

THE NEGLECTED BURDEN OF *PLASMODIUM VIVAX* MALARIA

KAMINI MENDIS, BARBARA J. SINA, PAOLA MARCHESINI, AND RICHARD CARTER

Roll Back Malaria, World Health Organization, Geneva, Switzerland; Multilateral Initiative on Malaria Secretariat, Fogarty International Center, National Institutes of Health, Bethesda, Maryland; Institute of Cell, Animal and Population Biology, Division of Biological Sciences, University of Edinburgh, Scotland

Abstract. We estimate that the global burden of malaria due to *Plasmodium vivax* is ~70–80 million cases annually. Probably ~10–20% of the world's cases of *P. vivax* infection occur in Africa, south of the Sahara. In eastern and southern Africa, *P. vivax* represents around 10% of malaria cases but < 1% of cases in western and central Africa. Outside of Africa, *P. vivax* accounts for > 50% of all malaria cases. About 80–90% of *P. vivax* outside of Africa occurs in the Middle East, Asia, and the Western Pacific, mainly in the most tropical regions, and 10–15% in Central and South America. Because malaria transmission rates are low in most regions where *P. vivax* is prevalent, the human populations affected achieve little immunity to this parasite; as a result, in these regions, *P. vivax* infections affect people of all ages. Although the effects of repeated attacks of *P. vivax* through childhood and adult life are only rarely directly lethal, they can have major deleterious effects on personal well-being, growth, and development, and on the economic performance at the individual, family, community, and national levels. Features of the transmission biology of *P. vivax* give this species greater resilience than the less robust *Plasmodium falciparum* in the face of conditions adverse to the transmission of the parasites. Therefore, as control measures become more effective, the residual malaria burden is likely increasingly to become that of *P. vivax*.

INTRODUCTION

Among the 4 species of malaria parasite that infect humans, *Plasmodium vivax* and *Plasmodium falciparum* vie for greatest prevalence in the world today. Of these 2 species, *P. falciparum* is justifiably regarded as the greater menace because of the high levels of mortality with which it is associated, its widespread resistance to antimalarial drugs, and its dominance on the world's most malarious continent, Africa. However, malaria due to *P. vivax* has also placed huge burdens on the health, longevity, and general prosperity of large sections of the human population. The debilitating impact of *P. vivax* malaria, although less than in former times, remains high, unacceptable, and, in most situations, ultimately preventable for well over 1 billion inhabitants of the planet. In the following discussion, we examine the nature of the current burden of *P. vivax* malaria across the world.

GEOGRAPHICAL DISTRIBUTION OF *P. VIVAX* MALARIA IN THE WORLD TODAY

The statistics we have used here to present the global incidence and distribution of *P. vivax* malaria outside of tropical Africa are based on those prepared for the 1999 World Health Report and presented in summary in Table 1. The data used were from national statistics reported by the regional offices of the World Health Organization between 1993 and 1998, but mainly for the years 1995 and 1996, and were prepared by one of us (R.C.) for the 1999 World Health Report according to the approach outlined in Appendix 1.

We have not attempted a similar analysis of *P. vivax* malaria in tropical Africa because of epidemiological and other conditions that prevail over most of this region and that present problems of recording and reporting malaria cases. Nevertheless, we offer the following overview of the prevalence of *P. vivax* malaria in Africa.

Plasmodium vivax is exceedingly rare in the countries of sub-Saharan West Africa. Here *P. falciparum* predominates, although *Plasmodium malariae* has been recorded in up to a third of cases, with *Plasmodium ovale* representing another

few percent of malarial infections; overall, *P. vivax* probably represents < 1% of recorded infection from this region.¹ The extreme rarity of *P. vivax* in West Africa is apparently due to the almost universal prevalence in native West Africans of the Duffy negative trait, an inherited red cell phenotype that lacks the receptor for invasion of the human red cell by the merozoites of *P. vivax*.^{2,3} As will be discussed below, in other situations, *P. vivax* malaria has been associated with high levels of mortality, probably indirectly through the presence of other diseases and conditions of poor health. This encourages speculation that the Duffy negative genes in West Africans could have been selected for by *P. vivax* malaria itself. If so, however, it would leave unanswered the question of why the Duffy negative trait, which imparts no evident disadvantage to the carrier, has not been selected to fixation in other long-standing *P. vivax*-endemic populations—as, for example, in Papua New Guinea. Indeed, the Duffy negative trait has recently been reported in inhabitants of Papua New Guinea,⁴ but at very low frequency, as it is in other parts of the world where *P. vivax* has long been prevalent.^{5–7} How and why the Duffy negative trait has been selected to virtual fixation in the West African population therefore remains a mystery.

Across the central tropical belt of Africa, the relative incidence of *P. vivax* probably remains low.⁸ However, in eastern and southern Africa and in Madagascar, *P. vivax* has been reported as representing anywhere up to ~20% of malaria infections.⁹ In Sudan, typically 5–10% of malarial infections are due to *P. vivax*, with the remainder being due to *P. falciparum* (Babiker H, unpublished data). A recent study from Ethiopia reported 20% of malaria cases as due to *P. vivax*,¹⁰ whereas in parts of this country, up to 40% of malaria cases may be due to *P. vivax*.¹¹ In 1996, ~1% of travelers from the United Kingdom returning with malaria from West Africa were diagnosed with *P. vivax* infections; of those returning from elsewhere in Africa, 9% had *P. vivax* (Records of the Malaria Reference Library, London School of Hygiene and Tropical Medicine, unpublished data). If it is accepted that there may be ~200–300 million clinical cas-

TABLE 1
Annual statistics on malaria, estimates from 1993–1997

Region*	Population at risk for malaria	Total malaria cases	Total cases of malaria due to <i>Plasmodium falciparum</i> or other species†	Total cases of malaria due to <i>Plasmodium vivax</i>
South and East Asia and Western pacific	1,284,000,000	86,461,294	44,400,333	42,060,961
Eastern Mediterranean	64,600,000	14,539,081	2,883,333	11,655,748
Central America and Caribbean	64,200,000	3,676,288	579,867	3,096,421
South America	23,500,000	11,324,643	3,347,010	7,977,633
Central Asia and Caucasus	8,480,000	166,506	0	166,506
World total of malaria-endemic countries outside Africa	1,444,780,000	116,334,318	51,210,543	65,123,775
Imported malaria (nonendemic countries)	1,590,000,000	33,036	11,043	21,993
Africa	550,000,000	200–300,000,000	Most of total	6–15,000,000

* Countries included in the regions designated here as South and East Asia and Western Pacific, Eastern Mediterranean, and Central Asia and Caucas are as given in the legend of Figure 1. Malaria-endemic countries in Latin America listed in Figure 1 have been further classified here as being in South America, and Central America and the Caribbean, with Mexico being included in the latter. Africa refers to sub-Saharan Africa, Sudan, Ethiopia, and the countries of the Horn of Africa.

† In sub-Saharan Africa and in Papua New Guinea, a variable proportion of cases, usually <20%, can be due to *Plasmodium malariae*, *Plasmodium ovale*, or both. In other parts of the world, these species are much less frequent or are absent altogether.

es of malaria per year in the whole of tropical Africa, of which ~3–5% may be due to *P. vivax* malaria, then on the order of 6–15 million cases of *P. vivax* malaria may occur each year in Africa, representing ~10–20% of the world's total *P. vivax* infections (Table 1).

Outside of Africa, it was estimated that for the period 1995–1996, the global incidence of *P. vivax* was 60–70 million clinical cases per year, representing a little over half (56%) of the total non-African malarial infections (Table 1). A total of 65% of these *P. vivax* cases was in southern Asia and the Western Pacific, where *P. vivax* represented 49% of all cases of malaria in the region; 12.5% of all *P. vivax* cases were in South America, where it represented 71% of all malaria in the region; 4.5% of *P. vivax* cases were in Central America, representing 81% of all cases of malaria there; and 20% were in the Eastern Mediterranean region, where *P. vivax* also represented 81% of all cases of malaria. About 0.2% of the world's *P. vivax* cases were in southeastern Europe and south-central Asia, where 100% of indigenous cases of malaria were reported as *P. vivax*.¹²

It is apparent from these figures that there is a geographical trend in the ratios of *P. vivax* to *P. falciparum*. This ratio is lowest, varying from 0–20%, in tropical Africa and Papua New Guinea, where transmission is most intense, rising to 50–70% in the regions of less intense tropical transmission in south Asia, the Western Pacific, and South America, and rising to 80–100% in the subtropical and more temperate regions of Central America, the eastern Mediterranean, the Middle East and southern Europe, and south-central Asia, where malaria transmission intensities are lowest. Indeed, this is the historically well recognized geographic trend in the relative prevalence of *P. vivax* and *P. falciparum* malaria. Broadly speaking, it arises because *P. falciparum* flourishes and overwhelms *P. vivax* where transmission conditions are most intense and advantageous to the parasites; under harsher conditions, however, *P. falciparum* transmission fades before the more robust *P. vivax*. This is demonstrated in Figure 1, which shows that as malaria transmission intensity increases, the *P. vivax*/*P. falciparum* ratio does indeed decline; this relationship holds within regions even more strongly than between them. Figure 1 comprises data from malaria-endemic countries outside the African region. For various reasons, data from the Af-

rican countries have not been included—for example, the fact that the presence of the Duffy negative trait creates a major bias against *P. vivax*.

HISTORIC BURDEN OF *P. VIVAX* MALARIA

At least from post-Colombian times until the middle of the 20th century, *P. vivax* malaria extended throughout almost the entire inhabited world, with the exception, presumably, of West and Central Africa (Figure 2). Its presence blighted the existence of all who lived—and died—in its shadow.^{13–15} The experience of life and death under malaria may be glimpsed from contemporary comment from western Europe in the early 19th century (most areas of which, by virtue of their latitude, can only have been affected by *P. vivax* and probably also quartan malaria, or malaria due to *P. malariae*). Thus, in 1827, the British physician John Macculloch described the typical inhabitant of malarious parts of Europe, which included areas of southern England, Sweden, Germany, Poland, Russia, Holland, and France, as well as large areas of Spain and Italy, most of Greece, Turkey, the Balkans, and beyond (where *P. falciparum* was also prevalent), as “the ghost of a man, a sufferer from his cradle to his grave; aged even in childhood and laying down in misery that life which was but one disease”¹⁶—and he or she laid down that life, on average, by 20–25 years of age.

Historical evidence does indeed suggest that *P. vivax* imposed a significant burden of mortality that may have resulted from its interaction with other diseases and conditions. In northern Europe, where malaria was entirely vivax or quartan malaria, the mortality rates doubled in the malarious areas, living in such areas costing the inhabitants a reduction of life expectancy at birth of ~20 years, compared with life expectancies at birth of 40–50 years in those who lived outside the malarious areas of England.^{13,16} In Sri Lanka, the malaria eradication efforts led to a major decrease in death rates in direct proportion to the previously high spleen rates recorded in endemic populations.¹⁷ A significant proportion of the malaria burden in Sri Lanka then was due to *P. vivax* malaria, suggesting that *P. vivax* contributed significantly to mortality.

The apparent severity of malaria in the northern (and presumably *P. falciparum*-free) locations in Europe—for ex-

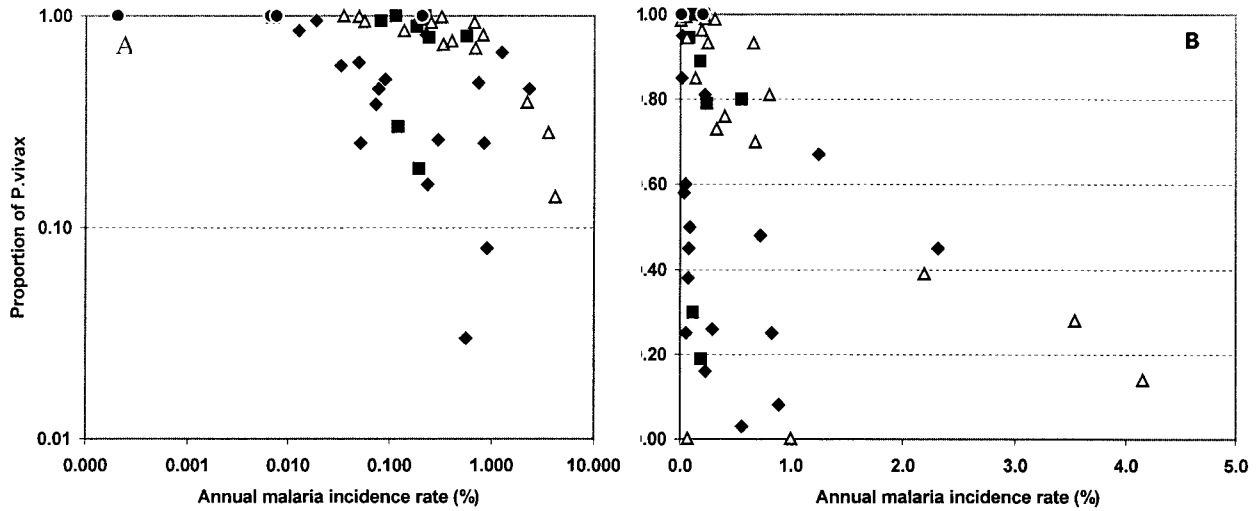


FIGURE 1. The variation of the proportion of malaria cases due to *Plasmodium vivax* with the annual malaria incidence rates in endemic countries (the rest being mainly due to *Plasmodium falciparum*) shown on logarithmic (A) and linear (B) scales. The data points shown here represent the following regions and countries: (solid diamonds) Asia: Bangladesh, Bhutan, Cambodia, China, India, Indonesia, Lao PDR, Malaysia, Myanmar, Nepal, Papua New Guinea, Philippines, Solomon Islands, Sri Lanka, Thailand, Vanuatu, and Vietnam; (solid squares) Eastern Mediterranean: Afghanistan, Iran, Iraq, Oman, Pakistan, Saudi Arabia, Syria, and Yemen; (solid circles) Central Asia and the Caucasus: Armenia, Azerbaijan, Tajikistan, and Turkey; (open triangles) Latin America: Argentina, Belize, Bolivia, Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, French Guyana, Guyana, Haiti, Honduras, Mexico, Nicaragua, Panama, Peru, Suriname, and Venezuela. The malaria incidence rates used here are our own estimates based on country reports of malaria data (see text). The *P. vivax* to *P. falciparum* ratio for each country is as reported by the countries.

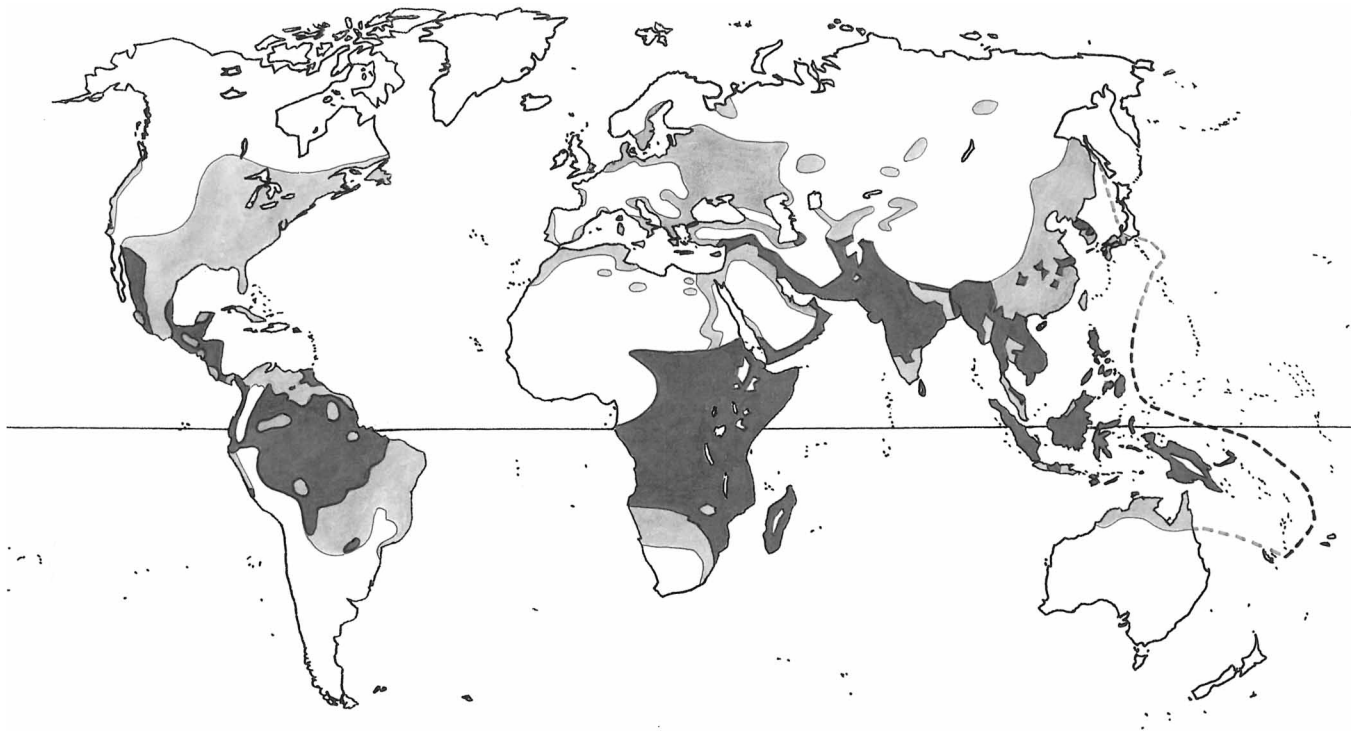


FIGURE 2. The approximate boundaries of the likely distribution of *Plasmodium vivax* at the maximum extent of its distribution as reached in different parts of the world between the mid-17th century and the early 20th century^{70,71} (light shading) and the approximate boundaries of *P. vivax* transmission and significant risk of infection in the late 20th century⁷²⁻⁷⁴ (dark shading). The boundary of malaria transmission on islands in the Western Pacific Ocean is indicated with a dashed line.

ample, in the south England marshlands of Essex and Kent, and in Holland—declined throughout the 19th century, as did its prevalence.^{13,18,19} The decline and ultimate disappearance of indigenous malaria from northern Europe may be accounted for by the effects of rising prosperity in the form of improved housing and environments, imposing a barrier between human hosts and mosquito vectors. By these means, the cycle of malaria transmission was broken throughout western Europe by the mid-20th century, as it was at the same time in the United States.²⁰

The loss of virulence of malarial infections in northwest Europe^{13,18,19} (and again, we are talking here of either *P. vivax* or, more rarely perhaps, *P. malariae*) is more puzzling. However, this trend also may well have followed the wake of prosperity through the rapidly improving health of northern Europeans toward the end of the 19th into the early 20th century. Many diseases and other determinants of ill health, such as poor nutrition, interact with each other and with malarial infection, so that the severity of one is exacerbated by the presence of another.^{21–23} Today's world is generally far healthier than that of 150 years ago. Together with the wide availability of drugs effective against *P. vivax* infections, it is probably for this reason that the burden of *P. vivax* malaria, although still widely prevalent, is far less than in former times.

THE BURDEN OF *P. VIVAX* TODAY

Although *P. vivax* malaria has receded completely from some regions, notably in the temperate Northern Hemisphere, it persists elsewhere across most of its historic territory (Figure 2). Moreover, moderate though the effects of *P. vivax* malaria may be now compared with former times, the global toll imposed by this parasite is great in relation to the standards of health and well-being that could otherwise be expected in today's world, even in many of the poorest nations. We discuss next the nature of this burden.

Clinical picture of *P. vivax* malaria. Malaria due to *P. vivax* in the nonimmune person is an acute and excruciating illness.^{24,25} In such a person, *P. vivax* malaria gives rise to a well-defined, recurring paroxysmal fever with a regular 48-hr periodicity. The fevers, which reach peaks of up to 40.5°C, are preceded, by half an hour or so, by chills and rigors and are succeeded by intense sweating.²⁵ An entire paroxysmal episode usually lasts 4–8 hr, after which the patient falls into an exhausted sleep. Malaria due to *P. vivax* differs from the experience of uncomplicated *P. falciparum* malaria in the nonimmune patient, in whom the paroxysm is less pronounced and the fever more continuous. Some of the insights we have today into the pathogenesis of malarial fevers in general—in particular, their mediation by the cytokines interleukin-6 and tumor necrosis factor alpha (TNF- α)—derive from studies on *P. vivax* infections.^{24,25}

Consistent with the temporary incapacitation of *P. vivax* paroxysmal attacks are the extremely high plasma levels of TNF- α that accompany them. During a *P. vivax* paroxysm, TNF- α can transiently reach levels much higher than those reported during severe and fatal infections of *P. falciparum*.^{25,26} The cytokine TNF- α has been implicated as a major mediator of the severe pathology of *P. falciparum*, whereas today, *P. vivax* has the reputation of a nonlethal and rela-

tively nondebilitating parasite. The difference in the apparent effects of TNF- α during acute infections with these 2 parasites probably has to do with its duration during an infection and its distribution within a host. *Plasmodium falciparum*, but not *P. vivax*, sequesters in postcapillary venules of internal organs, where TNF levels could be quite high. The process of sequestration, which is thought to be associated with the severe outcome of *P. falciparum*, can itself be enhanced by TNF. However, it is likely that the unremitting exposure to repeated high levels of TNF- α had much to do with the debilitating effects of chronic, untreated *P. vivax* malarial infection in former times; such infections run for several years.

Even today, there are occasional reports of severe and fatal *P. vivax* infections. These are associated with lung injury and respiratory distress,^{27,28} splenic rupture and associated pathology,²⁹ and even instances of cerebral malaria associated with apparently pure *P. vivax* infections.³⁰ Thus, under rare and yet poorly understood circumstances, *P. vivax* infections can still present in dangerous form.

Although rarely directly life-threatening, anemia is the most frequently observed pathological consequence of *P. vivax* malaria, both in the acute state and as a long-term effect of repeated or chronic infections. Dyserythropoiesis³¹ and hemolysis of infected and uninfected erythrocytes³² have both been implicated in anemia due to *P. vivax* malaria.

The impact of *P. vivax* malaria on pregnancy, a state highly vulnerable to *P. falciparum* malaria, is not well documented. Evidence for increased morbidity of *P. vivax* malaria in pregnancy is equivocal. A recent study conducted in a predominantly *P. vivax*-endemic region of Sri Lanka failed to detect a significant impact of malaria on pregnancy or the newborn—or, conversely, of pregnancy affecting the risk or severity of malarial infection.³³ Other studies, however, have shown higher parasite densities and a greater degree of anemia associated with *P. vivax* malaria in pregnancy as well as low birth weights.^{34,35}

The major difference in the pathogenesis of *P. falciparum* and *P. vivax* malaria during pregnancy almost certainly relates, as it does in other situations, to the fact that the blood stages of *P. vivax* do not sequester in deep organs, whereas those of *P. falciparum* do. For blood-stage parasites of *P. falciparum*, the placenta is a highly favored site. The influence of *P. vivax* malaria on pregnancy probably relates to the anemia it causes. This will likely be most affected by the level and duration of parasitemia experienced, to the frequency of *P. vivax* infection, and to access to health care. The different impacts of *P. vivax* and *P. falciparum* on pregnancy, and their frequently different susceptibility to currently used antimalarial drugs (see below), present difficult challenges for the management of malaria in pregnant women in situations where both species of parasite coexist. These have a bearing on health-delivery policies, such as the recently introduced intermittent presumptive treatment of malaria in pregnancy versus the conventional weekly prophylactic treatment.

Social and economic burden. *Plasmodium vivax*, and malaria in general, is linked with poverty. Malaria occurs in poor regions and poor countries, and its presence has a strong negative correlation with economic growth in families, communities, and nations. The social and economic bur-

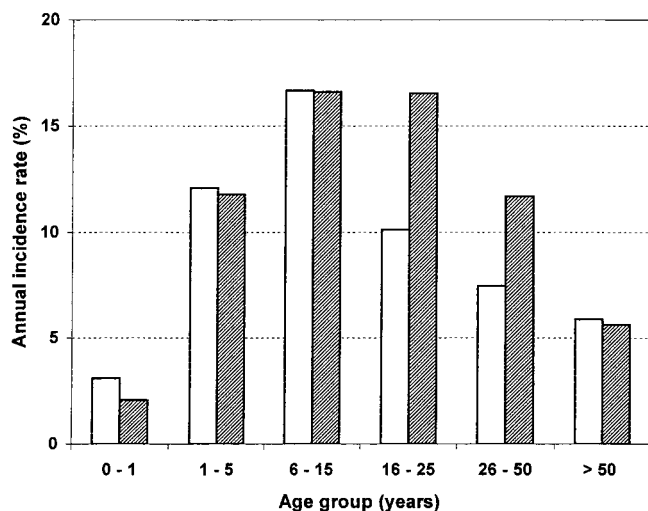


FIGURE 3. Annual incidence rates of malaria among boys and men (cross-hatched bars) and girls and women (open bars) of different age groups in a rural community of 3,625 people in a region that is endemic for both *Plasmodium vivax* and *Plasmodium falciparum* malaria in Kataragama, southern Sri Lanka, for the years 1986–1988 (Gamage-Mendis A, unpublished data; see also Figure 4).

den specifically attributable to *P. vivax* malaria derives from the following features. Where *P. vivax* prevails, people of all ages, adults and children alike, experience malarial disease. This is because, as discussed below, transmission rates are generally too low to induce an effective exposure- or age-acquired protective immunity to this parasite. As a general rule, every person in a moderately *P. vivax*-endemic area can expect to experience anywhere from 10 to 30 or more episodes of malaria in the course of childhood and working life. In an impoverished economy, each episode absorbs relatively large amounts of cash for treatment; it diverts others of the family from work to attend the sick; and it leads to the loss of 5–15 days of work or schooling by the affected patient.^{36,37} Those at greatest risk in many parts of the world are men of working age (i.e., ~15–50 years of age; Figure 3; for description of different regions of the world, see Appendix 2)—in other words, the very individuals upon whom economic productivity, especially agricultural productivity, most depends. In tropical agricultural communities, where *P. vivax* is often prevalent, its peak incidence coincides with rains and the season of crop planting. Its impact on farming communities, whose entire productivity depends on the short rainy season, can therefore be exceptionally harsh.

For the school-age child, the long-term effects of recurrent malarial infection are a significantly impaired educational attainment and possibly also permanent loss of cognitive faculty (Fernando D, unpublished data), leading to diminished economic productivity during later working life. The experience of recurrent malarial episodes throughout life leads to cumulative debilitation and loss of productivity, quality of life, and life expectancy.

On a macroeconomic scale, the presence of *P. vivax* or *P. falciparum* malaria is a major disincentive to trade, commerce, and investment. The evidence in support of this statement is too extensive to review here.³⁸ As a single example,

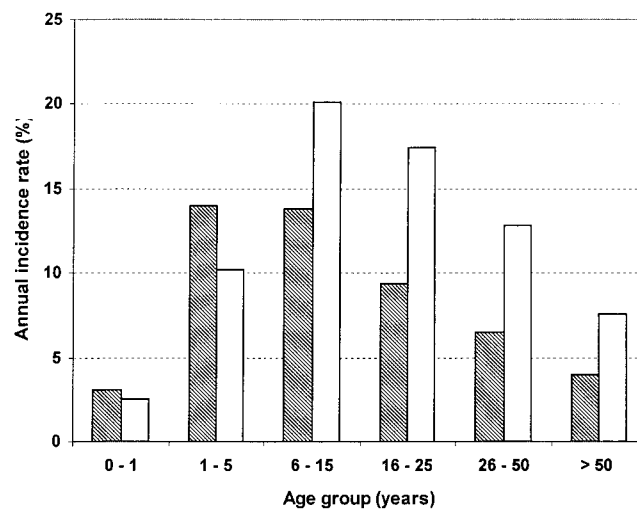


FIGURE 4. Annual age incidence rates of malaria due to *Plasmodium vivax* (cross-hatched bars) and *Plasmodium falciparum* (open bars) in a rural population of 3,625 people in Kataragama, southern Sri Lanka, for the years 1986–1988 (Gamage-Mendis A, unpublished data).

agricultural land in malarious southern states of the United States in the 1920s had about one-tenth to one-twentieth of the value of land of equivalent intrinsic productivity in malaria-free northern states, as is described by Sinton³⁹ in one of his reports.

COMPARATIVE BIOLOGY AND TRANSMISSION STRATEGIES OF *P. VIVAX* AND *P. FALCIPARUM* MALARIA

Acquired immunity. Because it occurs mainly under conditions of low to moderate transmission, populations living under endemic *P. vivax* malaria normally achieve relatively low levels of immunity to this infection. As with *P. falciparum* malaria, exposure-acquired protective immunity to *P. vivax* is the result of the experience of a succession of infections within a short time. Where transmission intensities of *P. vivax* are relatively high, as in Papua New Guinea, a fairly high degree of protective immunity (i.e., immunity against clinical disease) can be achieved by the age of 10–15 years.⁴⁰

In most other regions where *P. vivax* is prevalent, highly effective immunity to this parasite is never achieved. Nevertheless, degrees of immunity are found. The acute symptoms of *P. vivax* infection—for example, fever, body ache, and headaches—can be significantly less after several clinical episodes of this parasite, as indeed is also the case for *P. falciparum* infection.⁴¹ At low inoculation rates (e.g., not more than 2 or 3 inoculations of the parasites per year), the prevalence of *P. vivax* infections characteristically declines to a significant degree after 5–10 years of age. Interestingly, where both *P. vivax* and *P. falciparum* are prevalent together under low to moderate transmission intensities, the prevalence curve for *P. vivax* generally begins to fall at an earlier age than does that for *P. falciparum*, which typically continues to rise until 15–20 years of age (for an example of this from Sri Lanka, see Figure 4).

Views on the immunological interactions between *P. vivax*

and *P. falciparum* differ. Some epidemiological studies have been interpreted to indicate that *P. vivax* infections may confer some clinical protection against *P. falciparum* infections.^{41,42} There is little evidence for cross-protective immunity between *Plasmodium* species, however, from the extensive data from the study of human malarial infections induced under hospital conditions,^{43,44} which indicate that immunity to each species is acquired in a species-specific manner.

Prevalence of drug resistance in *P. falciparum* and its relative absence in *P. vivax*. Probably the single gravest development in malaria in the last century was the emergence and spread of resistance of *P. falciparum* malaria to chloroquine. First reported in 1957 in the Thai-Kampuchian border area⁴⁵ and soon after in South America,⁴⁶ it spread through the subsequent decades of the 20th century to all malaria-endemic regions of the world. Resistance of *P. falciparum* to several alternative drugs that were introduced in place of chloroquine has generally arisen and spread even faster.

In contrast, the first report of *P. vivax* malaria resistant to chloroquine was not until 1989 from Papua New Guinea,⁴⁷ some 30 years after resistance to this drug was first detected in *P. falciparum*. In the years that followed, isolated incidents of chloroquine-resistant *P. vivax* infections were reported in Indonesian New Guinea,^{48,49} Myanmar,⁵⁰ and India,⁵¹ and in travelers to Guyana.⁵² Although reports of chloroquine resistance in *P. vivax* have come from many geographical regions of the world, they have been isolated and sporadic until now. Systematic surveillance, including the monitoring of therapeutic efficacy in *P. vivax*-endemic regions of the world,⁵³ has failed to detect a significant increase in chloroquine resistance in these areas.

There has been much speculation as to why the emergence and spread of drug resistance in *P. vivax* malaria has not taken a rapid course, as it has for *P. falciparum*. The explanation may lie in a fundamental difference in the transmission strategies of the two parasites. The transmission stages, the gametocytes, of *P. falciparum* only appear in the peripheral blood circulation at least 10 days after the clinical threshold of an infection has been reached. If a *P. falciparum* infection is treated with an antimalarial drug, especially one such as chloroquine, which also kills young developing gametocytes, most or all gametocytes that may subsequently arise will have derived from asexual parasites that had survived that drug treatment. Such gametocytes will therefore carry any genes for drug resistance that had enabled their asexual progenitors to survive. When these gametocytes are taken up by a mosquito, the drug-resistant parasites will become part of the circulating pool of parasites in the mosquito and human populations. The transmission strategy of *P. falciparum* is therefore one that strongly assists the selection and spread of drug-resistant parasites.

In *P. vivax*, the transmission strategy is quite different. Mature and infective gametocytes of *P. vivax* appear in the blood of an infected person almost simultaneously with the asexual blood-stage parasites and before the clinical threshold of a blood infection is reached.⁵⁴⁻⁵⁶ Because *P. vivax* infections will not normally be treated with drugs until after the clinical threshold has been reached, it follows that gametocytes from drug-sensitive parasites will be transmitted

through mosquitoes mostly before the parasites become exposed to drug pressure—and therefore before any drug-resistant mutants could have been selected for in a blood infection. As a result, drug-sensitive parasites of *P. vivax* are at little disadvantage relative to those that are drug resistant. Consequently, the pressure for the selection and spread of drug-resistant parasites is expected to be low in *P. vivax*.

Transmission strategies of *P. vivax* and *P. falciparum* and human strategies for their control. The same differences in gametocyte production and transmission strategy that may underlie the differences in the selection of drug-resistant blood-stage parasites of *P. vivax* and *P. falciparum* have other important consequences in the control of these parasites. Thus, because drug treatment normally kills the asexual stages of *P. falciparum* before they are able to produce gametocytes (and because chloroquine kills gametocytes during the first 4–5 days of their development), the appropriate deployment of health services and drug treatment of *P. falciparum* infections can be very effective in reducing transmission rates of this parasite (until parasites resistant to the drugs arise). *Plasmodium vivax*, on the other hand, should be less vulnerable to control by these means. This is because mosquitoes will mostly have become infected during the presymptomatic period of a *P. vivax* blood infection and therefore before drug treatment could have prevented onward transmission of the parasites through mosquitoes.

Plasmodium falciparum should therefore be susceptible to control by widespread, effective drug treatment, but *P. vivax* malaria much less so. Thus, under effective drug control, the prevalence of *P. falciparum* malaria should fall relative to that of *P. vivax*. On the other hand, once resistance develops in *P. falciparum*, the drug-resistant forms of this species would be expected to increase rapidly in relation to *P. vivax*.

This appears to have been the pattern followed in Sri Lanka after 1964, after the termination of the malaria eradication campaign by DDT (dichlorodiphenyltrichloroethane) spraying (Figure 5). Before the campaign began in the early 1950s, *P. falciparum* and *P. vivax* had been prevalent to a similar degree, causing between them typically 1–3 million cases of malaria per year. In the year the campaign was abandoned, 150 cases of malaria were reported for the whole country. Of the explosive resurgence of malaria in Sri Lanka in 1968, however, only ~0.2% of the half-million cases reported in that year were due to *P. falciparum*. By this time, a health service based on rapid diagnosis and treatment of malaria with chloroquine was available throughout the malaria-endemic regions of Sri Lanka, and for the next 2 years, in spite of the diagnosis of around a half-million cases of malaria per year, < 0.5% were due to *P. falciparum*. From ~1971 onward, however, the proportion of *P. falciparum* began to rise. As the second wave of returning malaria peaked in 1975, the proportion of *P. falciparum* likewise peaked at around 15%, already around 100 times higher than during the first 1968–1969–1970 peak. By this time, there was evidence of chloroquine-resistant *P. falciparum* in Sri Lanka.

As the third peak of malaria took off in 1985, the proportion of *P. falciparum* cases passed 20%, a level that has been sustained into the 1990s. During this time, *P. vivax* malaria in Sri Lanka appears to have remained totally susceptible to chloroquine. Another, more recent illustration of

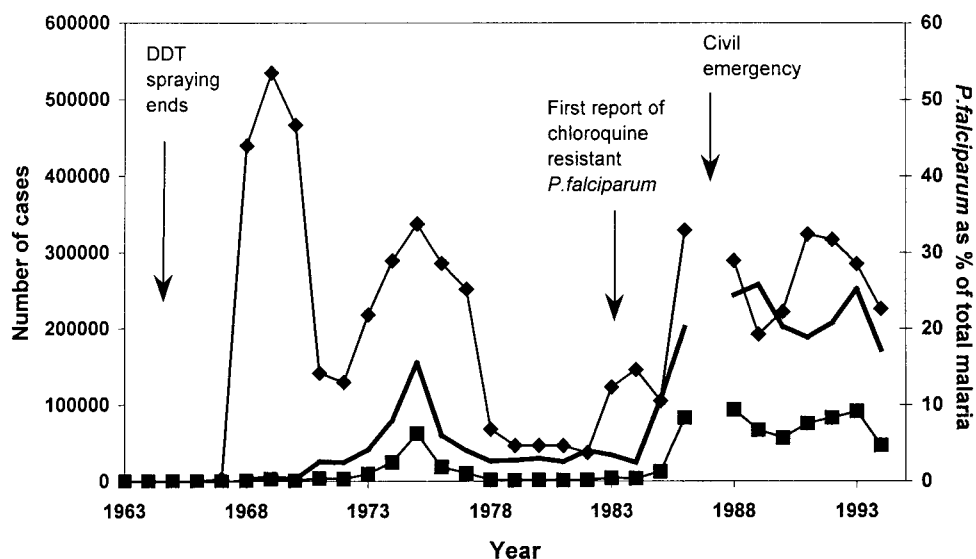


FIGURE 5. The incidences of malaria due to *Plasmodium vivax* (solid diamonds) and *Plasmodium falciparum* (solid squares) in Sri Lanka 1963–1995, showing *P. falciparum* as a percentage of total malaria (line). DDT = dichlorodiphenyltrichloroethane.

the relative ease with which *P. falciparum* succumbs to effective control measures, particularly drug treatment, is the experience of eradicating malaria from one of the Vanuatu islands in the 1990s by the deployment of a combination of mass drug administration, use of insecticide-treated bed nets, and use of larvae-eating fish as a mosquito-control measure.⁵⁷ Before the intervention began, the island's prevalence of *P. falciparum* exceeded that of *P. vivax* by > 50%; however, *P. falciparum* was wiped out entirely within a year of beginning the intervention, although it took 5 years or more to eliminate *P. vivax* from the island.

THE FUTURE OF *P. VIVAX* MALARIA

As we have discussed, *P. vivax* is a very different parasite from *P. falciparum*, both in the patterns of its burden on human populations and in its strategy for transmission and survival. *Plasmodium falciparum* thrives only in situations that are highly conducive to malaria transmission. Under the most favorable transmission conditions, *P. falciparum* almost invariably out-competes *P. vivax* to become the predominant malaria species. On the other hand, *P. falciparum* is also relatively more vulnerable to attack by almost any form of malaria control; it does poorly in well-managed human environments. Therefore, most locations where *P. falciparum* transmission is rampant reflect major failures to institute effective health services and to achieve decent living environments. This is less true of *P. vivax* malaria, which can persist under a variety of less favorable conditions, natural or instituted by humans, in which *P. falciparum* cannot. Thus, as more powerful antimalaria campaigns, many perhaps directed primarily against *P. falciparum*, come into prominence, the residual burden of malaria around the world is likely to become increasingly that of *Plasmodium vivax*.

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Authors' addresses: Kamini Mendis and Paola Marchesini, Roll Back Malaria Project, World Health Organization, 1211 Geneva, 27 Switzerland. Barbara J. Sina, Multilateral Initiative on Malaria Secretariat, Fogarty International Center, National Institutes of Health, Bethesda, MD. Richard Carter, Institute of Cell, Animal and Population Biology, Division of Biological Sciences, University of Edinburgh, West Mains Road, Scotland.

Reprint requests: Kamini Mendis, Roll Back Malaria Project, World Health Organization, 1211 Geneva, 27 Switzerland, Telephone: +41-22-791-3751, Fax: +41-22-791-4824 (e-mail: mendisk@who.ch).

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APPENDIX 1

THE GLOBAL ESTIMATION OF MALARIA PREVALENCE BY SPECIES OUTSIDE AFRICA

Sources of information. The accompanying method of analysis was used to generate the information in Table 1 from data presented in malaria reports from the World Health Organization regional offices. Included are data from the reports from the Western Pacific Regional Office for the year 1996, from the South East Asian Regional Office for the year 1995, from the Eastern Mediterranean Regional Office covering the years 1993–1996, from the American Regional Office covering years 1994–1997, and from the European Regional Office for 1996.

To conduct the analysis, the following data were extracted, where possible, for each country represented in the reports: 1) the reported number of deaths attributed to malaria; 2) the reported number of identified cases of malaria (all *Plasmodium* species, by microscopic diagnosis, clinical diagnosis, or both); 3) the proportion of microscopically diagnosed cases due to *Plasmodium falciparum*; and 4) the human population reported by each national government to be at moderate to high risk of malaria transmission.

The aim of the analysis was to generate the following malariometric indexes for each country and region: 1) the total number of cases of malaria; 2) the number of patients infected with each species of malaria; and 3) the numbers of deaths due to malaria.

Unfortunately, because of logistic and other difficulties involved, the malaria cases reported in national government statistics usually vastly underrepresent the true numbers. Because of this, it was necessary to devise an approach that might yield numbers closer to the real ones. This approach is described as follows.

Methodological approach. First, it was taken that the only reasonably reliable (generally with a much less than 50% error associated with it) reported malaria statistic from around the world would be the proportions of the different *Plasmodium* species, mainly *P. falciparum* and *P. vivax*, from each country or region of a country.

Second, it was taken that the reporting of deaths is a more accurate statistic in national records than the reporting of specific nonfatal illness, such as a case of malaria. Diagnosis of malaria as a cause of death would be relatively reliable (probably within a 50% error margin). It was necessary to make a guess at the reliability of government-reported number of malaria-related deaths on a country-by-country basis. Advice was given by country malaria experts in selected cases. On the basis of these, the government-reported numbers of deaths was multiplied by a range of correction factors that in most cases lay between 2 and 10. It was assumed that the majority of fatal cases of malaria would be due to *P. falciparum*.

Third, an estimate was made of the likely *P. falciparum* case-fatality rate in a specific country. These estimates took into account the general setting, health services, and degrees of antimalarial drug resistance in the location. Reported malaria case-fatality rates from a wide variety of situations were studied in reaching these estimates (Alles HK, unpublished data; Vietnamese Government, unpublished data).^{58–61} On the basis of these studies, estimated *P. falciparum* case-fatality rates in the endemic countries were used in the range 0.01–0.3%.

With these 3 sets of corrected figures, it was possible to calculate values for the absolute numbers of cases of malaria due to both *P. falciparum* and *P. vivax* (assuming, as was almost invariably the case, that *P. vivax* was the main or only other *Plasmodium* species involved). Thus, dividing the estimated/corrected number of malaria (*P. falciparum*) deaths by the estimated/corrected *P. falciparum* case-fatality rate, the estimated/corrected total number of cases of *P. falciparum* is obtained. From the proportion of all government-reported cases of malaria that were diagnosed as due to *P. falciparum*, a figure for the total number of all malaria cases, and also of *P. vivax* cases, could be obtained.

Checking the method for accuracy. This method clearly lays itself open to potentially large inaccuracies, certainly in the case of specific estimates for individual countries. Unlike the unprocessed government data, however, there is no reason to suppose that these inaccuracies will be strongly biased in any particular direction, either up or down. On this basis alone, the regional estimates—that is, the totals for all the countries in a particular region—from this method are likely to be closer to reality than the uncorrected figures.

However, other specific checks were included in making the individual country estimates. Plausible ranges of values for 2 other test parameters were laid down as references. Thus, malaria case incidence rates (which could be calculated by dividing the case numbers estimated by the above procedure by the size of the populations that were reported by the government to be at moderate to high risk of malaria) were required to lie within the range of 0.01–4 cases of malaria per person per year as the outer limits of plausibility. Also, the ratios of the estimated number of malaria cases to the number of cases reported by the government were required to lie between 3–100 as the plausible range of discrepancy between them.

In judging how well the individual estimates for numbers of malaria cases behaved in generating values for these 2 test parameters, the plausibility of the values for these test parameters was also looked at in relation to the specific country circumstances. For example, in a setting with an expected low malaria risk and very well managed government services, the imposed values for malaria deaths and case-fatality rates could be seriously questioned if the test parameters came out at or beyond the upper end of their “permitted” ranges.

The process is therefore one first of generating best-estimate values for the corrections to the reported malaria deaths and the malaria case-fatality rates. These, together with the proportion of *P. falciparum* and *P. vivax* among government-reported cases, are used to estimate realistic numbers of cases of *P. falciparum* and *P. vivax* malaria. In the second step, the outcome is checked for plausibility against test parameters and in the general context of the country in question. After these tests, adjustments can be made if necessary to the original best estimate until the most acceptable all-around outcome is reached. The application of this checking procedure generally left no great margin to maneuver in choosing values. It was difficult to move the overall best estimate mortality-related values for whole regions by > 30–50% without imposing unreasonable values for test parameters for a large number of the component countries.

APPENDIX 2 DISTRIBUTION OF MALARIAL DISEASE BY AGE AND SEX

South and East Asia and the Western Pacific. In most of this region, including the Mekong countries, China, Indonesia, the Philippines, India, and Sri Lanka, the incidence of malarial infection is spread throughout life. The incidence of *Plasmodium falciparum* tends to peak broadly between 10–40 years of age and that of *Plasmodium vivax* more sharply and earlier, when the patient is aged ~2–15 years. Point prevalence of either species in the age groups at highest risk tends to be ~0.3–3%. In the economically most productive age group of people ~15–50 years of age, the risk of malarial infection in boys and men relative to girls and women is between 1.3:1 and 2.5:1 and is due to differences in occupation that place men at a higher risk of exposure to infection.^{62,63} A major exception to this generalization concerning malaria risk is the situation of pregnant women, who are at a generally higher risk of developing malarial disease and at ~3 times the risk of developing severe malaria than nonpregnant women or men of the same age when they become infected with *P. falciparum*.^{64,65} The risk of acquiring even *P. vivax* has been found to be greater in the pregnant than nonpregnant state⁶⁶ although there is no associated risk of severe complications during pregnancy.

Within the Pacific region, the islands of Papua New Guinea, the Solomon Islands, and the Vanuatu islands have much higher levels of malaria transmission, and the above generalizations do not apply. Peak prevalences of *P. vivax* lie between 1–15 years, much as elsewhere in the region, whereas peak prevalences of *P. falciparum* fall between 5–20 years of age. Within the age groups at highest risk, however, the point prevalence of both *P. vivax* and *P. falciparum* are very much greater than elsewhere in the region, generally 5–50% for either species.^{40,67,68} Differences between sexes in risk of malaria are probably less marked than in the other countries of the region.

Eastern Mediterranean. Malaria transmission rates are, with the exception of those in the Sudan, relatively low throughout this region, and the incidence of malaria and risk of death from malaria can be expected to be spread throughout life, but mainly in early adulthood and middle age. For occupational reasons, the risks of malaria and of death from malaria can be expected to be several times greater in men than in women, except during pregnancy.

North and South America. Transmission intensities of malaria are generally low to moderate through this region, and incidence of malaria can be generally expected to be spread throughout life in most settings, with the peaks occurring in early adulthood. In a few areas, namely French Guiana, Guyana, and Suriname, transmission intensities are relatively very high (and mainly *P. falciparum*); the incidence of malaria can be expected to be highest in early childhood and low in adolescence and adulthood. Elsewhere, transmission intensities are low (and mainly *P. vivax*), and point prevalence is generally much less than 1%. Risk of malaria spreads throughout life, but young and middle-age adults are at the highest risk—especially men, who, for occupational reasons, may be at 2–3 times the risk of malaria infection than women.^{66,69}