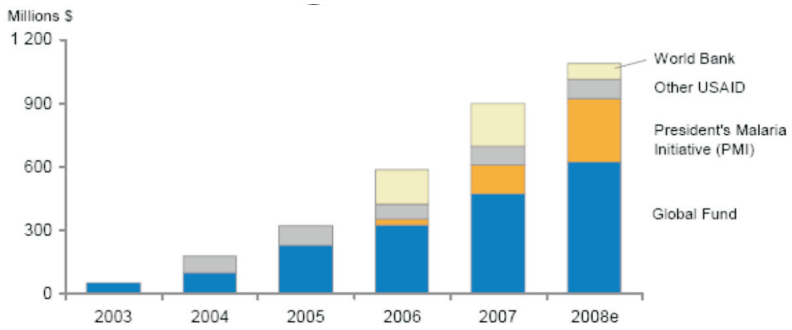



***Fig. 10.*** *Health development assistance funding for malaria. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

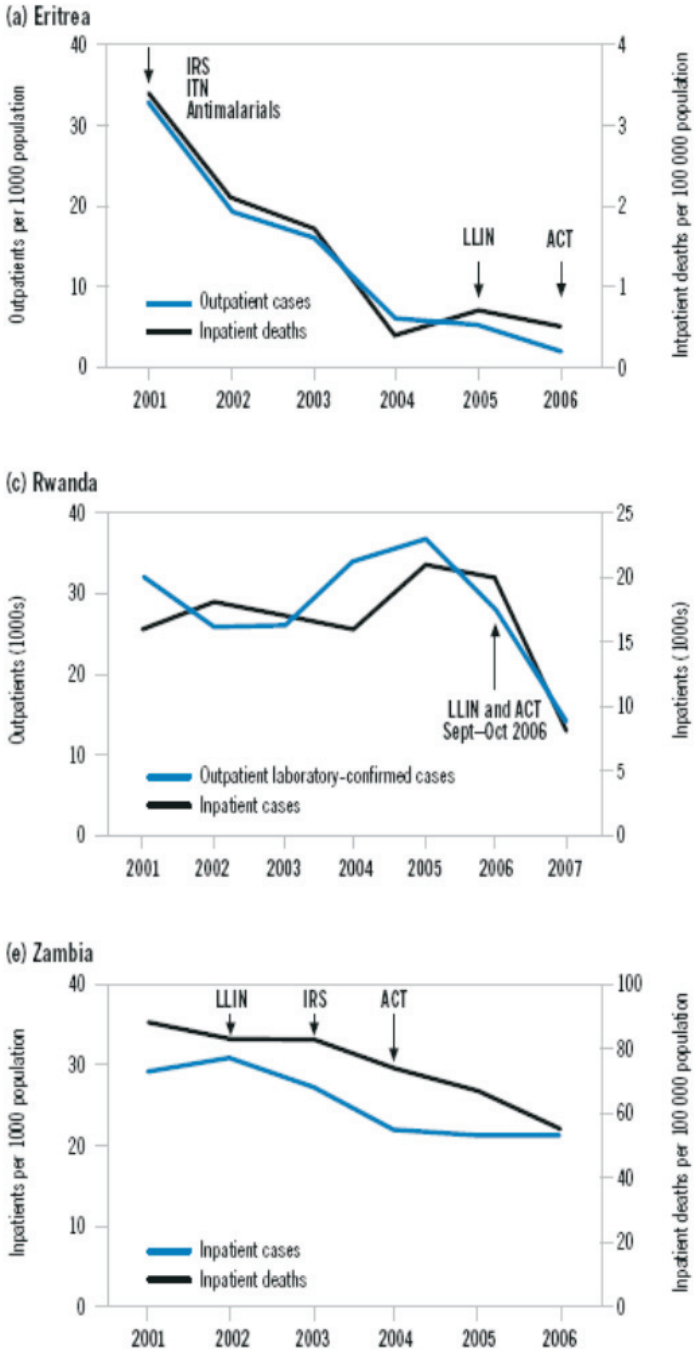
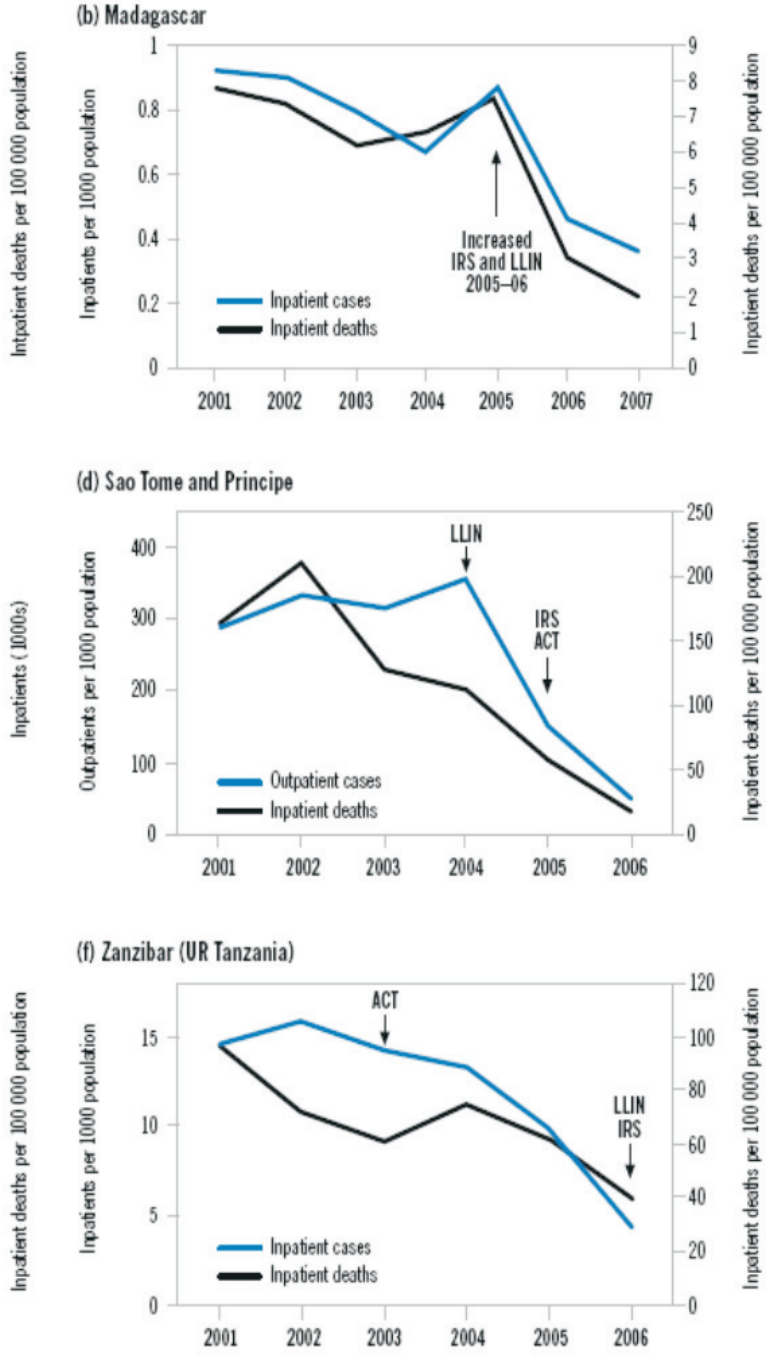



***Fig. 11.*** *Trends in malaria cases (inpatients and outpatients) and deaths (inpatients) in relation to interventions, six African countries, 2001–2006 (National Malaria Control Program data). Data from the World Malaria Report, 2008.*


(b) Madagascar
Inpatient deaths per 100 000 population
Inpatients per 1000 population
Inpatient deaths per 100 000 population
Increased IRS and LLIN 2005–06
Inpatient cases
Inpatient deaths
(d) Sao Tome and Principe
Inpatients ( 1000s)
Outpatients per 1000 population
Inpatient deaths per 100 000 population
LLIN
IRS ACT
Outpatient cases
Inpatient deaths
(f) Zanzibar (UR Tanzania)
Inpatient deaths per 100 000 population
Inpatients per 1000 population
Inpatient deaths per 100 000 population
ACT
LLIN IRS
Inpatient cases
Inpatient deaths

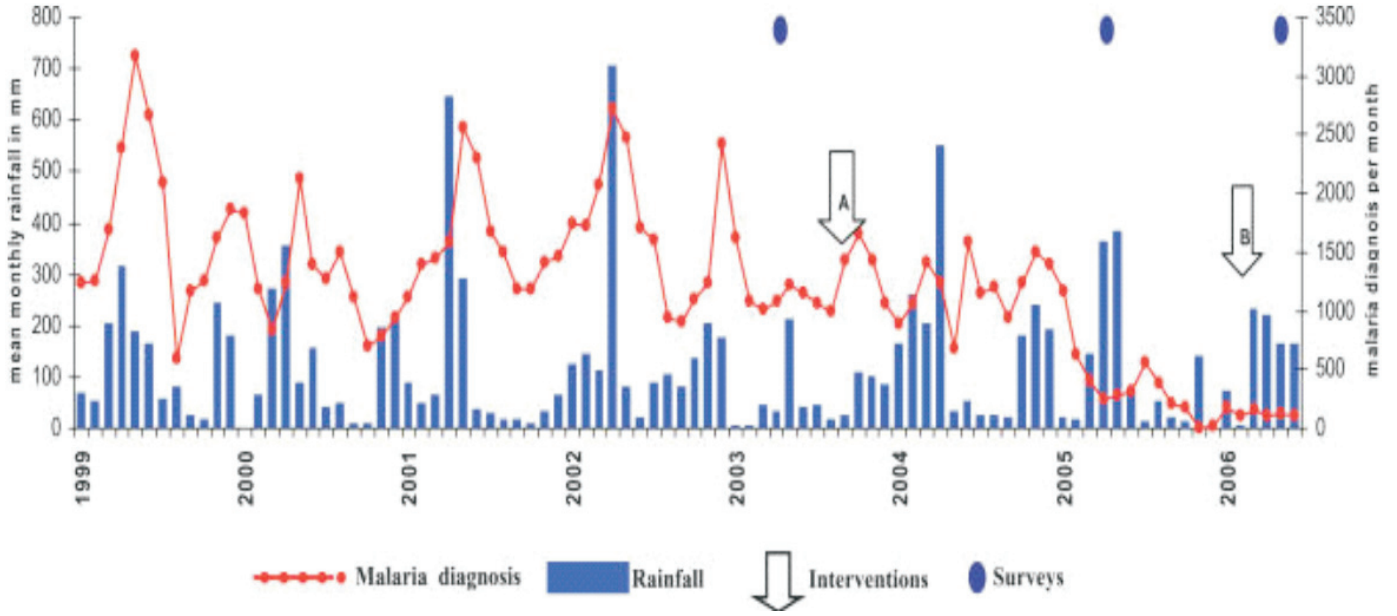



***Fig. 12.*** *Effect of artemisinin-based combination treatments (ACTs) and long lastinginsecticide-treated nets (LLINs) on transmission in Zanzibar 1999–2006. Malaria interventions, monthly rainfall, and reported clinical malaria diagnoses in children under 5 years of age in North A district, Zanzibar. (A) Start of ACTs for uncomplicated malaria, September 2003; (B) Introduction of LLINs, February 2006. Data from ref. 46.*

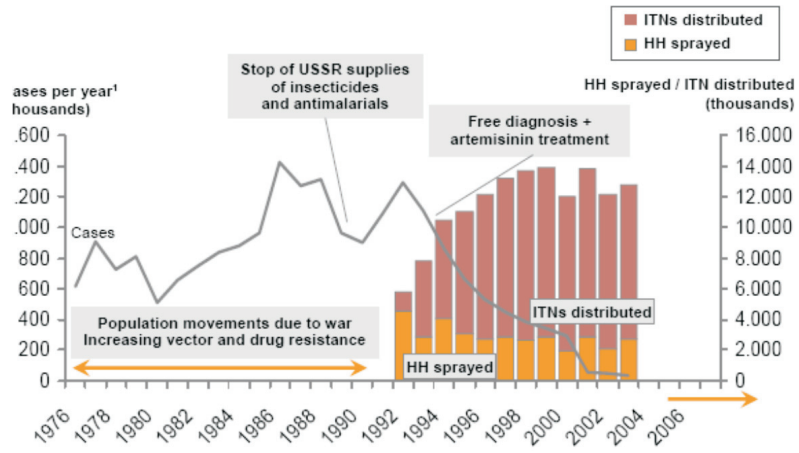



***Fig. 13.*** *Malaria control in Vietnam. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

Since 2005, the PMI has committed $1.25 billion to malaria activities in 15 African countries: the geographic coverage of the PMI program is shown in Figure 9. The Bill & Melinda Gates Foundation contributes about $200 million annually to malaria research and control activities, and many other U.S. organizations have provided funding for control and research (Table 10). Overall funding for malaria operations through development assistance is growing as shown in Figure 10.

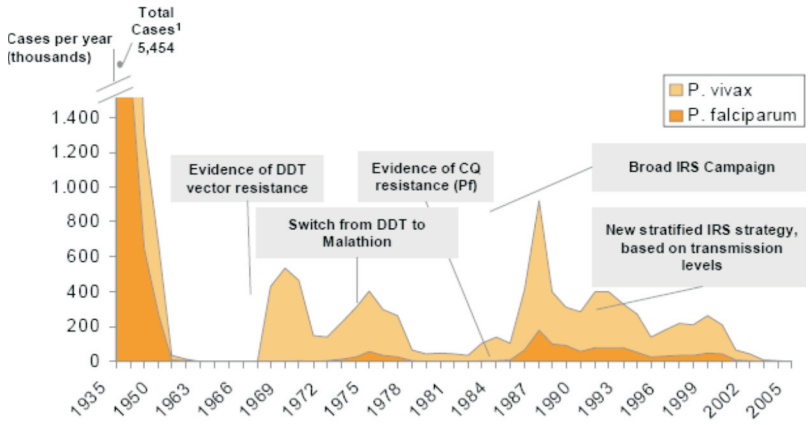



***Fig. 14.*** *Malaria Cases in Sri Lanka, 1935–2005. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

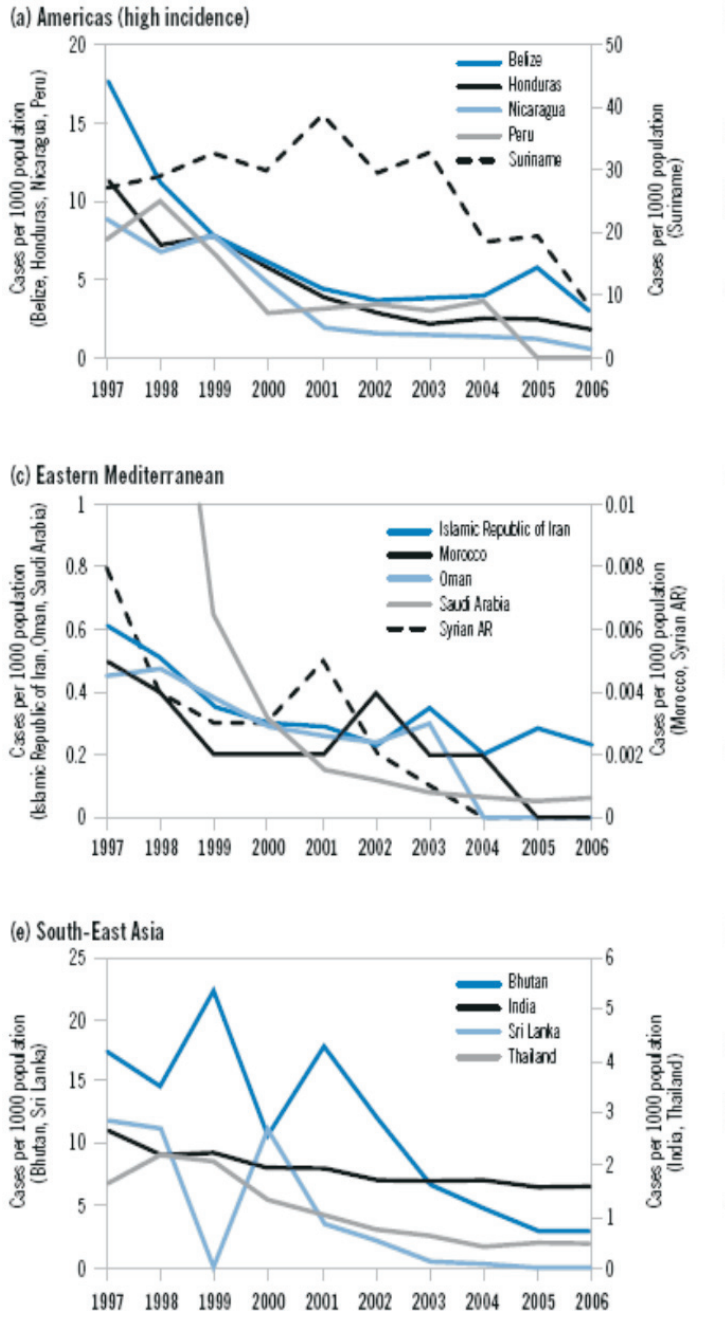
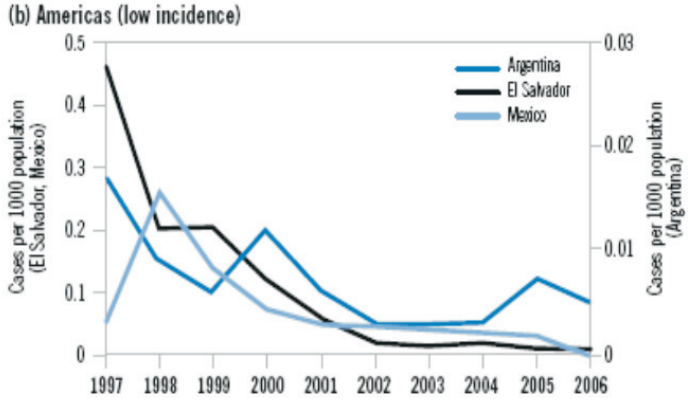
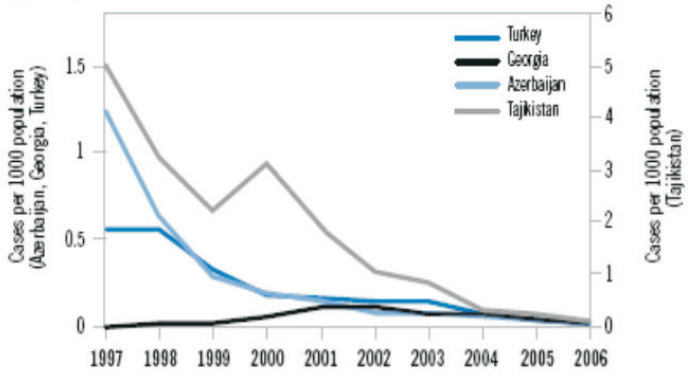
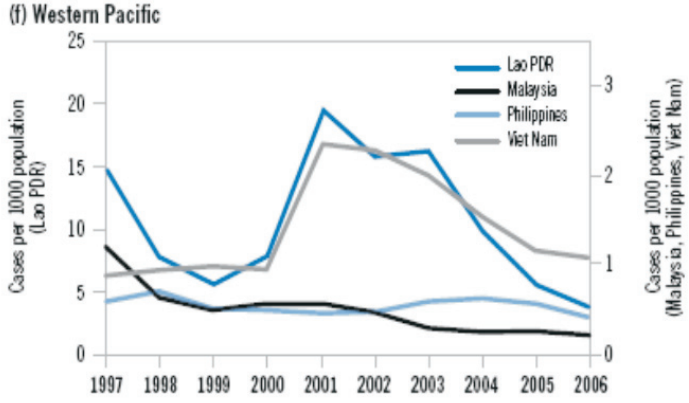



***Fig. 15.*** *Trends in reported malaria cases in selected countries, by WHO Region, 1997–2006. Data from World Malaria Report, 2008.*


(b) Americas (low incidence)
Argentina
El Salvador
Mexico
Cases per 1000 population (El Salvador, Mexico)
Cases per 1000 population (Argentina)
0.5
0.4
0.3
0.2
0.1
0
0.03
0.02
0.01
0
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006


(d) Europe
Turkey
Georgia
Azerbaijan
Tajikistan
Cases per 1000 population (Azerbaijan, Georgia, Turkey)
Cases per 1000 population (Tajikistan)
1.5
1
0.5
0
6
5
4
3
2
1
0
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006


(f) Western Pacific
Lao PDR
Malaysia
Philippines
Viet Nam
Cases per 1000 population (Lao PDR)
Cases per 1000 population (Malaysia, Philippines, Viet Nam)
25
20
15
10
5
0
3
2
1
0
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006

## Results

There have been remarkable decreases in incidence of malaria cases, deaths, and hospital admissions in several countries over the past several years[1,3]. Particularly impressive have been the decreases in southern Africa; the use of DDT following a major epidemic complemented by addition of ACTs for treatment resulted in a major decrease in cases – from 77% in 2003 to 52% in 2007. Dramatic decreases have also been documented in Rwanda, Eritrea, Malawi, Zambia, Zanzibar (part of Tanzania), Madagascar, and parts of Ethiopia; recent dramatic decreases in malaria cases and deaths in selected countries in Africa are shown in Figure 11. Decrease in malaria in one district in Zanzibar after initiation of ACTs and LLINs is shown in Figure 12 and provides an example of the impact of these tools. Vietnam and Sri Lanka show good success in recent malaria control in Asia (Figures 13 and 14). As always, sustainability is crucial when dealing with such a resilient infection. Disease surveillance requires particular attention[27]. Sri Lanka's epidemics in the late 1960s and late 1980s illustrate how malaria can resurge if control measures lapse (in the 1970s). Similar catastrophic resurgent epidemics have occurred in India and Madagascar (1980s – 1990s). Recent decreasing trends in malaria in the Americas, Eastern Mediterranean, Europe, South East Asia, and the Western Pacific regions of WHO are shown in Figure 15.

## Conclusion

Surveillance, research, training, and sustainability are the keys to malaria eradication. The steps from research to implementation leading to eradication are shown in Figure 16. Continual refine-

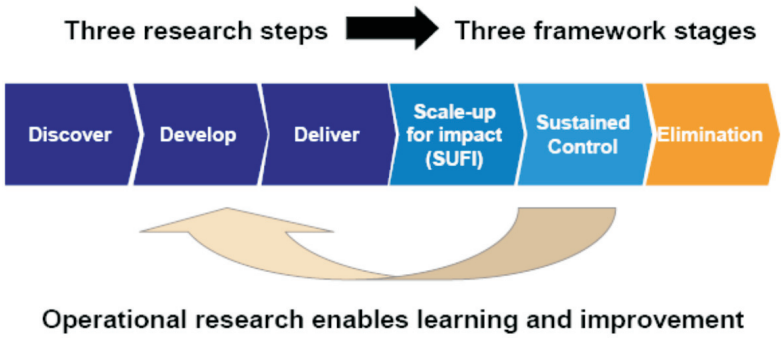



***Fig. 16.*** *Research provides tools for control and elimination. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

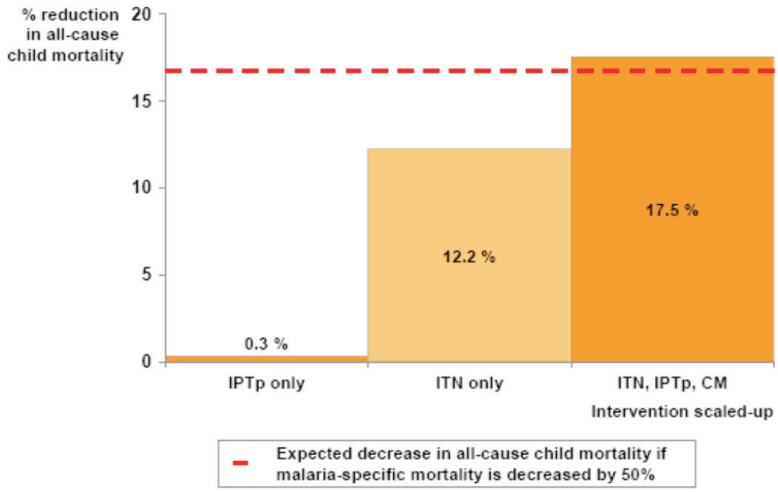



***Fig. 17.*** *Modeling of Impact of Prevention and Treatment Interventions on Child Mortality. IPTp, Intermittent preventive treatment in pregnancy; ITN, insecticide treated net; CM, case management of malaria. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

ments of modeling exercises will be needed as activity and surveillance data accrue from the field to assist in strategic planning and resource allocation (Figure 17). It is expected that up to \$5–6 billion per year will be needed for eradication for the next 10 years before costs begin to fall based on decreasing inputs for treatment and more on prevention (Figures 18A and 18B). Provisions for the current economic crisis will have to be made by countries, international organizations and foundations, to assure that malaria control and elimination milestones are met.

Malaria causes devastating effects in tropical countries, particularly in children and pregnant women. The economic toll is considerable due to the medical and psychological impact of the disease, impairment of cognition and schooling, deterrents to having a healthy workforce and decreased investments in business and development projects. The recent control and elimination initiatives have brought enthusiasm and increased coverage of interventions in many countries. However, there is disparity of access, use and quality of treatment and prevention in all endemic countries[42]. Ultimately, drugs and vaccines that block malaria transmission will allow the goal of eradication to be achieved. As these and other antimalaria tools are developed, research to assure proper delivery of current strategies and to incorporate new ones will be required.

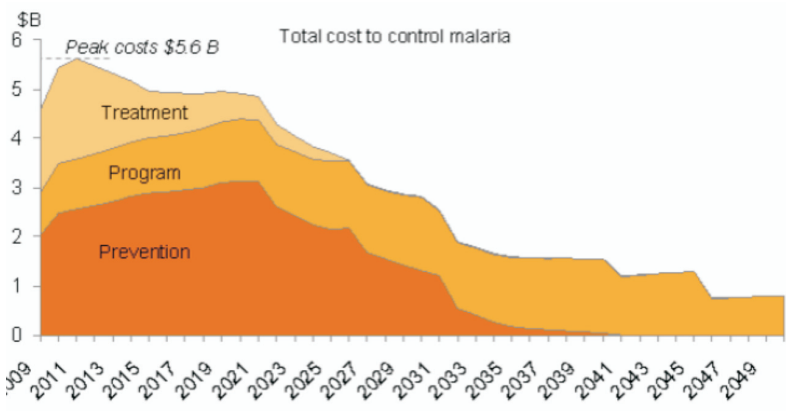



***Fig. 18A.*** *Malaria control costs through 2050: by intervention category. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

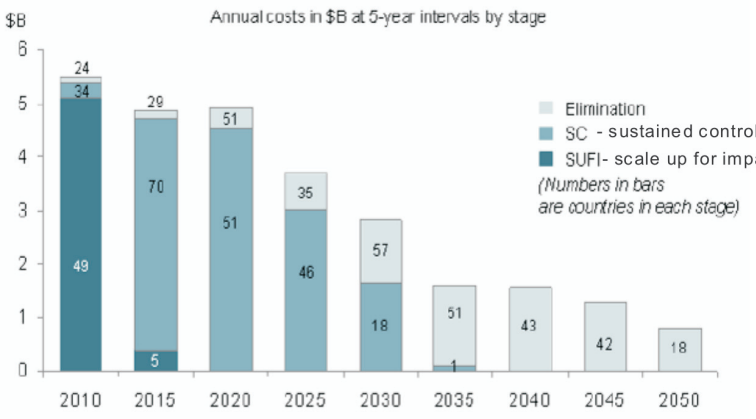



***Fig. 18B.*** *Malaria control costs through 2050: by framework stage. Data from the Global Malaria Business Plan, Roll Back Malaria Partnership 2008.*

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