

# CONTROL AND ELIMINATION OF *PLASMODIUM VIVAX* MALARIA

## A TECHNICAL BRIEF

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World Health  
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# Foreword

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The *Global Technical Strategy for Malaria 2016–2030* sets the most ambitious targets for malaria since the eradication era, namely to eliminate malaria from at least 35 countries and reduce case incidence and mortality rates by 90% globally. *Plasmodium vivax* presents a major challenge to achieving these targets. In 2013, it was estimated to be responsible for 16 million cases globally, and almost half the cases of malaria outside of Africa. It predominates in countries that are prime candidates for elimination, accounting for more than 70% of cases in countries with less than 5000 cases of malaria each year. Not only does *P. vivax* present a barrier to elimination, it is also increasingly recognised that *P. vivax* infections can be as debilitating as *P. falciparum* malaria, causing severe disease and death.

The principles for controlling *P. vivax* malaria are the same as those for *P. falciparum* malaria but programmes face challenges when deploying available tools against *P. vivax*. In many areas where *P. vivax* malaria is common, mosquitoes bite early in the evening, obtain blood meals outdoors and rest outdoors. Therefore, insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) may be less effective in reducing the transmission of *P. vivax* parasites. Blood-stage infections of *P. vivax* often occur with low parasite densities and can be missed using routine microscopy or rapid diagnostic tests; the dormant hypnozoite stage in liver cells, which can cause multiple relapses, is entirely undetectable with current diagnostic methods. Furthermore, gametocytes are often produced, and the parasite transmitted to the mosquito, before symptoms appear. There is only one option for treating the liver stage, primaquine, which requires a treatment course of 14 days to which patients may not fully adhere. Primaquine is contraindicated in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency and cannot be given to pregnant women or children under 6 months of age.

Current tests to determine whether or not patients are G6PD deficient are generally not suitable for use in the peripheral health facilities where most patients seek treatment.

More effective control of *P. vivax* malaria, and its eventual elimination, will require a better understanding of how existing tools can be best deployed against *P. vivax* and how their coverage can be extended to populations who currently do not benefit from them. It will also require the development of new tools that will help to reduce *P. vivax* transmission, and increase the ability of malaria programmes to detect and treat infections. International donors and domestic governments need to invest in the additional measures needed to extend the fight against *P. vivax* malaria, and in the research required to develop new tools. A comprehensive response to *P. vivax* malaria will relieve some of the most vulnerable populations of a significant illness that causes disruption to schooling and work, and can be fatal. If *P. vivax* malaria is conquered, not only will international targets to eliminate malaria from 35 countries by 2030 be achieved, but a pathway will be set for the eventual eradication of this ancient disease.



**Dr Pedro L. Alonso**

Director of the WHO Global Malaria Programme

# Abbreviations

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ACT	artemisinin-based combination therapy
CFR	case fatality rate
CI	confidence interval
CYP2D6	cytochrome P450 polymorphism
G6PD	glucose-6-phosphate dehydrogenase
GMP	Global Malaria Programme, WHO
ICD	International Classification of Diseases
ICU	intensive care unit
IM	intramuscular
IQR	interquartile range
IRS	indoor residual spraying
ITN	insecticide-treated mosquito net
IV	intravenous
MPPT	mass primaquine preventive treatment
NADPH	nicotinamide adenine dinucleotide phosphate
NMCP	national malaria control programme
OR	odds ratio
<i>P.</i>	<i>Plasmodium</i>
PART	presumptive anti-relapse therapy
PCR	polymerase chain reaction
<i>PvAPI</i>	<i>P. vivax</i> annual parasite incidence
RDT	rapid diagnostic test
SP	sulfadoxine-pyrimethamine
TES	therapeutic efficacy study
WHO	World Health Organization



# Executive summary

*Plasmodium vivax* causes significant morbidity and mortality, and poses unique challenges for malaria control and elimination. It has the widest geographical distribution of the four human malarias, and accounts for about half of malaria cases outside sub-Saharan Africa. Severe cases and deaths due to *P. vivax* malaria have been reported from all endemic regions. In areas where both *P. vivax* and *P. falciparum* coexist, the incidence of *P. vivax* decreases less rapidly than that of *P. falciparum*. Hence, *P. vivax* persists as the principal cause of malaria in these areas and as the main barrier to elimination of the disease.

Control and elimination of *P. vivax* malaria presents different challenges to those seen with *P. falciparum*, because *P. vivax* tolerates a wider range of environmental conditions and can be transmitted from infected humans to mosquitoes before symptoms develop in the people infected. Therefore, prompt and effective treatment has less influence on transmission of *P. vivax* than is the case with other malaria species. Conventional control methods of minimizing human contact with mosquito vectors – through insecticide-treated mosquito nets and indoor residual spraying – may be less effective against *P. vivax*. This is because, in many areas where *P. vivax* predominates, vectors bite early in the evening, obtain blood meals outdoors and rest outdoors. In addition, vector control has no impact on the human reservoir of latent hypnozoite stage parasites residing in the liver, which are responsible for an appreciable proportion of morbidity.

*P. vivax* malaria is difficult to detect and treat because the parasitaemia is typically low in comparison to that of *P. falciparum*, and current diagnostic tests cannot detect dormant forms residing in the liver. Hence, there may be a large reservoir of infected people who are unaware of their condition and are only diagnosed when they relapse. In addition, elimination of *P. vivax* liver-stage parasites requires a 14-day course of primaquine, which can produce serious side-effects (haemolytic anaemia) in patients who have severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Testing for G6PD deficiency is technically challenging and

relatively expensive; thus, many clinicians are reluctant to prescribe primaquine to patients whose G6PD status is unknown. Weighing that risk against the possibility of repeated clinical attacks, with their attendant risk of debilitating or life-threatening illness and onward transmission to others, is difficult.

Successful control and elimination of *P. vivax* malaria calls for specific additional interventions: targeting of outdoor-biting and outdoor-resting mosquitoes where these represent the main source of transmission; ensuring that microscopy services are able to detect low-density *P. vivax* infections, or that bivalent rapid diagnostic tests are used in areas where *P. falciparum* and *P. vivax* coexist; where possible, testing all patients for G6PD deficiency before administering primaquine; and treating both blood and liver stages of *P. vivax* malaria. *P. vivax* needs to be adequately reflected in global, regional and national plans for malaria control and elimination. Also, the implementation of such plans should be monitored at regular intervals through *P. vivax*-specific indicators on programme coverage and disease incidence.

More effective control of *P. vivax* malaria, and its eventual elimination, requires new tools, in particular against the hypnozoite reservoir that currently evades most methods of detection and treatment. Investments in research and progress in developing new tools are also needed.

In many endemic countries, the poorest and most marginalized communities have both the highest risks associated with *P. vivax* malaria and the least access to effective preventive, diagnostic and curative services. Pregnant women and infants, for example, cannot be provided with primaquine to prevent multiple relapses. *P. vivax* malaria control and elimination requires a commitment to remove the barriers that affected populations face in accessing interventions. Controlling and eliminating *P. vivax* malaria is therefore very much a development challenge – one that is inextricably linked with health system strengthening, poverty reduction and equity.

# 1. THE CHALLENGE OF *P. VIVAX* MALARIA

## 1.1 GEOGRAPHICAL DISTRIBUTION OF INFECTION AND INCIDENCE OF DISEASE

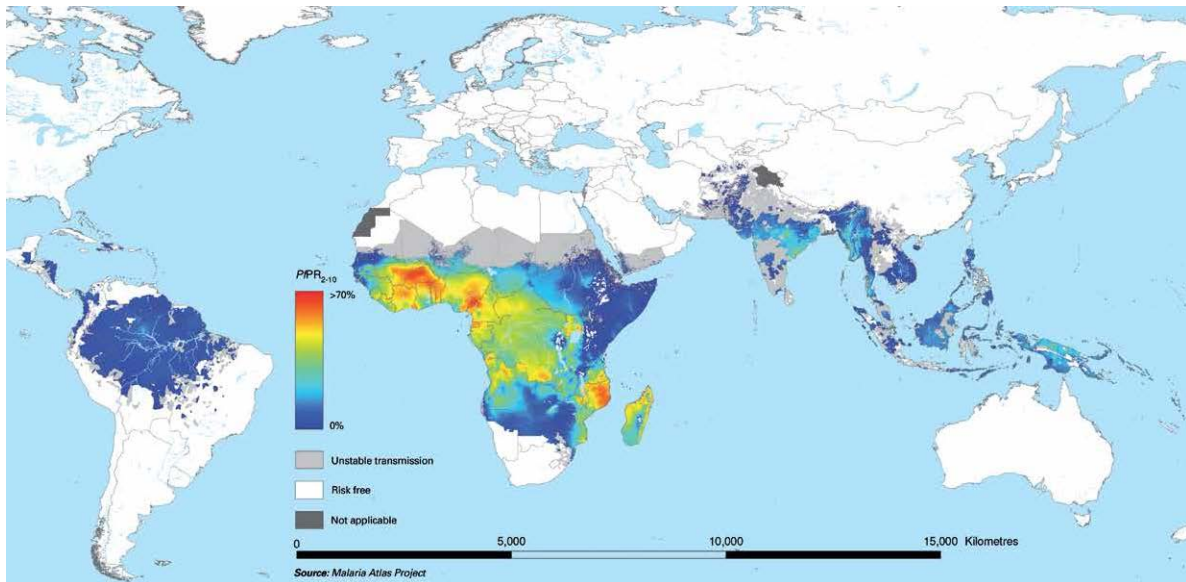
*Plasmodium vivax* has the widest geographical distribution of the four human malarias, with about 35% of the world's population being at risk (1) (Fig. 1.1). The distribution of *P. vivax* is governed by:

- the distribution of suitable mosquito vectors – more than 70 species of anopheline mosquito can transmit *P. vivax* malaria (2), although only 40 are thought to make a significant contribution to its transmission (3);
- climatic conditions that are conducive for parasite development in the vector, notably temperature (4); and
- human genetics; in particular, the distribution of a trait known as Duffy negativity, which is common in many African populations but rare elsewhere. In individuals without the Duffy antigen, red blood cells are largely resistant to infection with *P. vivax*. Thus, *P. vivax* is rare in many parts of Africa, although evidence from returning travellers suggests that it may be present at low endemicity in almost all sub-Saharan African countries (5).

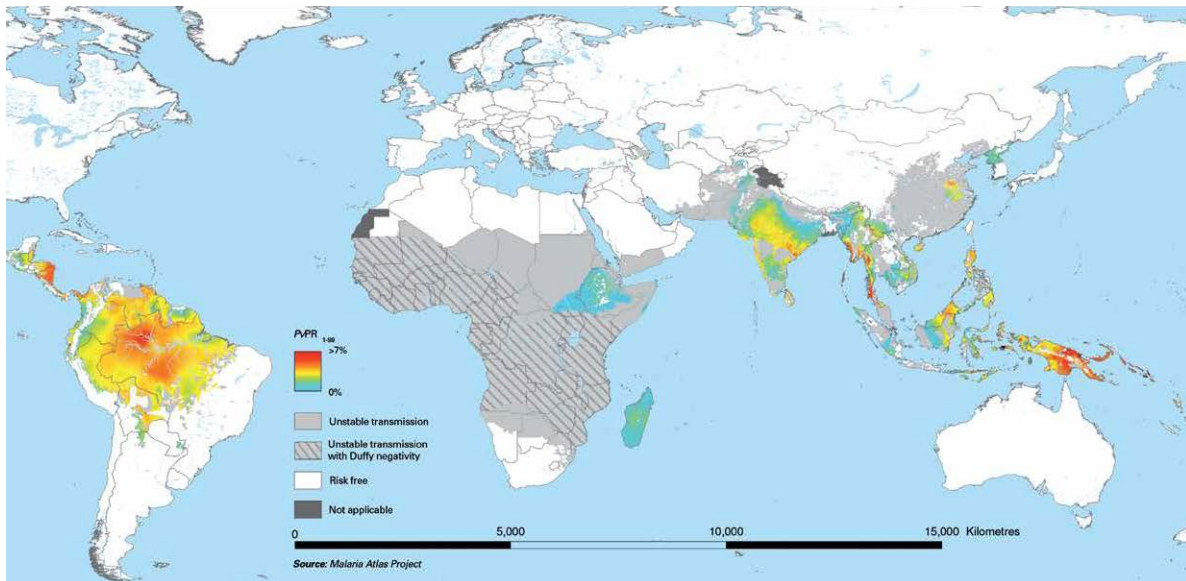
The contemporary distribution of *P. vivax* also reflects the success of malaria control efforts. The number of countries reporting locally acquired cases of *P. vivax* decreased from 58 in 2000 to 49 in 2013.

Fig. 1.1. The spatial distribution of *P. falciparum* and *P. vivax*

(a) Estimated annual mean *P. falciparum* parasite prevalence rate standardized to the 2–10 year age range (PfPR2–10), shown as a continuum of blue to red with a range from 0% to >70% (6).



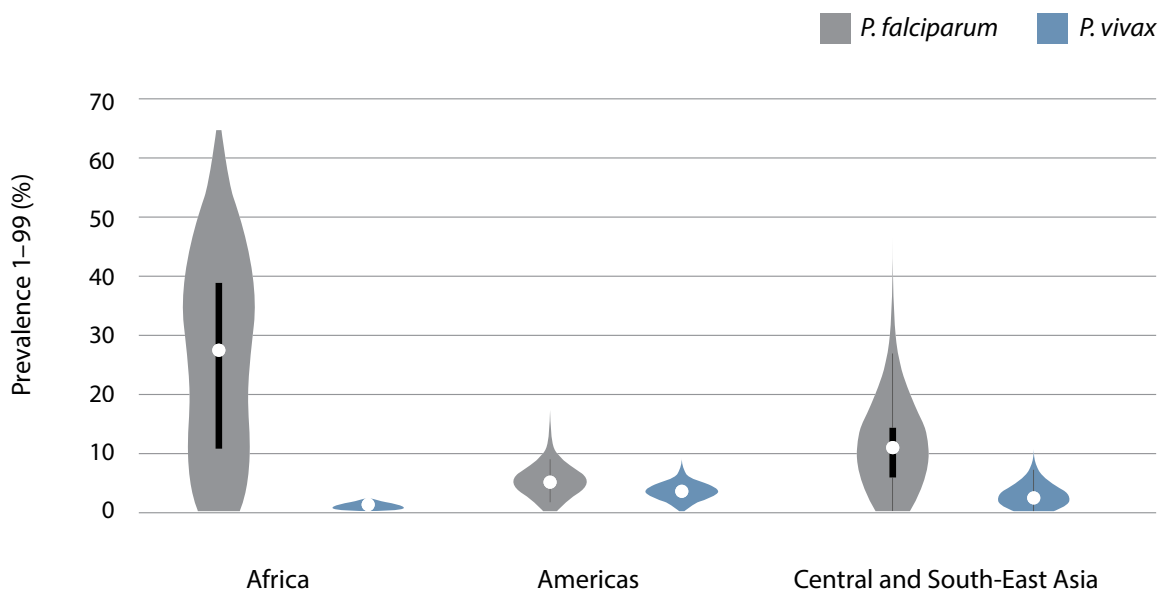
(b) Estimated annual mean *P. vivax* parasite prevalence rate standardized to the 1–99 year age range (PvPR1–99), shown as a spectrum of blue to red with a range from 0% to 7% (1).



**Note:** Areas in which Duffy negativity gene frequency is predicted to be >90% are shown in hatching. Dark grey areas are those with unstable transmission (annual reported cases <0.1/1000/year).

Globally, parasite prevalence rates of *P. vivax* generally range from 0% to 7% among affected populations (1). *P. vivax* parasite prevalence rates are generally lower than those estimated for *P. falciparum* (Fig. 1.2). However, at many locations globally, particularly outside of Africa, *P. vivax* is more common than *P. falciparum*.

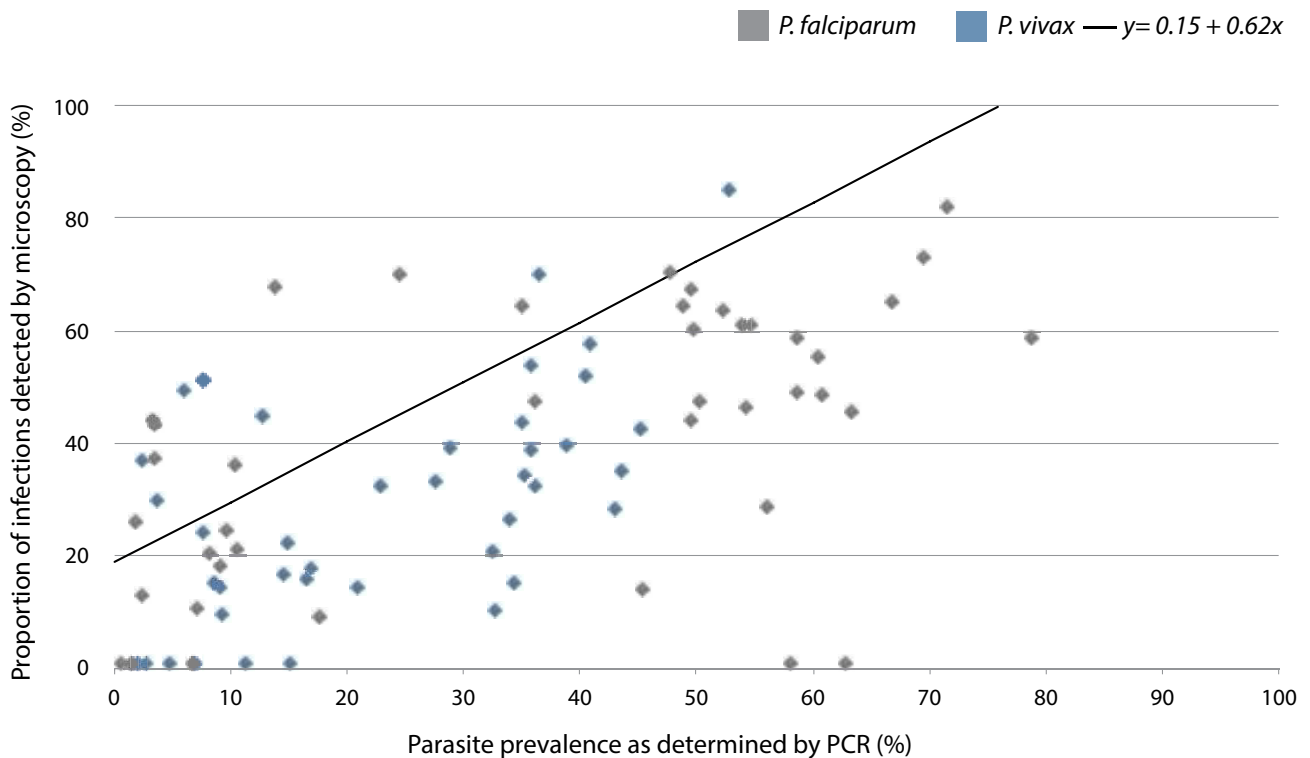
Fig. 1.2. Comparison of *P. falciparum* and *P. vivax* prevalence by geographical region



**Note:** The shaded areas show a kernel density plot of parasite prevalence within each geographical region. The width of the shaded areas represents the relative frequency of the various prevalence levels. The black central bar represents the interquartile range (IQR) and the white circles indicate the median values – from Battle et al. (7) – prevalence values, obtained from the mapped *P. falciparum* and *P. vivax* endemicity surfaces (1,6).

Population surveys that use microscopy or rapid diagnostic tests (RDTs) do not detect all infections. The proportion of infections detected by microscopy or RDTs diminishes with decreasing parasite prevalence (Fig. 1.3). The proportion of infections detected by microscopy appears to be similar for *P. falciparum* and *P. vivax* for equivalent infection rates. However, the proportion of missed infections overall may be higher for *P. vivax* than for *P. falciparum*, because parasite prevalence rates for *P. vivax* in populations are generally lower.

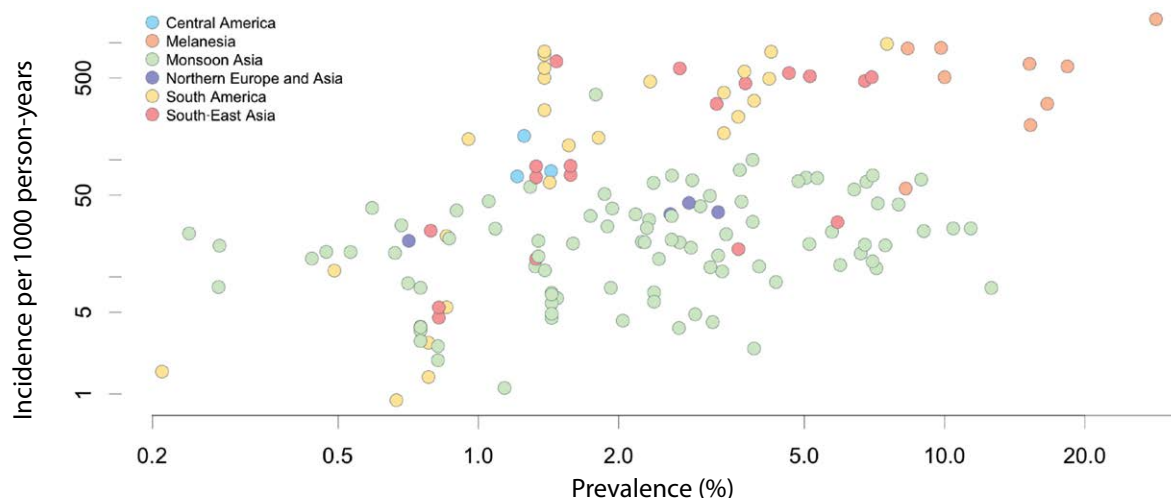
Fig. 1.3. The proportion of infections detected by microscopy versus the proportion detected by polymerase chain reactions (PCRs) for *P. falciparum* and *P. vivax*



Note: Derived from data in Okell et al. (8), supplementary information.

Only surveys where both *P. vivax* and *P. falciparum* were detected are shown. Of the 44 data points for each species, all but four were for all age groups; those four points considered children aged <5 years only.

There is a positive correlation between *P. vivax* malaria case incidence and *P. vivax* parasite prevalence. However, there is considerable variation in the rates of case incidence for any level of parasite prevalence (Fig. 1.4). This is partly explained by geographical differences in the relationship between incidence and prevalence.

Fig. 1.4. Relationship between *P. vivax* malaria case incidence and *P. vivax* parasite prevalence

Note: Scatterplot of 176 concurrently measured *P. vivax* incidence and prevalence records; from Battle et al (7).

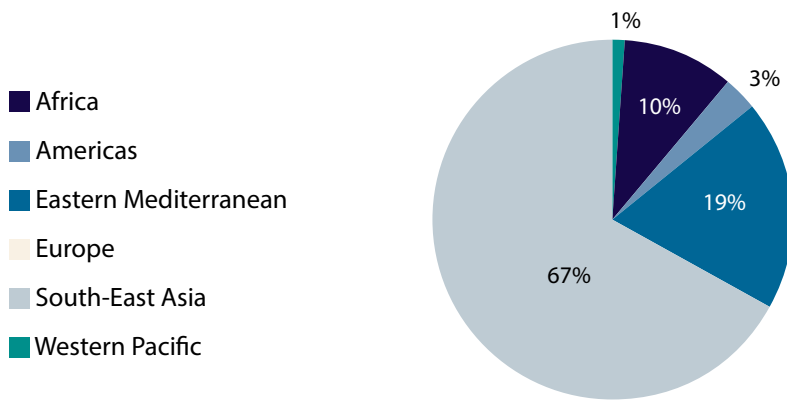
There were an estimated 15.8 million symptomatic cases of *P. vivax* malaria globally in 2013 (uncertainty range 11.9–22.0 million), of which two thirds occurred in the WHO South-East Asia Region (Table 1.1, Fig. 1.5a) (9). *P. vivax* malaria comprised 8% of all estimated malaria cases globally in 2013, but represented 47% of cases outside sub-Saharan Africa, and <1% of cases in the WHO African Region (Fig. 1.5b). These WHO estimates may underrepresent the true burden of *P. vivax* malaria, because clinical symptoms can sometimes occur without detectable parasitaemia, and because some mixed infections may be classified as *P. falciparum*, which tends to occur at higher parasite densities.

Table 1.1 Estimated symptomatic *P. vivax* malaria cases by WHO region in 2013 (9)

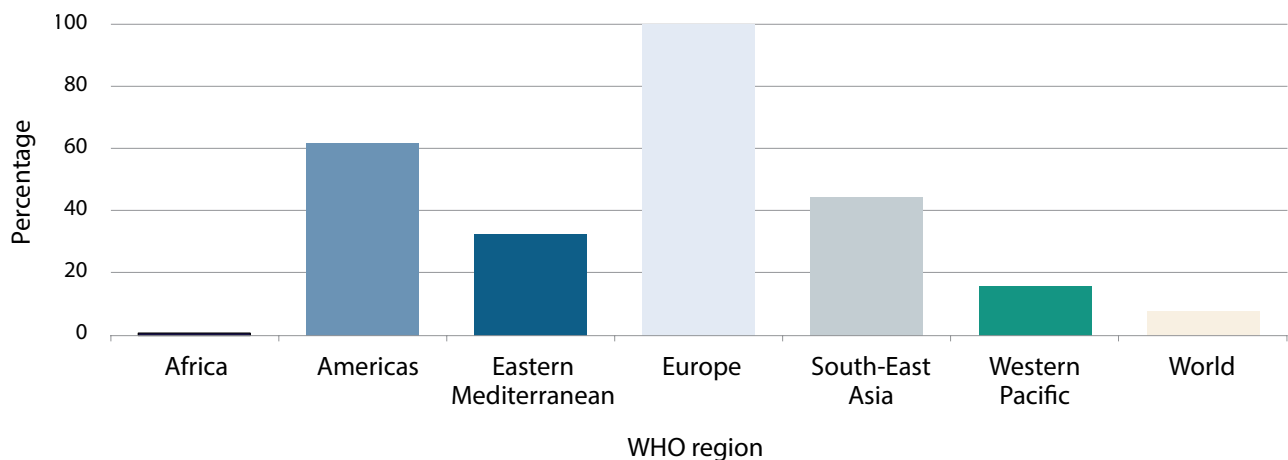
Region	Estimated <i>P. vivax</i> cases ('000s)			Estimated cases from all species ('000s)		
	Estimate	Lower	Upper	Estimate	Lower	Upper
Africa	1 400	1 000	1 700	163 000	90 000	243 000
Americas	500	400	600	700	600	900
Eastern Mediterranean	3 000	2 300	3 800	9 000	6 000	14 000
Europe	2	2	2	2	2	2
South-East Asia	11 000	7 000	17 000	24 000	17 000	36 000
Western Pacific	200	100	400	1 000	1 000	2 000
<b>World</b>	<b>15 800</b>	<b>11 900</b>	<b>22 000</b>	<b>198 000</b>	<b>124 000</b>	<b>283 000</b>
<b>Outside sub-Saharan Africa</b>	<b>14 200</b>	<b>10 200</b>	<b>20 300</b>	<b>30 000</b>	<b>22 400</b>	<b>41 500</b>

Fig. 1.5. Distribution of symptomatic *P. vivax* malaria cases by WHO region, 2013

(a) Percentage of global total of *P. vivax* cases occurring in each WHO region. (Source: WHO)

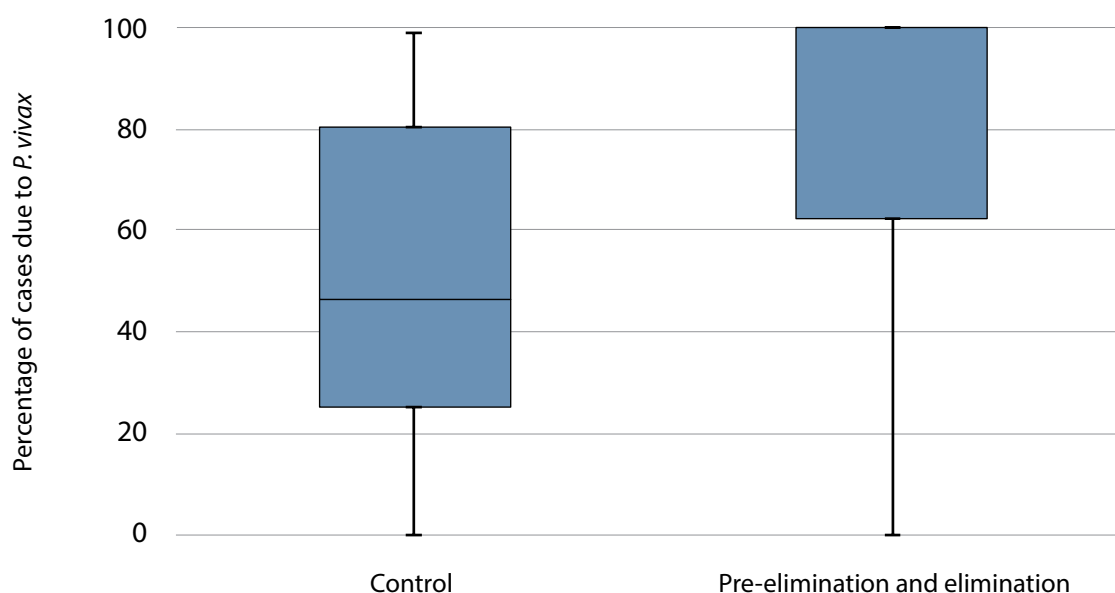


(b) Percentage of total cases (*P. vivax* plus *P. falciparum*) in each region due to *P. vivax*. (Source: WHO)



In areas where both species coexist, the incidence of *P. vivax* appears to decrease more slowly than that of *P. falciparum*. Thus, the proportion of all cases due to *P. vivax* increases as the incidence of malaria is reduced; *P. vivax* predominates in countries in the pre-elimination and elimination programme phases (Fig. 1.6).

Fig. 1.6. Percentage of cases due to *P. vivax* by programme phase outside of sub-Saharan Africa, 2013  
(Source: WHO)



In many areas where *P. vivax* is prevalent, malaria transmission rates are low and affected populations attain little immunity; thus, people of all ages are at risk of acquiring disease (10). However, in more highly endemic areas, immunity to *P. vivax* is acquired more rapidly than immunity to *P. falciparum*; consequently, *P. vivax* incidence and prevalence rates peak at an earlier age than in *P. falciparum* (11,12).

In many endemic countries, migrant populations (e.g. those who travel for seasonal work), the rural poor, and other marginalized groups have both the highest risks associated with *P. vivax* infection and disease, and the least access to effective preventive and curative services. Controlling and eliminating *P. vivax* malaria is therefore very much a development challenge – one that is inextricably linked with health system strengthening, poverty reduction and equity.

## 1.2 BIOLOGICAL CHARACTERISTICS AND CHALLENGES FOR CONTROL

*P. vivax* has several distinct biological characteristics that affect its geographical distribution and present challenges for its control and elimination (Table 1.2). *P. vivax* gametocytes – the sexual stages of the parasite that are infective to anopheline mosquitoes – appear in the blood of an infected person earlier in the course of an infection than they do in *P. falciparum* infection. Hence, many patients have sufficient gametocytaemia to allow transmission before an infection is diagnosed or treated (10,13,14).



Within the mosquito, *P. vivax* sporozoites develop faster (~10 days at 25 °C) than those of *P. falciparum* (12 days) and across wider temperature ranges, contributing to a broader geographical distribution (1,6,15). Thus, for *P. vivax*, vector control must be undertaken over a wider area, and methods that aim to reduce vector longevity may be less effective. In addition, the two main methods of vector control, insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS), are not always as effective against *P. vivax* as they are against *P. falciparum*. This is because some important vectors in *P. vivax* endemic areas have primarily early-biting, outdoor-feeding and outdoor-resting behaviours (2). The ability of vector control to reduce disease episodes is also reduced by the reservoir of infection in the human liver stage (hypnozoites), which can result in cases occurring without the bite of infectious vectors.

Table 1.2. Key characteristics of *P. vivax* malaria

Stage of <i>P. vivax</i>	Implications for control and elimination
<b>Life cycle in mosquito</b>	
Sporogony occurs at lower temperatures than for <i>P. falciparum</i> .	Broader geographical range and longer transmission season.
Shorter duration of sporogony than <i>P. falciparum</i> .	Interventions that aim at reducing vector longevity can be less effective for <i>P. vivax</i> .
Some important vectors in certain <i>P. vivax</i> endemic areas have primarily outdoor-feeding, outdoor-resting and early-biting behaviours.	Conventional preventive measures (ITNs and IRS) may provide less protection.
<b>Life cycle in human</b>	
<b>Human liver stage (hypnozoite)</b>	
<i>P. vivax</i> has a dormant hypnozoite stage that can cause multiple relapses after a primary infection, but is undetectable with current diagnostic methods.	Contributes to clinical case-load without the additional bite of an infective mosquito.
	Increases transmission potential ( $R_0$ ).
	Means that a potential source of reintroduction of <i>P. vivax</i> to receptive areas can escape detection.
	Makes it more difficult to identify measurable end-points of clinical trials and therapeutic efficacy tests because current diagnostic tests cannot differentiate between relapse, recrudescence and reinfection.
	Confounds measurement of the protective efficacy of vector control measures.
The latency period of <i>P. vivax</i> relapse varies according to parasite 'strain'.	Long latency relapse extends the geographical range of <i>P. vivax</i> in subtropical and temperate areas.
	Short latency relapses contribute to increased morbidity and increased transmission in tropical areas.
	The variation in latency and frequency of relapse may confound the clinical end-point in trials of schizontocidal drugs and radical therapy, and complicate the interpretation of surveillance data.
Recommended treatment for liver stage requires a treatment course of at least 14 days, and is contraindicated in pregnant or lactating women, and children aged <1 year, because of safety concerns.	Many patients do not adhere to a full, 14-day therapeutic course and thus suffer relapse episodes.
	Some of the most vulnerable population groups do not have access to anti-relapse therapy.

Table 1.2. Key characteristics of *P. vivax* malaria (continued)

Stage of <i>P. vivax</i>	Implications for control and elimination
<b>Life cycle in human (continued)</b>	
<b>Human blood stages</b>	
<b>Asexual stage</b>	
Preferentially infects reticulocytes (young red blood cells).	Repeated destruction of replacement blood cells causes chronic anaemia. Complicates efforts for laboratory culture of asexual parasites and inhibits discovery of new tools.
Blood-stage infections frequently occur at low parasite densities.	Infections often missed by routine microscopy and RDTs, leading to underestimation of the prevalence of infection, especially in low transmission areas and elimination settings. Despite lower parasite density, loss of red blood cells can result in anaemia as severe as in <i>P. falciparum</i> .
<b>Sexual stage</b>	
Appears early in the course of infection, often before overt symptoms arise.	Increases the risk of onward transmission.
<i>P. vivax</i> gametocytes are short-lived (3–4 days) in the human circulation ( <i>P. falciparum</i> mature gametocytes are viable for 10–14 days).	Effective schizonticidal treatment of a <i>P. vivax</i> infection both abolishes infectivity and reduces gametocyte carriage.
<b>Host genetics</b>	
Although effective against hypnozoites, primaquine induces haemolysis in individuals with hereditary G6PD enzyme deficiency.	Unknown G6PD status impedes the widespread use of primaquine because testing for G6PD deficiency is generally not available at point-of-care in endemic settings. Limited access to primaquine therapy results in increased morbidity and infectious reservoirs that prolong transmission risk, lengthen the elimination process and promote the reintroduction of <i>P. vivax</i> elsewhere.
Resistance to <i>P. vivax</i> infection by individuals with infection in the Duffy negative blood group is not absolute.	Duffy negative populations are also at risk of <i>P. vivax</i> infection; therefore, <i>P. vivax</i> epidemiology needs to be better defined in Africa.
Individuals with hereditary cytochrome P450 polymorphism (CYP2D6) may have reduced primaquine bioavailability because of the interaction between CYP2D6 and primaquine metabolism.	Complicates the interpretation of primaquine clinical trial data as CYP2D6 phenotypes may be mistaken for resistance.

**Note:** G6PD, glucose-6-phosphate dehydrogenase; IRS, indoor residual spraying; ITN, insecticide-treated mosquito net; RDT, rapid diagnostic test.

Sporozoites injected through the bite of anopheline mosquitoes into a human host migrate to the liver within minutes and develop into one of the following:

- A tissue schizont which, after thousands of mitotic divisions, releases merozoites into the bloodstream. The merozoites predominantly invade reticulocytes (immature red blood cells that typically comprise only 1–2% of a human's red blood cells) (Box 1.1). The preference for invading reticulocytes leads to low parasite densities that are more difficult to detect than *P. falciparum*, which invades blood cells of any age (12).
- A dormant liver stage, known as a hypnozoite, which can relapse weeks or months after a primary infection. The hypnozoite presents particular challenges for control and elimination of *P. vivax* malaria because it is undetectable using currently available diagnostic methods (and will therefore be missed in parasite prevalence surveys or in active case detection). It is not susceptible to drugs that target blood-stage forms of the parasite, and the only available drug, primaquine, causes the destruction of red blood cells (haemolysis) in people with a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) (16). G6PD deficiency affects about 400 million people in countries where malaria is endemic (Box 1.2).

There is variation in the proportion of infections that relapse (relapse rate), the time before relapse (latency), the interval between subsequent relapses, and the total number of relapses. In temperate and subtropical areas, *P. vivax* exhibits an extended period before relapse (~10 months), which may enable it to persist during winter months when environmental conditions are not suitable for transmission by *Anopheles* mosquitoes. The latency period is shorter in tropical areas but the time to relapse can vary; *P. vivax* in the Americas appears to have a longer latency than *P. vivax* in Asia and the Pacific (Fig. 1.7).

Where further relapses follow the first relapse, they often occur with short intervals, irrespective of the initial latency. In tropical areas, children often have 4–6 relapses at intervals of 4–6 weeks following an initial infection (17). Among Indonesian soldiers returning to Java from Papua who were not provided with primaquine therapy, 78% suffered a relapse, with an average of 2.7 relapses per person per year (18).

Relapses may contribute to increasing severity of anaemia, but also a more rapid acquisition of immunity, despite lower blood parasite densities. Thus, the rate and the number of symptomatic relapses may decline with age, through the acquisition of immunity (19).

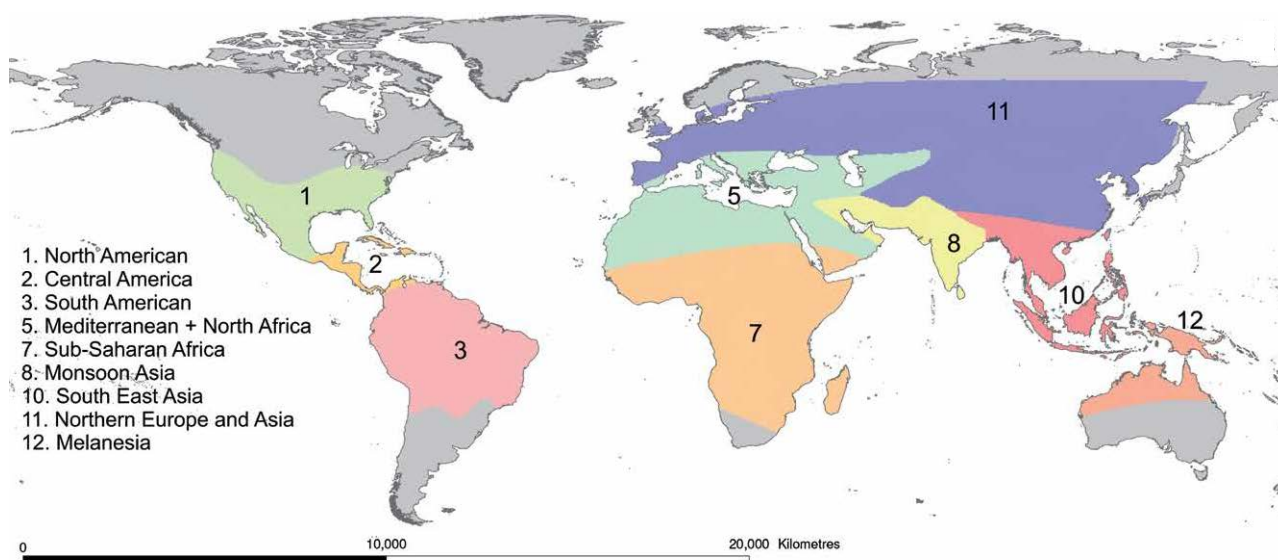
The mechanisms that trigger relapse are not fully understood. One possibility is that the relapse may occur during months when environmental conditions are suitable for transmission by *Anopheles* mosquitoes, as suggested by the longer relapse intervals in temperate areas. Hypnozoites also appear to be activated by a febrile illness, such as that caused by another malaria episode

(which may also indicate suitable transmission conditions) (19,20). Where both *P. falciparum* and *P. vivax* occur, an episode of *P. falciparum* malaria is frequently followed by episodes of *P. vivax* malaria (21,22).

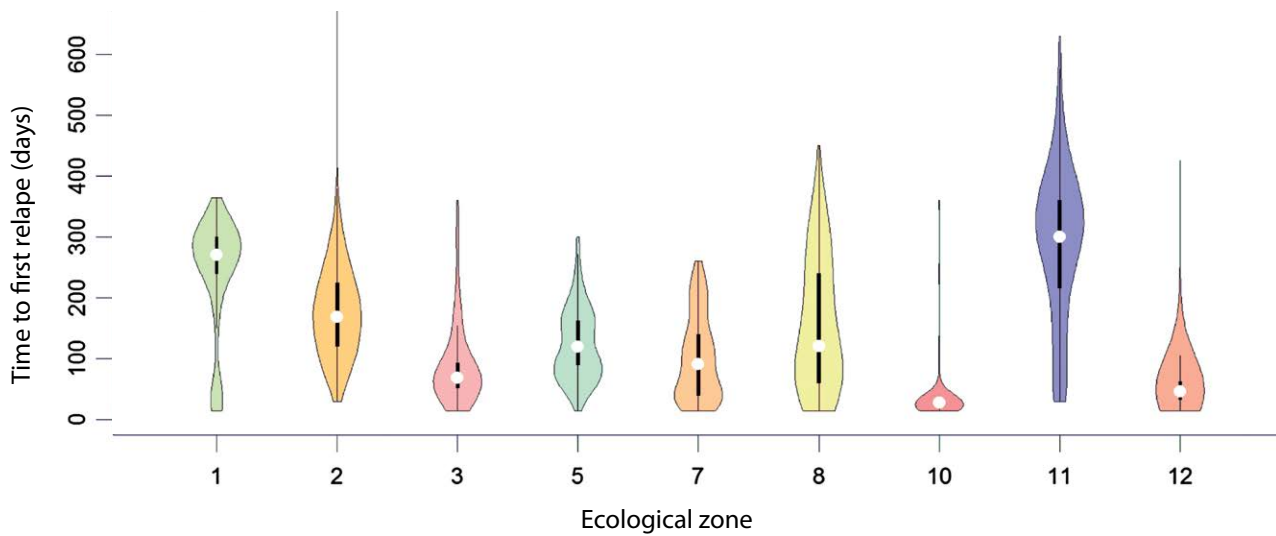
Few studies have examined the relative contributions of new mosquito inoculations and relapses to the overall force of blood-stage infection. Investigations in a highly endemic area of Papua New Guinea, where parasites have a short relapse frequency of about a month, found that relapses caused about 50% of blood-stage infections and more than 60% of clinical episodes in the first 3 months following treatment (23). The proportion of blood-stage infections that arise from relapses may vary according to relapse patterns and infection rates in the community. However, it is evident that liver stages can contribute significantly to disease burden, even in areas of high transmission, and malaria control programmes may need to invest significant resources in resolving hypnozoite infections, as well as in preventing new mosquito infections.

Fig. 1.7. Geographical variation in time to first *P. vivax* relapse

(a) Geographical zones used by Battle et al. (24) to describe the time to first relapse.

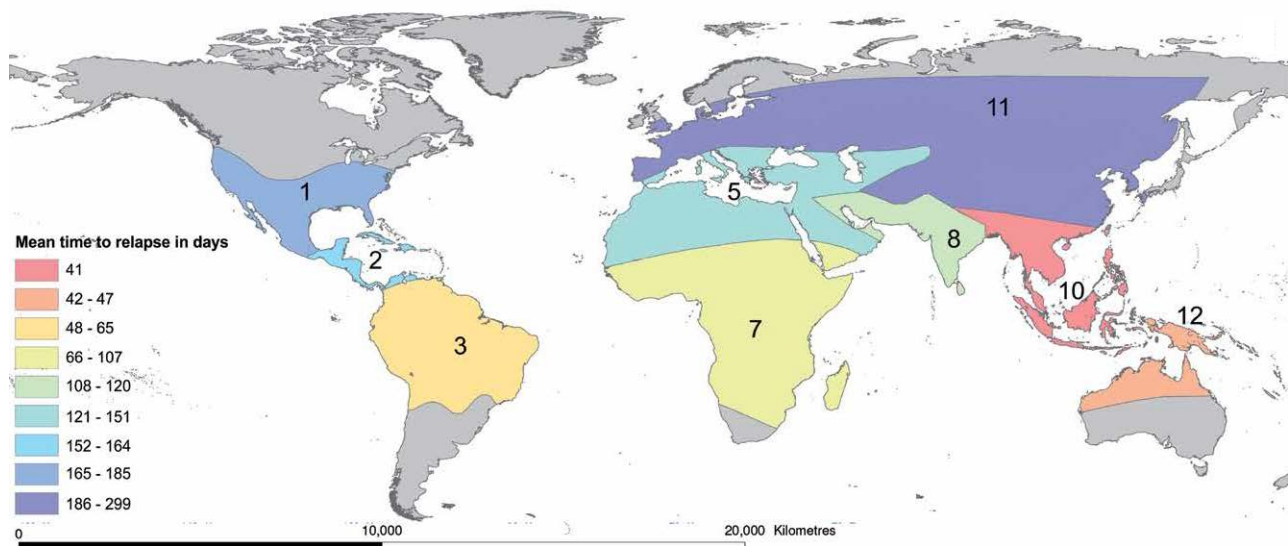


(b) A kernel density plot of the time to relapse within each geographical zone, Battle et al. (24)

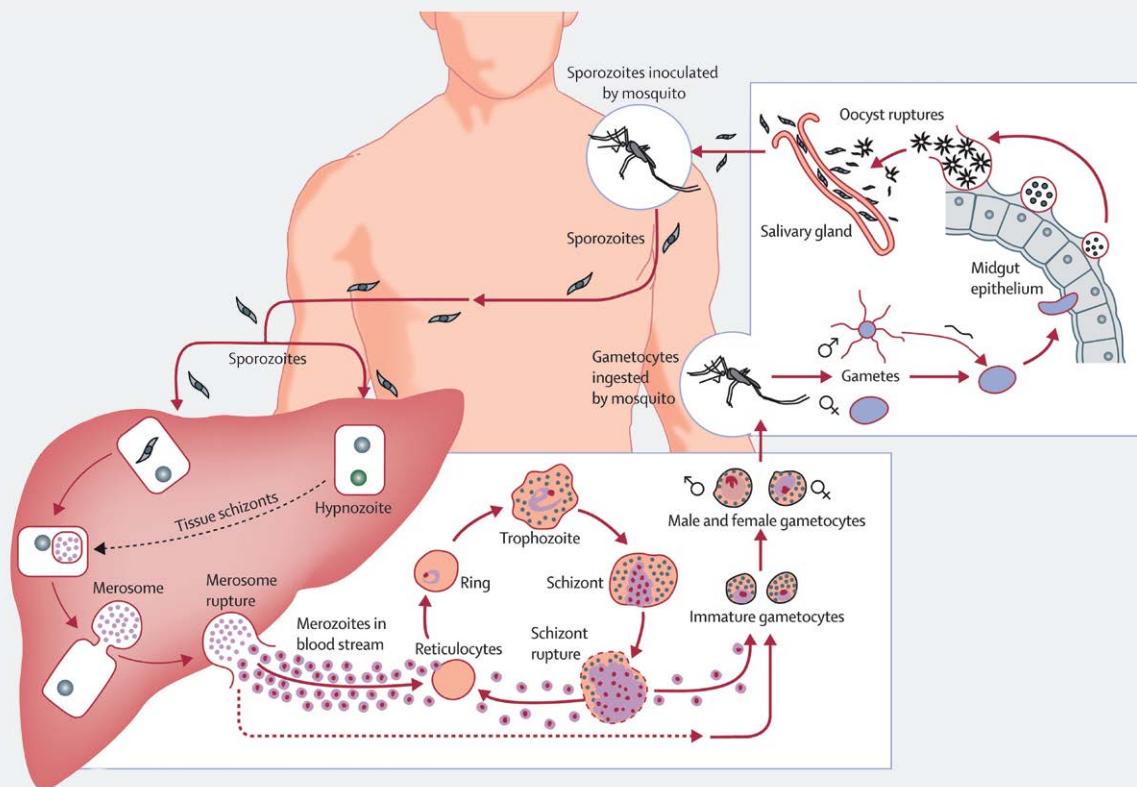


**Note:** The black central bar represents the IQR and the white circles indicate the median values. The maximum value for zone 2 extends beyond the plot. Violin plots are coloured areas according to zoogeographical zone in (a).

(c) Predicted mean time to relapse in days, Battle et al. (24)



## Box 1.1. Life cycle *P. vivax*



Source: Abstracted from Mueller et al. (2009) (12)

Sporozoites inoculated into the skin by female *Anopheles* mosquitoes reach the bloodstream and enter hepatocytes in the liver. Here *P. vivax* can either differentiate into tissue schizonts that, after thousands of mitotic replications in individual hepatocytes, release merozoites into the bloodstream, or differentiate into a dormant stage called a hypnozoite that, upon activation after weeks, months or years, causes clinical relapse. The merosome featured here has, so far, only been described in malaria in rodents but is predicted to be present in late-stage liver infections with *P. vivax*. The merozoites of *P. vivax* mainly invade reticulocytes. Some *P. vivax* parasites can differentiate into mature gametocytes, which are infective to anopheline mosquitoes before a clinical infection and illness develops. On uptake in the blood meal of *Anopheles* mosquitoes, gametocytes begin the sexual cycle, which includes release of the male and female gametes, fertilization, and formation of a motile ookinete that crosses the midgut epithelium of the mosquito. Differentiation into a new replicative form known as the oocyst, release of sporozoites, migration and invasion of the salivary glands ends this complex life cycle. In all, the parasite undergoes more than 10 stages of cellular differentiation and invades at least four types of cells within two different hosts.



## Box 1.2. G6PD deficiency

G6PD deficiency is an X-linked genetic disorder with an estimated allele frequency of 8.0% (IQR: 7.4–8.8%) among countries in which malaria is endemic (25).

### Estimated G6PD-deficient population by WHO region

WHO region	G6PDd allele frequency <sup>1</sup>	G6PDd males (000's) <sup>2</sup>	G6PDd females (000's) <sup>3</sup>	Homozygous females (000's) <sup>4</sup>
Africa	12.1	53 267	33 792	8.7
Americas	2.6	9 081	5 225	0.4
Eastern Mediterranean	9.0	27 620	16 536	3.6
Europe	2.9	2 080	1 149	0.1
South-East Asia	5.8	68 588	38 525	5.2
Western Pacific	9.2	41 793	23 250	2.2
<b>World</b>	<b>8.0</b>	<b>202 428</b>	<b>118 476</b>	<b>20.3</b>

1. Average of median estimate of G6PD deficiency allele frequency in countries within region

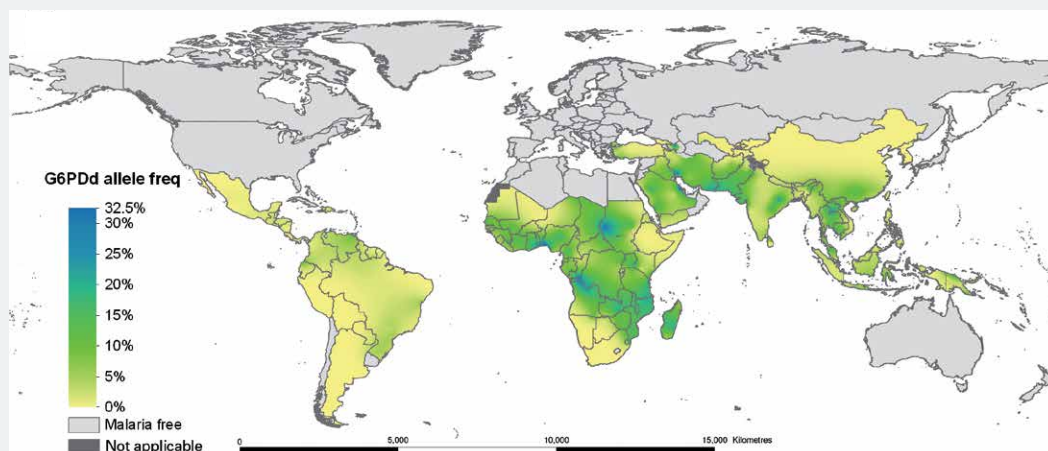
2. Sum of median estimated number of males with G6PD deficiency in malaria-endemic countries

3. Sum of median estimated number of females with G6PD deficiency in malaria-endemic countries

4. Sum of median estimated number of females homozygous for G6PD deficiency in malaria-endemic countries

The highest allele frequencies have been estimated in sub-Saharan Africa and the Arabian peninsula, peaking at 32.5% (as shown in the map below). Allele frequencies are generally lower across central Asia and South-East Asia, rarely exceeding 20%, but most G6PD-deficient individuals are from Asian countries (because of the larger population sizes in those countries). Lowest allele frequencies are estimated in the Americas ( $\leq 1\%$ ), with G6PD deficiency virtually absent from Argentina, Bolivia, Costa Rica, northern Mexico and Peru.

### Estimated G6PD deficiency allele frequencies

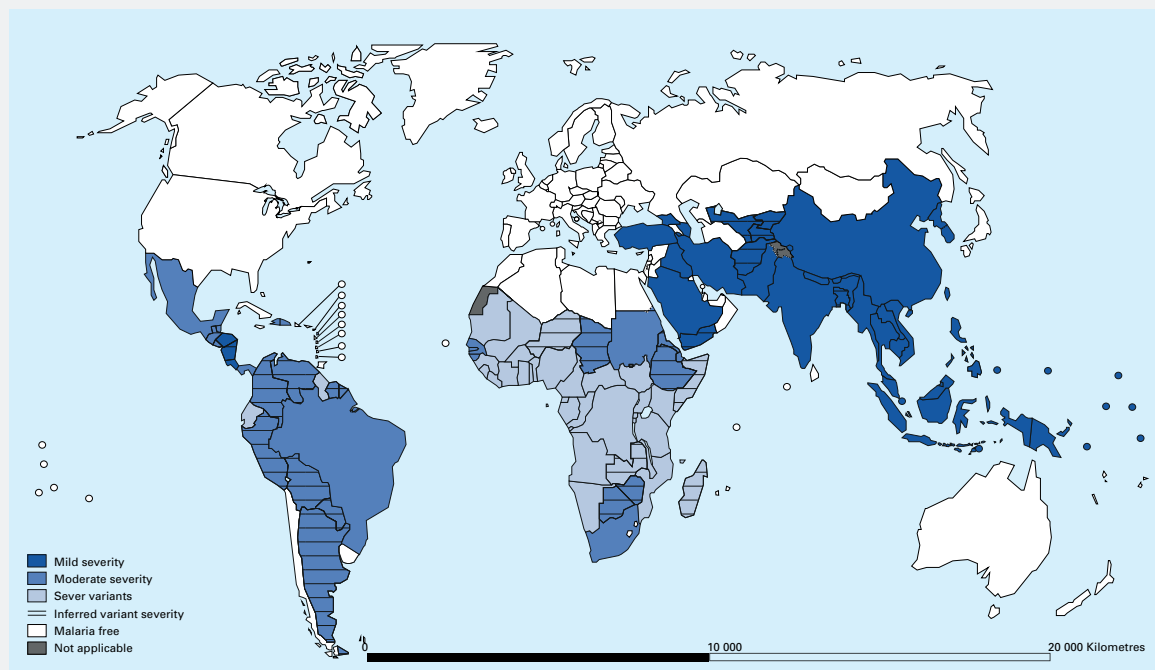


Source: Howes et al. (2013)

## Box 1.2. G6PD deficiency (continued)

Over 180 G6PD gene variants confer differing degrees of enzyme activity deficiency in red blood cells. These variants have distinct geographical distributions (25).

### Severity of G6PD deficiency

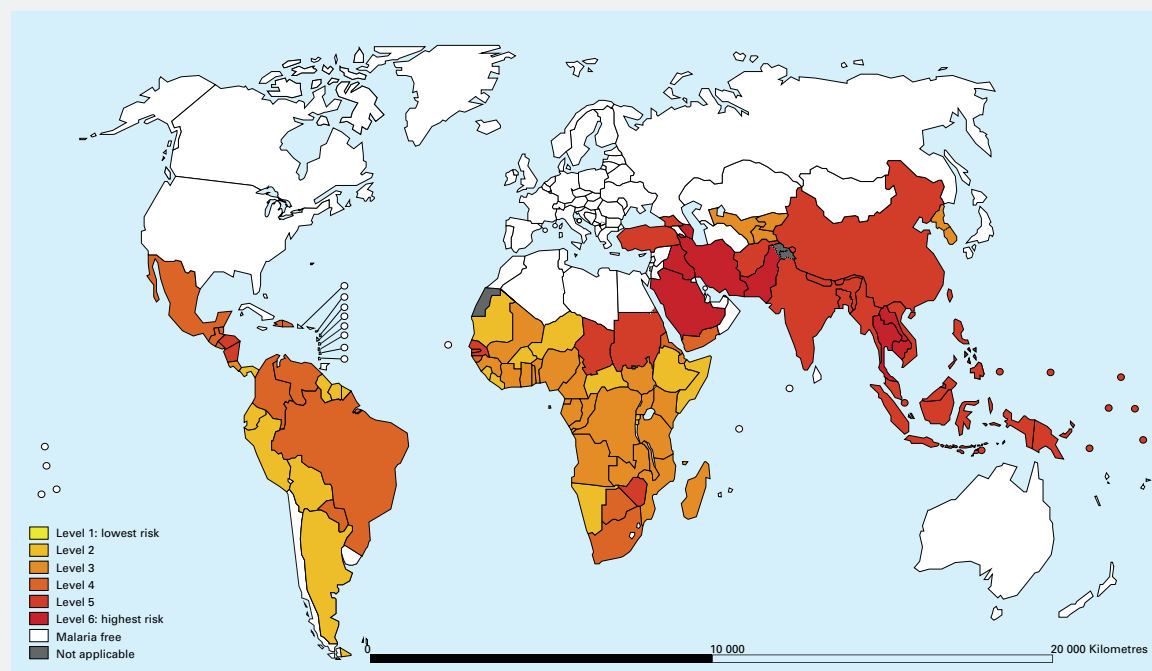


Source: Howes et al. (2013) (25)



## Box 1.2. G6PD deficiency (continued)

### Index of risk for G6PD deficiency accounting for the prevalence of G6PD deficiency by country and the severity of variants



Source: Howes et al. (2013) (25)

G6PDd risk index		Variant severity		
		Class III only	Class II uncommon	Class II common
National G6Pd prevalence	Rare: $\leq 1\%$	Level 1 (n = 1)	Level 2 (n = 7)	Level 3 (n = 7)
	Common: $>1-10\%$	Level 2 (n = 13)	Level 4 (n = 15)	Level 5 (n = 20)
	High: $>10\%$	Level 3 (n = 20)	Level 5 (n = 5)	Level 6 (n = 11)

Because the disorder is X-linked, it is either wholly absent or present (hemizygous) in males, whereas in females it may be absent, homozygous or heterozygous. Homozygous deficiency in females is relatively rare, but heterozygosity is common and results in two distinct populations of red blood cells expressing deficient and normal G6PD levels (lyonization). The overall level of G6PD activity in female heterozygotes can vary from near normal to severely deficient, depending on the proportion of deficient red cells. Therefore, only a proportion of heterozygous females will be diagnosed as phenotypically G6PD deficient.

## 1.3 SPECTRUM OF DISEASE

The spectrum of disease associated with *P. vivax* infection ranges from asymptomatic parasitaemia, to uncomplicated febrile illness, to severe and fatal malaria (26,27). *P. vivax* malaria can be difficult to diagnose because:

- it can occur at low parasite densities, below microscopically detectable levels (12); and
- parasites may also be confined to spleen and bone marrow, so are not detected with current diagnostic tools, and a large parasite biomass, which may be associated with severe disease, may be hidden.

In non-immune individuals, *P. vivax* malaria gives rise to a well-defined paroxysmal fever with a periodicity of 24 or 48 hours, usually preceded by chills with rigour. Other symptoms and signs include headache, anorexia, myalgia, abdominal pain, cough, diarrhoea, restlessness, delirium and anaemia. The pattern of fever or other clinical features cannot be used to distinguish *P. vivax* from *P. falciparum* malaria or other causes of febrile illness; a parasitological or molecular test is essential for diagnosis.

*P. vivax* malaria causes severe anaemia, particularly in infancy and in prolonged, untreated or recurrent infections. It has also been associated with malnutrition in childhood, and with spontaneous abortion and intrauterine growth retardation in pregnant women. Acute *P. vivax* disease has also been associated with severe malaria and death. The spectrum of reported severe *P. vivax* syndromes is similar to that seen with *P. falciparum*; however, the relative frequency and significance of each syndrome differs. Clinical manifestations of severe *P. vivax* malaria include severe anaemia (<5 mg haemoglobin/dL), thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock. Coma and other neurological complications are rare, as is the case with severe *P. falciparum* malaria outside of Africa. Metabolic acidosis and coma occur less frequently in severe *P. vivax* malaria. As with *P. falciparum*, comorbidities are important contributors to severe complications of *P. vivax* infection.

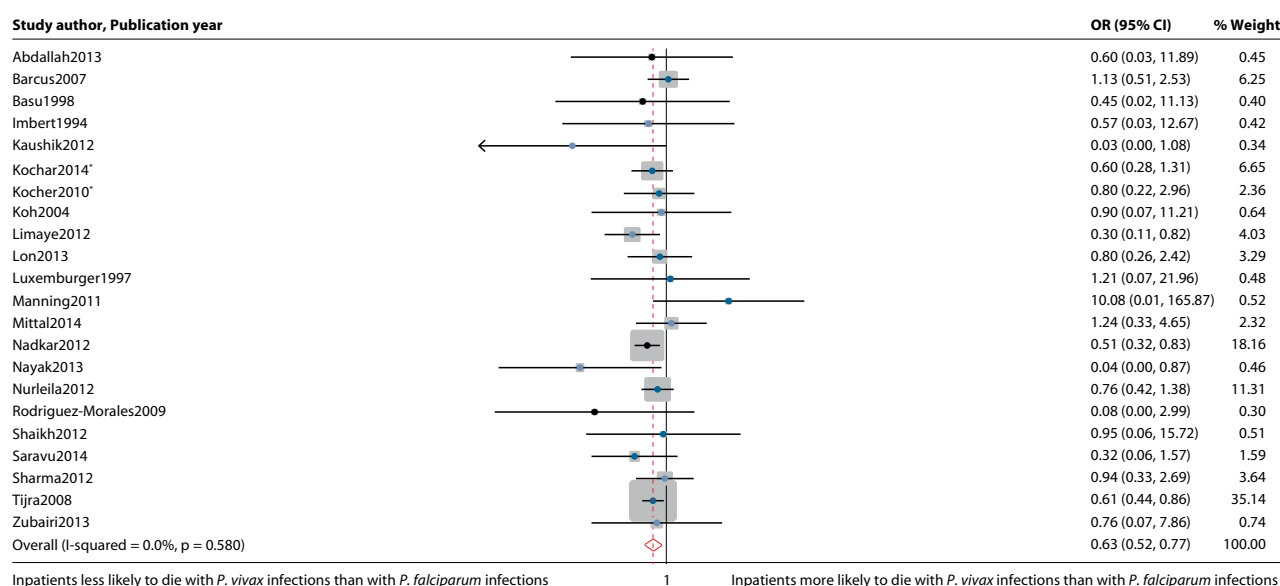
Severe *P. vivax* malaria is characterized by lower blood-stage parasitaemia than is observed in severe cases of falciparum malaria. Unlike *P. falciparum* infection, *P. vivax*-associated pathogenesis is not associated with significant microvascular obstruction of vital organs. Nevertheless, low blood-stage parasitaemia may mask parasite sequestration outside the vascular system (e.g. in the spleen), which may explain how severe syndromes can develop at relatively low levels of parasitaemia. The severity of anaemia observed with low parasitaemia may also be due to the cumulative impact of multiple *P. vivax* relapses.

## 1.4 RISK OF SEVERE DISEASE AND DEATH

### 1.4.1 Risk among patients admitted

The risk of fatality subsequent to severe *P. vivax* disease was summarized in 16 hospital-based studies by Baird (28), of which 10 were retrospective and six prospective. Using this database and subsequent studies, the median case fatality rate (CFR) among inpatients with severe disease, as reported in 43 studies with documented species-specific numbers of severe disease and death, was 3.1% (IQR: 0.0–9.3%) (Fig. 1.8). Five of these studies were able to rule out the possibility of a mixed infection with *P. falciparum* using polymerase chain reaction (PCR). The median CFR from severe *P. falciparum* disease where it occurred and was reported among 22 of the same hospitals was 11.6% (IQR: 4.9–22.8%). The odds of an inpatient dying from a *P. vivax* malaria infection were just under two thirds that of those with severe *P. falciparum* infections (odds ratio [OR]: 0.63, 95% confidence interval [CI]: 0.52–0.77, Fig. 1.8). This ratio is unlikely to reflect the relative risks of dying among patients who acquire malaria in the community, since it is generally expected that the risk of developing severe disease for *P. vivax* malaria, and being admitted, is less than that for *P. falciparum* malaria. Nonetheless, the studies do show that severe cases and deaths due to *P. vivax* can occur in all endemic regions.

Fig. 1.8. Case fatality from *P. vivax* compared to *P. falciparum* infections



#### Notes:

- Weights are from random effects analysis.
- CFRs from 22 studies are shown in relation to *P. vivax* endemicity. An asterisk denotes studies that used PCR to rule out *P. falciparum* malaria as a contributory factor.
- Hospitals were defined as located in areas of stable (dark blue areas, where *P. vivax* annual parasite incidence (PvAPI) is  $\geq 0.1/1000/\text{year}$ ), unstable (light blue areas, where *PvAPI*  $< 0.1/1000/\text{year}$ ) or no risk (black, where *PvAPI* =  $0/1000/\text{year}$ ) of transmission by extracting the values from the Malaria Atlas Project's global surface of the estimated limits of *P. vivax* transmission (1) at their point locations.

### 1.4.2 Risk in relation to total number of *P. vivax* cases

The population-attributable risks of severe disease or death from *P. vivax* and *P. falciparum* malaria have rarely been estimated or compared. A prospective population-based study in Papua, Indonesia, undertaken in 2004–2009, documented an estimated annual total of 294 000 *P. vivax* cases (29). The risk of death from *P. vivax* malaria was estimated as ranging from 0.012% to 0.063%, depending on the extent to which health-facility data were considered to capture all malaria deaths. The risk of severe disease can be estimated as ranging from 0.29% to 0.82%, using similar methodology. Equivalent risks among an estimated 473 000 clinical episodes of *P. falciparum* were 0.042–0.12% for mortality and 0.53–1.51% for severe disease (i.e. an OR of 0.52 for death and of 0.54 for severe disease).

Routine case and death reporting is incomplete in many malaria-endemic countries. However, mortality surveillance systems in Brazil, Colombia and Venezuela capture 80% or more of total deaths. When compared to the number of reported cases, the mean CFR for deaths ranged from 0.012% to 0.18% between 2000 and 2012 (Table 1.3). The CFR for *P. falciparum* malaria in these countries ranged from 0.077% to 0.35%, with the odds of dying of *P. vivax* infection from 0.035 to 0.14 those of dying of *P. falciparum* infection.

Table 1.3 Case fatality rates calculated from routine case and death reporting

Country	<i>P. vivax</i>			<i>P. falciparum</i>			Odds Ratio (95% CI)
	Estimate (%)	Lower (%)	Upper (%)	Estimate (%)	Lower (%)	Upper (%)	
Brazil	0.016	0.012	0.021	0.087	0.082	0.130	0.140 (0.0821–0.2390)
Colombia	0.012	0.005	0.023	0.077	0.054	0.109	0.145 (0.0787–0.2693)
Venezuela	0.018	0.009	0.028	0.346	0.198	0.494	0.035 (0.0214–0.0562)

**Source:** Total number of all-cause deaths as estimated by the United Nations Population Division (<http://esa.un.org/unpd/wpp/Excel-Data/mortality.htm>, accessed 24 June 2015), cause-specific number of deaths extracted from the WHO mortality database ([http://apps.who.int/healthinfo/statistics/mortality/causeofdeath\\_query/start.php](http://apps.who.int/healthinfo/statistics/mortality/causeofdeath_query/start.php), accessed June 2015), cause-specific mortality data for Venezuela for years 2010–2012 extracted from the Venezuela Ministry of Health website (<http://www.mpps.gob.ve/>, accessed 24 June 2015), and species-specific number of cases as estimated by WHO (World Malaria Report 2014).

Data on *P. vivax* morbidity and mortality recorded in travellers from non-endemic countries revealed CFRs ranging from 0% to 0.087% (weighted average 0.059%). If case notification in non-endemic countries is considered to be reasonably complete, these data can be considered analogous to a population-based study, although the level of risk to which patients have been exposed is heterogeneous (because the countries they travel to differ).

Most travellers are expected to have little prior exposure, and therefore little immunity, to malaria. The odds of dying among *P. vivax* cases are about 10% of that for *P. falciparum* cases (OR: 0.10; 95% CI: 0.06–0.17) among travellers from non-endemic countries.

This brief analysis reveals a fourfold difference in CFRs: from 0.012% in Colombia to 0.063% in Indonesia. The variation may be due to the difficulties in estimating CFRs; alternatively, it may reflect differences between study populations in transmission intensity, relapse rates, initial health status and access to services. If CFRs lie between the extremes observed here then, based on the 15.8 million estimated *P. vivax* cases in 2013, the total number of malaria deaths that could be attributed to *P. vivax* in 2013 would lie between 1900 and 10 000 globally. The number of *P. vivax* deaths outside sub-Saharan Africa would lie between 1700 and 8900 (i.e. between 3.5% and 16% of the total number of deaths outside sub-Saharan Africa). Evidently, *P. vivax* malaria represents a significant public health problem outside Africa. A clearer picture of severe *P. vivax* malaria is emerging, but further study is required to refine existing knowledge of the spectrum of syndromes and their risks of severe morbidity and mortality.

## 2. STRATEGIES FOR THE CONTROL AND ELIMINATION OF *P. VIVAX* MALARIA

The basic principles for controlling *P. vivax* malaria are the same as those for *P. falciparum* malaria:

- reduce transmission by the mosquito vector from humans to mosquitoes and from mosquitoes to humans through vector control;
- prevent establishment of infections in human beings through chemoprevention; and
- rapidly detect, diagnose and treat infections (and ultimately eliminate infections in the human population) through provision of accessible diagnostic testing and treatment services.

Many of the interventions used for controlling malaria are not as effective against *P. vivax* as they are against *P. falciparum*. Thus, in areas where these species coexist, the incidence of *P. falciparum* has been seen to decrease more rapidly than *P. vivax*, which may then persist as the principal cause of malaria and pose the main challenge to eliminating malaria. Successful control and elimination of *P. vivax* malaria therefore calls for specific, additional interventions, notably against the liver stage of the parasite. This section summarizes the available options for control and elimination of *P. vivax* malaria, particular challenges faced, potential opportunities and specific recommendations from WHO.

### 2.1 VECTOR CONTROL

#### 2.1.1 PRINCIPLES

Vector control is critical in reducing transmission of *P. vivax* malaria, because the *P. vivax* gametocytes often appear before a patient develops symptoms and seeks treatment. Thus, transmission can continue despite the best efforts at prompt diagnosis and treatment of cases.

It is particularly important to prevent infections in pregnant or lactating women and infants, because these populations cannot be treated with primaquine, and are thus more liable to relapse and to experience repeated episodes of malaria after the initial (primary) infection.

### 2.1.2 CHALLENGES

- *P. vivax* gametocytes appear in the blood of an infected person early in the course of an infection; hence, transmission may occur before an infection is diagnosed or treated.
- *P. vivax* can undergo sporogony in a wide range of anopheline species at subtropical temperatures (16 °C for *P. vivax* versus 18 °C for *P. falciparum*), meaning that the geographical range over which vector control must be undertaken is wider for *P. vivax* than for *P. falciparum*.
- Sporogony of *P. vivax* in the vector is shorter (~10 days at 25 °C) than for *P. falciparum* (12 days); thus, control methods that aim to reduce vector longevity may prove to be less effective for *P. vivax*.
- In many areas of low and unstable transmission outside of Africa where *P. vivax* is common and often predominates, many vectors can bite early in the evening, obtain blood meals outdoors and rest outdoors. Therefore, ITNs and IRS – which are most effective against the anopheline mosquitoes that bite later in the evening, and rest and feed indoors – may prove less effective in reducing *P. vivax* transmission than in many settings in Africa where *P. falciparum* prevails.
- Transmission reduction is made more challenging for *P. vivax* because, after a single infectious bite, the reservoir of latent infection (the hypnozoite) can generate multiple recurrent blood-stage infections, markedly increasing the potential for both illness and onward transmission from a single sporozoite inoculation.
- Relapse in *P. vivax* is a confounding factor in the evaluation of the effects of vector control on transmission reduction. This is because cases occur even when individuals use appropriate personal protection methods or when vector control is widely implemented.

### 2.1.3 OPPORTUNITIES

Although transmission can occur before treatment commences, most schizontocidal drugs are active against *P. vivax* gametocytes, in contrast to the situation with *P. falciparum*. Also, *P. vivax* gametocytes are short-lived; thus, vector-control programmes may be aided by effective case detection and treatment. Moreover, the application of primaquine therapy against relapse kills any gametocytes that might persist after cessation of blood schizontocidal therapy.

Several innovative ideas have emerged to address the challenge of outdoor transmission. The use of insecticide-treated hammock nets or long-lasting insecticidal hammocks has been shown to have protective efficacy against *P. vivax* and *P. falciparum* in South America (30) and in the Mekong region (31,32). In parts of Asia, the use of topical repellents, treated materials and treated clothing has been effective, especially when these measures are used in combination (33,34); however, other studies have found uncertainty about protective effects (32,35). In Ethiopia, the combined use of ITNs and repellents was found to be protective against both *P. falciparum* and *P. vivax* (36).

Habitat manipulation, larviciding and biological control (using predatory fish, entomo-pathogens and parasites) may help to reduce malaria transmission (37). However, larval source reduction and management is only applicable in settings where mosquito breeding sites are few, fixed and findable.

In some settings, application of insecticides (sponging or spraying) on cattle may be beneficial in reducing vector density (38,39). New tools such as insecticide-treated wall liners and insecticide-incorporated plastic sheeting have been tested, but their specific protective effect against *P. vivax* has yet to be demonstrated (40,41).

## 2.1.4 RECOMMENDATIONS

- Ensure high and sustained coverage with appropriate, environmentally safe vector-control strategies according to local epidemiology and vector behaviours (e.g. indoor or outdoor biting). WHO recommendations regarding ITNs, IRS and larval control are summarized in the following documents:
  - *Insecticide-treated mosquito nets: A WHO position statement* (42);
  - *Indoor residual spraying: An operational manual for IRS for malaria transmission, control and elimination* (43);
  - *Guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets* (44); and
  - *Larval source management – a supplementary measure for malaria vector control: An operational manual* (45).
- In the absence of a formal WHO recommendation on the use of complementary tools, local vector bionomics and disease transmission dynamics should be taken into account to assess which tools may be effective. The greatest impact on vector control is likely to come from a mix of different strategies targeting different life stages, based on local vector abundance, ecology and behaviour.
- Special attention should be paid to ensuring that vector-control measures are used by pregnant and lactating women, and children aged <1 year. Migrant populations (including nomadic groups, seasonal workers, internally displaced people, refugees and military forces) also represent high-risk groups that require special attention, especially if they are non-immune entrants to malaria-endemic areas or, conversely, if they are carriers of disease into malaria-receptive areas.



- Vector surveillance should seek to collect information on the presence, abundance and behaviour of known or putative vector species, in order to develop and monitor the strategies for vector control and personal protection. Accurate identification of vector species by means of morphological or molecular methods is critical to this effort. Breeding sites and risk areas should be mapped, and susceptibility patterns of vectors to insecticides should be monitored. It may be helpful to monitor environmental parameters, especially meteorological features that influence transmission, such as rainfall and temperature.
- To maintain malaria-free status, vector-surveillance activities should continue after malaria elimination has taken place, to monitor the receptivity of areas (to identify remaining vector breeding sites and assess the risk of outbreaks).
- Strategies for malaria health education and public awareness, and for community inclusion in planning and implementation, will influence uptake and acceptance of locally applicable vector control and personal protection tools. An understanding of local human behaviour patterns will allow adaptation of strategies and application of tools that are both socially acceptable and effective (e.g. devising tools for overcoming the risk associated with greater numbers of people sleeping outside during warmer months, who are thus unprotected against vector attacks).

## 2.2 CHEMOPREVENTION

### 2.2.1 PRINCIPLES

The use of preventive chemotherapy of *P. vivax* malaria may take the following forms:

- Chloroquine prophylaxis given to prevent *P. vivax* malaria in pregnant women in endemic areas where transmission is high.
- Presumptive treatment for *P. vivax* with a full therapeutic course of primaquine to the whole population at risk, to prevent relapses from the hypnozoite reservoir. This mass primaquine preventive treatment (MPPT) has been applied in areas where transmission is seasonal, to prevent onward transmission from relapses (46). Such “spring treatment” is generally applied to remaining active foci of *P. vivax* transmission in elimination settings. Because there are no diagnostic tests for hypnozoites, it is not possible to screen patients for hypnozoites before treatment. This differs from primaquine radical cure, which is reserved for *P. vivax* confirmed cases.

- Chemoprophylaxis focusing on preventing transmission from travellers, migrant workers or occupational groups that are exposed to malaria and return to areas that are eliminating or have eliminated malaria. Travellers take primaquine throughout the duration of their stay in an endemic area and 1 week after return (causal prophylaxis).
- Presumptive anti-relapse therapy (PART). Travellers who have taken chemoprophylaxis during travel (as above) receive a full therapeutic course of primaquine, to prevent relapses from the hypnozoite reservoir. PART may focus on preventing transmission from travellers, migrant workers or occupational groups that have been exposed to a relatively high risk of malaria and return to areas that are eliminating or have eliminated malaria (47).

### 2.2.2 CHALLENGES

The only approved drug for attacking the liver stages, primaquine, causes mild to severe haemolysis in patients with G6PD deficiency. Primaquine is not licensed for use as a chemoprophylactic agent or for presumptive treatment (as described above) in any country, although some governments do recommend this off-label use.

### 2.2.3 RECOMMENDATIONS

- Chemoprophylaxis could be an important strategy in selected population subgroups in which G6PD-deficiency testing can be undertaken, such as military, and in groups that have high exposures to malaria and present a high risk of introducing malaria into populations otherwise exposed to very low risk or no risk of infection.
- The use of chloroquine in pregnant women is recommended only for preventing relapses in women who had vivax malaria disease during their pregnancy (because primaquine is contraindicated in pregnancy). Routine chloroquine prophylaxis as a means of preventing vivax malaria in pregnancy in areas where transmission is high is not recommended.
- WHO does not currently recommend the use of MPPT and causal prophylaxis as general strategies.

## 2.3 DIAGNOSIS OF *P. VIVAX* INFECTIONS

### 2.3.1 PRINCIPLES

Clinical signs and symptoms cannot distinguish *P. vivax* from *P. falciparum* malaria or many other causes of febrile illness. Therefore, parasitological confirmation by microscopic examination of a Giemsa-stained blood smear (i.e. microscopy), or use of an immunochromatographic assay that employs monoclonal antibodies to parasite antigen (i.e. an RDT) is necessary. The limit

of detection for expert microscopists is considered to be about 4–20 parasites/ $\mu$ L of blood, but in clinical settings, microscopy is considered to be unreliable below 50 parasites/ $\mu$ L (48). The limit of detection for most RDTs is 200 parasites/ $\mu$ L. At low parasite densities (<200 parasites/ $\mu$ L), RDTs are less sensitive for *P. vivax* than for *P. falciparum*, but product performance in the detection of *P. vivax* has greatly improved in recent years (49).

### 2.3.2 CHALLENGES

- *P. vivax* frequently presents at a lower parasite density (typically 10 times lower) than *P. falciparum*, making *P. vivax* infections more difficult to detect with RDTs and microscopy. Thus, low-density, single-species infections with *P. vivax* may remain undiagnosed and be recorded as testing negative, whereas mixed infections may be recorded as *P. falciparum*.
- The liver stage, the hypnozoite, is undetectable using currently available diagnostic methods.
- In some areas where *P. vivax* occurs, poor accessibility of services prevents patients from receiving a diagnostic test. Private sector providers, in particular, may not provide diagnostic testing. In areas of very low transmission, clinicians may not consider malaria as a possible cause of fever and thus not request a malaria diagnosis.
- Quality assurance of microscopy may be lacking or irregularly conducted.

### 2.3.3 OPPORTUNITIES

RDTs enable increased access to diagnostic testing with minimal training and at relatively low cost (usually <US\$ 1 per test). Most RDTs are stable at ambient temperature for many months, and they are available from many commercial sources. Several tests achieve a panel detection score of >90% for both *P. vivax* and *P. falciparum* at thresholds of 200 parasites/ $\mu$ L (49). These tests are suitable for the diagnosis of acute vivax malaria.

### 2.3.4 RECOMMENDATIONS

- Parasitological confirmation by microscopy or by RDT is recommended in all patients suspected of malaria before a course of treatment is started. Efforts should be made to ensure access to diagnostic testing in the private sector as well as the public sector.
- The results of parasitological diagnosis should be available within a short period of time (<2 hours) of the patient presenting. In the absence or delay of parasitological diagnosis, patients with suspected severe malaria and other high-risk groups should be treated immediately on presumptive clinical grounds.

- Microscopy: WHO standards for malaria microscopy training, certification and quality assurance should be put in place (50,51). Poor sensitivity is the primary diagnostic threat in the clinical setting; thus, training of clinical microscopists should be aimed at maximizing detection. For ruling out low parasite density infections, repeated blood film examination in patients suspected of having malaria should be carried out before confidently reporting the patient as negative for *P. vivax* parasites.
- RDTs: Where the quality of microscopy services cannot be assured, the use of RDTs is recommended (51). In areas where *P. falciparum* and *P. vivax* coexist, bivalent RDTs should be used, in order to differentiate *P. falciparum* from *P. vivax*. The RDTs used should be those that have been assessed through the WHO product-testing programme and that meet WHO recommended procurement criteria (49).
- Diagnostic capabilities, including quality assurance, should be maintained even when malaria is eliminated or close to elimination.

## 2.4 DIAGNOSIS OF G6PD DEFICIENCY

### 2.4.1 PRINCIPLES

The only available drug for treating the liver stage of *P. vivax* infection, primaquine, causes mild to severe (potentially life-threatening) haemolysis in patients who are G6PD deficient. Risk of primaquine-induced haemolysis is dose dependent; it also depends on the degree of G6PD deficiency. Primaquine is eliminated rapidly and haemolysis is therefore self-limiting provided no further drug is taken. Over 180 genetic variants of G6PD deficiency have been described that contribute to variation in levels of deficiency. In countries in which malaria is endemic, G6PD deficiency occurs with an average allele frequency of 8% (Box 1.2).

The aim of G6PD testing is to ascertain whether a patient can safely receive primaquine. Levels of G6PD activity in the blood-cell population around 30% of normal values or above are thought to confer an acceptable risk with normal therapeutic doses of primaquine. This value is based on the detection parameters of the nicotinamide adenine dinucleotide phosphate (NADPH) fluorescent spot test, which has been extensively used in operational settings, both in guiding treatment decisions and to guide which patients should be included in clinical trials (49).

### 2.4.2 CHALLENGES

Screening for G6PD deficiency is not generally available outside hospitals. Three main categories of tests to measure G6PD activity are currently used:

- Two of these, the fluorescent spot test and spectrophotometric assay, are able to detect G6PD deficiency in hemizygous males

and homozygous females, but can be problematic in the detection of G6PD deficiency in heterozygous females, because the subpopulation of healthy erythrocytes may show normal G6PD activity (52).

- The cytochemical assay detects G6PD deficiency in heterozygous women reliably, because it examines the activity of individual red blood cells; however, it is more expensive and difficult to perform.

At present, these tests are not suitable for routine use in most field settings because they require a functioning cold chain, laboratories and skilled workers, or are too expensive. They are currently primarily used for research and surveys, and in a few clinical settings where they can be readily deployed.

Genotyping can help to detect heterozygous females but is expensive and requires sophisticated equipment. Moreover, the genetic variants need to be known in advance. At present, more than 180 alleles for G6PD deficiency are known but more may exist. Testing may suggest that a patient has normal G6PD activity when in fact the patient is deficient but has a gene variant that is not currently recognized.

### 2.4.3 OPPORTUNITIES

- Rapid screening tests based on dye reduction that can be used at peripheral health facilities have recently become commercially available. These show promise, but require more thorough assessment before they can be recommended for routine diagnosis of patients before primaquine therapy.
- G6PD testing has been reported as part of national newborn screening in India, the Philippines and Viet Nam (53); however, the coverage of such testing is incomplete.

### 2.4.4 RECOMMENDATIONS

- Where feasible, all patients should be tested for G6PD deficiency before administering primaquine. Testing for G6PD deficiency in vivax malaria cases should be considered an integral part of ensuring universal access to diagnosis and treatment.
- G6PD testing should be incorporated into treatment guidelines, and services made available as tools are developed (possibly with referral of patients from lower to higher level health facilities).
- Where no G6PD test is available, it is difficult to generalize on the correct approach to patient management, because each individual assessment depends on the risk of adverse consequences (related to the likely dose of primaquine required, the prevalence and severity of G6PD deficiency in the area, the degree of anaemia and the availability of blood transfusion) and the potential benefits (related to the probability of relapse). In some circumstances, the assessment will favour withholding primaquine, and in others it will favour starting radical treatment after educating the patient about the possible risks, and informing the patient that they should stop the drug if they become ill or their urine becomes red or black.

## 2.5 TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

### 2.5.1 PRINCIPLES

Complete treatment of *P. vivax* malaria requires treatment of both blood and liver stages, to achieve clinical cure, and to prevent relapses, onward transmission and progression to severe disease. Most drugs that are active against *P. falciparum* malaria are also effective against the asexual stages of *P. vivax*, the exception being the antifolates (pyrimethamine, proguanil, sulfonamide, sulfadoxine and dapson), which act slowly and are vulnerable to the rapid development of drug resistance.

In most endemic areas, chloroquine remains effective against *P. vivax*. However, at least one true case of chloroquine resistance (with whole blood concentrations of chloroquine plus desethylchloroquine 100 ng/ml on the day of failure) has been reported from nine countries (Brazil, Ethiopia, Indonesia, Malaysia, Myanmar, Papua New Guinea, Peru, Solomon Islands and Thailand) (54).

Mefloquine, atovaquone plus proguanil, halofantrine, dihydroartemisinin-piperaquine and artesunate-pyronaridine have all shown good efficacy against chloroquine-resistant *P. vivax* in clinical trials. Artemisinin-based combination therapies (ACTs) are highly effective in the treatment of vivax malaria, with the exception of artesunate plus sulfadoxine-pyrimethamine (SP), where resistance significantly compromises efficacy. Initial responses to ACTs are all rapid, reflecting the high sensitivity of *P. vivax* to artemisinin derivatives; partner drugs may offer temporary protection, but relapses commonly follow unless primaquine is given. There are differences in the subsequent recurrence pattern, reflecting the elimination kinetics of the partner drugs. For example, recurrences, presumed to be relapses, occur earlier following artemether-lumefantrine than following dihydroartemisinin-piperaquine or artesunate-mefloquine, because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. This same temporal pattern of recurrence with particular drugs is seen in the *P. vivax* infections that follow up to a third of acute falciparum malaria infections in South-East Asia (21,22).

Most schizontocidal drugs are active against *P. vivax* gametocytes (55) (although not against *P. falciparum* gametocytes) and if administered promptly they may help to reduce transmission of *P. vivax*. However, only primaquine is currently available for attacking the liver stages. For radical cure, WHO recommends a 14-day treatment course of primaquine. Primaquine has mainly been assessed together with chloroquine, and the two appear to have a synergistic effect for radical cure. Asexual stages of *P. vivax* are susceptible to primaquine; thus, chloroquine plus primaquine can be considered as a combination treatment for blood-stage infections, in addition to providing radical cure.

Primaquine has also been shown to be safe and efficacious when administered with dihydroartemisinin-piperaquine 28 days after the start of an acute attack (18).

### 2.5.2 CHALLENGES

- Primaquine causes mild to severe haemolysis in patients with G6PD deficiency. Current tests for G6PD deficiency are not suitable for use in most clinical settings because they require laboratories and skilled workers, or are too expensive.
- In settings where G6PD-deficiency testing is not available and deficiency prevalence is high, the risk of haemolysis may be prohibitive, especially in south Asia and South-East Asia where severe variants commonly occur (56). Thus, while primaquine may be included in national treatment guidelines, it is often not used or not available because of reluctance among clinicians to prescribe it due to safety concerns.
- Current guidelines recommend that primaquine should not be given to pregnant or lactating women with children aged <6 months, or to children aged <6 months because of safety concerns. These groups are vulnerable to morbidity and mortality caused by vivax malaria, such as chronic and severe anaemia, severe malaria, miscarriage and impaired cognitive development.
- For those that do receive the 14-day primaquine course, there are significant problems with adherence to treatment. However, unqualified insistence on adherence may be harmful to undiagnosed G6PD-deficient patients.
- Short-course, high-dose regimens of primaquine (210–420 mg total dose) can improve patient adherence, but they are associated with more gastrointestinal side-effects and they increase the risk of haemolysis for those who are G6PD deficient. However, trials have shown that a 5-day treatment course (75 mg total dose) is not effective against relapse (57,58).
- Adherence to the 8-week regimen of a single weekly dose is likely to be problematic, and although the lower doses involved (0.75 mg/kg) may mitigate the risk of haemolysis in G6PD-deficient patients, the safety of this regimen in such patients has not been fully established.
- There are no data on the pharmacodynamics or pharmacokinetic interactions between primaquine and the various ACTs that are likely to be used against *P. vivax*; also, the safety of those regimens has not been adequately assessed. Moreover, there is little information on the efficacy of primaquine when given with ACTs, either concurrently or in a staggered regimen. One study demonstrated good safety and efficacy of primaquine (0.5 mg/kg daily for 14 days) when administered 28 days after commencement of treatment with dihydroartemisinin-piperaquine (18).

### 2.5.3 OPPORTUNITIES

Drugs in the development pipeline, including tafenoquine, may provide shorter duration or single-dose treatment for radical cure. However, tafenoquine, as with all 8-aminoquinolines, has similar G6PD safety issues to those seen with primaquine.

### 2.5.4 RECOMMENDATIONS

#### Treatment of blood-stage infection

Recommendations for the treatment of acute uncomplicated vivax malaria are contained in the latest edition of the malaria treatment guidelines (59).

- In areas with chloroquine-susceptible infections, WHO recommends that adults and children are treated with either an ACT (except pregnant women in their first trimester) or chloroquine.
- With the exception of artesunate +SP, where resistance to SP compromises its efficacy, the same treatment for blood-stage infections can be offered for both *P. falciparum* and *P. vivax* malaria. A unified policy for treating both *P. falciparum* and *P. vivax* infections offers operational efficiencies and decreases the use of chloroquine for *P. falciparum* malaria where this species has been misdiagnosed as *P. vivax*; ACTs are also the treatment of choice for mixed infections.
- In the first trimester of pregnancy primaquine should be used instead of ACTs.
- In areas where *P. vivax* is known to be resistant to chloroquine, ACTs based on either mefloquine, lumefantrine or piperaquine are the recommended treatment of choice. Artesunate-amodiaquine may also be effective in some areas.

#### Preventing relapse

- To achieve a radical cure (cure and prevention of relapse), a 14-day course of primaquine is recommended, after exclusion of G6PD deficiency. Use of primaquine is recommended in all transmission settings. For frequent relapsing *P. vivax*, total doses of 3.5 mg base/kg (0.25 mg/kg/day) are required for temperate settings and 7 mg base/kg (0.5 mg/kg/day) for tropical settings. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.
- Primaquine is contraindicated in women who are pregnant or breastfeeding (unless the child is aged >6 months and known not to be G6PD deficient) and in infants aged <6 months. The safety and efficacy of primaquine against relapse when combined with any of the recommended ACTs for chloroquine-resistant *P. vivax* has not been established except with dihydroartemisinin-piperaquine.



- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg body weight, once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision (to check for potential primaquine-induced adverse haematological effects), with ready access to health facilities with blood transfusion services.
- Some heterozygous females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (>80% of normal) can only be differentiated with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and be given the 14-day regimen of primaquine; they should be counselled on how to recognize signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.
- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on an assessment of the benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes, and the capacity of the health services to identify and manage primaquine-induced haemolytic anaemia.
- Pregnant women with acute vivax malaria should be treated with chloroquine (all trimesters) or an ACT (second or third trimesters). In areas with chloroquine-resistant *P. vivax*, or in which a unified treatment policy is implemented, quinine should be used in the first trimester and an ACT in the second and third trimesters. Primaquine is contraindicated in pregnant women, infants aged <6 months and lactating women (unless the child is known to be G6PD deficient). As an alternative, chloroquine chemoprophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy. Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to complete radical cure.
- Methods to improve adherence can include directly observed therapy (DOT), where each dose is given by a trained health worker, or improved packaging and health messages. Programmes may be reluctant to strongly promote full adherence for fear of inadvertently encouraging continuation of therapy in patients experiencing symptoms of acute haemolytic anaemia. Patients should be advised of the possible risks and informed that they should stop the drug if they become ill or their urine becomes red or black.

- As primaquine becomes more widely used, and as it is combined more frequently with other partner drugs for which safety data are lacking, there is an increasing need to improve pharmacovigilance in all areas where primaquine will be deployed. This will allow improvements in knowledge of drug safety and increase the ability to detect rare side-effects.
- At a minimum, pharmacovigilance reports should include data on the patient (age, gender, pregnancy status and concomitant illnesses), the treatment (dose and duration of treatment, concomitant medicines), the adverse event (symptoms, severity and time of onset post-treatment) and the reporter. These data can be collected at clinics and hospitals, and should be reported to a central agency or programme that can compile and report on the data. Particular attention should be paid to the symptoms of haemolytic anaemia where primaquine is widely used.

## 2.6 TREATMENT OF SEVERE *P. VIVAX* MALARIA

### 2.6.1 PRINCIPLES

The association of severe illness with very low levels of parasitaemia has been shown in *P. vivax*. A relatively low-grade parasitaemia does not provide reassurance of a good prognosis in this species, in contrast to the situation with *P. falciparum*.

In a study in a Brazilian hospital, the criteria for severe *P. falciparum* malaria correlated well with a diagnosis of *P. vivax* and admission to an intensive care unit (ICU), although the parasite densities associated with ICU admission were relatively low (500 parasites/ $\mu$ L blood) (60). Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Large-scale multicentre trials in patients in Asia and Africa have demonstrated clear superiority of intravenous (IV) artesunate over quinine in reducing CFRs in severe falciparum malaria. IV artesunate also leads to a rapid clinical response in patients with severe vivax malaria (61,62).

### 2.6.2 CHALLENGES

There have been no clinical trials comparing the mortality of IV artesunate versus quinine for severe *P. vivax* infection.

## 2.6.3 RECOMMENDATIONS

- Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds (Box 2.1).
- The antimalarial treatments recommended for severe vivax malaria are the same as those for falciparum malaria. Adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) should be treated with IV or intramuscular (IM) artesunate for at least 24 hours, and until they can tolerate oral medication. Children weighing <20 kg should receive a higher dose of artesunate (3 mg/kg body weight per dose) than larger children and adults (2.4 mg/kg body weight per dose). If parenteral artesunate is not available then artemether should be used in preference to quinine.
- Following parenteral artesunate for at least 24 hours, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment with primaquine should be given after recovery (59).

### Box 2.1. Definition of severe vivax malaria (59)

Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds (i.e. one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. vivax* asexual parasitaemia).

- **Impaired consciousness:** A Glasgow coma score <11 in adults or a Blantyre coma score <3 in children.
- **Prostration:** Generalized weakness so that the person is unable to sit, stand or walk without assistance.
- **Multiple convulsions:** More than two episodes within 24 hours.
- **Acidosis:** A base deficit of >8 mEq/L or, if not available, a plasma bicarbonate level of <15 mmol/L or venous plasma lactate ≥5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- **Hypoglycaemia:** Blood or plasma glucose <2.2 mmol/L (<40 mg/dl).
- **Severe malaria anaemia:** Haemoglobin concentration ≤5 g/dL or a haematocrit of ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with a parasite count of >10 000/μL.
- **Renal impairment:** Plasma or serum creatinine >265 μmol/L (3 mg/dL) or blood urea >100 000/ μL.
- **Jaundice:** Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with parasite count >100 000/ μL.
- **Pulmonary oedema:** Radiologically confirmed or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation.
- **Significant bleeding:** Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesia or melaena.
- **Shock:** Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).

## 2.7 DRUG RESISTANCE

### 2.7.1 PRINCIPLES

Various approaches have been used to assess the efficacy of antimalarial drugs in *P. falciparum*: therapeutic efficacy studies (TES or in vivo studies), in vitro assays and use of molecular markers. However, only TES is currently practical for control programmes for use in monitoring drug resistance in *P. vivax*. To interpret and compare results within and between regions, and to follow trends over time, therapeutic efficacy monitoring must follow standardized procedures as described by WHO (63).

- To confirm the presence of chloroquine resistance, it is necessary not only to check for recurrence of infections for 28 days, but also to measure the concentration of chloroquine in the blood at the time of recurrence. In the case of chloroquine, resistance can be confirmed by measurement of the whole blood concentration at the time of recurrence. Any *P. vivax* infection that has grown in vivo through a chloroquine whole blood concentration of >100 ng/ml must be chloroquine resistant. Nevertheless, adequate blood levels for other antimalarial drugs need to be refined.
- Resistance to chloroquine was first reported in 1989 from Australia among travellers to Papua New Guinea (64). Treatment failure on or before day 28 or prophylactic failure with chloroquine has been observed in 21 countries (65). However, measurement of the concentration of chloroquine in blood was not done in all of these studies. At least one true case of chloroquine resistance (with whole blood concentrations of chloroquine plus desethylchloroquine 100 ng/ml on the day of failure) has been reported in nine countries: Brazil, Ethiopia, Indonesia, Malaysia, Myanmar, Papua New Guinea, Peru, Solomon Islands and Thailand (54).
- Treatment failure following administration of primaquine has been reported in some *P. vivax* strains, particularly those from the Western Pacific, South-East Asia, South America, and parts of Africa (47,66). However, these data are not conclusive of primaquine resistance owing to several potential confounding factors, such as geographical variations in relapse patterns, unsupervised therapy, risk of reinfection and the difficulty of finding a valid control group (63,65,67). It may also be necessary to rule out slow metabolizing cytochrome P450 2D6 phenotypes to confirm resistance (68).

### 2.7.2 CHALLENGES

- A major difficulty in interpreting TES results for *P. vivax* is the inability to distinguish reliably between a relapse and a recrudescence and reinfection. Molecular markers for genotyping *P. vivax* are less useful in TES than in *P. falciparum* because relapses may be caused by either the same genotype that caused the initial illness or a different one. Relapse is unlikely if parasitaemia recurs within 16 days of administering treatment but,

after that time, relapse cannot be distinguished from a recrudescence or reinfection. This may be of particular importance in ACTs with a relatively short half-life, such as artemether-lumefantrine.

- There is no standardized in vitro method for *P. vivax*. Although short-term in vitro culture of field isolates enables assessment of *P. falciparum* susceptibility to schizonticides, it is rarely done outside of specialized research laboratories. The development of similar in vitro tests for *P. vivax* is challenging because the parasite preferentially invades young red blood cells, limiting its reproductive capacity and ability to adapt in continuous in vitro culture. Moreover, chloroquine preferentially kills young rather than mature stages of *P. vivax* trophozoites (69), and *P. vivax* infections present variable proportions of these subpopulations, so chloroquine-sensitive infections dominated by mature forms would appear highly resistant. Hence, parasite growth must be experimentally controlled.
- No molecular markers have yet been identified for chloroquine resistance.
- Monitoring primaquine efficacy requires treatment with a schizonticidal drug with a short half-life in an environment where there is no (or minimal) risk of reinfection and with patient follow-up adapted to the regional characteristics of the parasite (sometimes up to 1 year). Results must be compared with known relapse rates in the region, or with results in a control group in whom primaquine is contraindicated. In addition, an interaction between a cytochrome P450 polymorphism (CYP2D6) and primaquine metabolism may reduce the apparent efficacy of primaquine by reducing bioavailability in patients with the condition (68). It is currently not possible to widely test for this condition, and it is therefore difficult to monitor primaquine efficacy in a standardized manner.

### 2.7.3 RECOMMENDATIONS

WHO has provided recommendations for the monitoring and management of antimalarial drug resistance in *Methods for surveillance of antimalarial drug efficacy* (63):

- National malaria control programmes (NMCPs) should establish sentinel sites for the surveillance of antimalarial drug efficacy. Experience suggests that four to eight sites per country will achieve a balance between representativeness and practicality. The sentinel sites should represent all the epidemiological strata in the country, but it is essential to select a “manageable” number of sites to ensure proper monitoring and supervision. Where feasible, NMCPs should use the same sites to monitor drug efficacy against both *P. falciparum* and *P. vivax*.

- A follow-up of 28 days only is recommended because no molecular markers have yet been identified to differentiate between reinfection, relapse and recrudescence. Since ACTs are increasingly used for the treatment of *P. vivax* infections, particularly in situations where it is resistant to chloroquine, the sensitivity of *P. vivax* to ACTs should also be routinely monitored.
- Since *P. vivax* infection has a dormant liver stage and thus has the potential to relapse, many countries recommend primaquine therapy for radical cure. Administration of primaquine concurrently or soon after administration of chloroquine may conceal resistance to chloroquine alone, because of the synergistic effect against chloroquine-resistant parasites that leads to underestimation of the risk of therapeutic failure or resistance to chloroquine. The decision to add primaquine to chloroquine or ACTs during the TES will be determined by the objective of the study; that is, whether the objective is to assess the efficacy of the first-line treatment (including efficacy against early relapses) or the efficacy of blood-stage treatment alone. In the latter case, primaquine therapy should be postponed until after the 28-day follow-up. Nonetheless, if local health policy includes mandatory administration of primaquine with chloroquine/ACT, the failure rate should be considered to be that of the combination of primaquine plus chloroquine/ACT.
- Countries should consider changing the first-line treatment for malaria if the total failure rate (defined as the sum of the patients presenting with early treatment failure, late clinical failure or late parasitological failure) exceeds 10%. The selection of a new antimalarial treatment for use at public health level in the context of national treatment guidelines should be based on an average cure rate of  $\geq 95\%$  as assessed in clinical trials.

## 2.8 SURVEILLANCE

### 2.8.1 PRINCIPLES

Surveillance for planning and implementation of malaria control and elimination requires information on:

- the need for malaria interventions, particularly the:
  - size of populations at risk;
  - level of risk (as judged by disease incidence or parasite prevalence, morbidity or mortality rates);
  - nature of the risk, taking into account the behaviour of human populations and vectors;<sup>a</sup>
- resources available for malaria control and elimination (programme financing, staff and commodities);
- existing levels of service provision (access of populations to services and intervention coverage); and
- trends in disease incidence.

<sup>a</sup> Public health surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation and evaluation of public health practice ([http://www.who.int/topics/public\\_health\\_surveillance/en/](http://www.who.int/topics/public_health_surveillance/en/)).

In short, effective surveillance enables programmes to focus resources where and when they are needed to achieve maximal impact.

In the initial phase of malaria control, there are often so many malaria cases that it is not possible to examine and react to each confirmed case individually; rather, analysis is based on aggregate numbers, and action is taken at a population level. As transmission is progressively reduced, it becomes increasingly possible, and necessary, to track and respond to individual cases. In the elimination phase, the primary emphasis of programmes is on detecting all malaria infections, whether symptomatic or not, to ensure that they are radically cured sufficiently early, and that they do not generate secondary cases.

### 2.8.2 CHALLENGES

Information systems do not always enable *P. vivax*-specific services (diagnostic testing and treatment) or health events (e.g. hospital admissions) to be recorded or reported. Although International Classification of Diseases (ICD) codes exist for admitted patients, severe morbidity and mortality associated with *P. vivax* are likely to be underreported because of a lack of awareness among clinicians and a lack of standard definitions of severe vivax malaria. In some areas where *P. vivax* occurs, poor accessibility prevents patients from using health services, or patients may use private sector providers that are not included in public sector information systems.

*P. vivax* infections may be underdiagnosed, because infected individuals may have:

- asexual parasites in blood and other tissues that are below the detection threshold for microscopy and RDTs;
- mixed infections in which *P. vivax* densities are lower than those of *P. falciparum*, and hence missed; or
- undetectable liver-stage parasites (hypnozoites) for which there are no diagnostic assays.

In each scenario, *P. vivax* will go undetected and will therefore be underreported even if patients present to health services. In some areas, the most common type of *P. vivax* infection may be asymptomatic, with very low parasite densities – such cases do not present to health services.

Use of more sensitive molecular assays for malaria detection is more costly and may not be suited to field use in routine surveillance. There can be a lag-time of several weeks between collection of samples and analysis in the laboratory; this delay in obtaining results means that such assays are of limited use in responding to focal outbreaks. Currently, the use of deoxyribonucleic acid (DNA) detection based techniques is limited to special circumstances such as confirmation of malaria in drug trials and survey research.

### 2.8.3 OPPORTUNITIES

More sensitive methods for detecting malaria infections are continually being developed, and advances in information technology and communications offer prospects for increased timeliness of reporting, increased sharing of data (between levels of a health system and between different information systems) and enhanced data analysis to inform programmes.

### 2.8.4 RECOMMENDATIONS

- WHO recommendations for surveillance of malaria, including standards for data recording and reporting, are summarized in the manuals *Disease surveillance for malaria control* (70) and *Disease surveillance for malaria elimination* (71).
- Data on the coverage of additional vector-control measures and personal protection (which may influence *P. vivax* transmission) should be routinely reported by vector-control programmes.
- Information systems should be designed to enable monitoring of the proportion of suspected cases receiving bivalent or *P. vivax*-specific diagnostic tests, and the treatment prescribed to patients (particularly if primaquine was prescribed and G6PD-deficiency testing was carried out). Efforts should be made to capture information from private sector health-care providers, which frequently account for a substantial proportion of treatments given. Health-facility surveys should be used to estimate these indicators in situations where routine information systems cannot be adapted to collect relevant data. Household surveys should be undertaken to estimate the proportion of patients seeking care in the private sector.
- Cases of *P. vivax* malaria identified through passive case detection, whether or not there is coinfection with *P. falciparum*, should be noted in routine health information systems. An assessment of routinely recorded cases by relevant variables (e.g. age group, gender, occupation and pregnancy status) should be undertaken to establish which populations are most at risk of *P. vivax* malaria. Routinely reported data should be disaggregated by selected relevant variables, so that progress of programmes in populations most at risk can be monitored.
- Standard definitions for severe *P. vivax* malaria and vivax-associated mortality are needed. Information systems should enable severe vivax malaria morbidity and mortality to be reported. All reported malaria deaths should be investigated to ascertain risk factors, and to ascertain whether they were likely to have been due to *P. vivax*.
- As countries progress to elimination, PCR or other highly sensitive tools should be employed to determine the prevalence of asymptomatic, submicroscopic infections as a reference point for assessing the sensitivity of routine methods of diagnosis.



- In the elimination phase, each case should be investigated to determine whether it is imported or locally acquired, and reporting systems should clearly distinguish between these two types of cases. An annual assessment of the *P. vivax* transmission season, when mosquitoes are able to transmit malaria and when new malaria cases begin to appear, will contribute to differentiating new cases from relapses in the case investigation.
- Active *P. vivax* foci should be investigated to understand the characteristics of transmission in each focus, and to enable decisions about which interventions should be adopted.
- In the prevention of reintroduction phase, ministries of health should maintain high vigilance and efficient surveillance.

## 3. INNOVATIONS NEEDED

A major barrier to the successful control and elimination of *P. vivax* malaria is a lack of tools that address the specific biological challenges posed by the parasite. Development and deployment of new tools is also constrained by gaps in knowledge surrounding the biology and epidemiology of *P. vivax* malaria; fundamental research in these areas is required.

### 3.1 DEVELOPMENT OF NEW TOOLS AND STRATEGIES

The biology of *P. vivax* presents several challenges that make it difficult to control and eliminate the parasite with existing tools. This section highlights the major challenges and the innovations needed.

#### 3.1.1 VECTOR CONTROL

In regions where *P. vivax* is prevalent, the effectiveness of conventional methods of vector control, such as ITNs and IRS, may be compromised because vectors bite and rest outdoors. Research is needed to:

- characterize the vectors responsible for *P. vivax* transmission at different sites, and determine in what circumstances conventional vector-control interventions can be effectively deployed;
- assess the effectiveness of personal protective methods (e.g. repellents and insecticide-impregnated clothing) and other tools, and which mix of interventions is most effective in different settings; and
- develop vector-control interventions that target outdoor-biting and outdoor-resting mosquitoes, and those found in urban settings.

### 3.1.2 DIAGNOSIS OF *P. VIVAX* BLOOD-STAGE INFECTIONS

*P. vivax* infections occur with low parasite densities, and are therefore more likely to be overlooked when patients seek treatment or when community-based surveys are undertaken. Research is needed to develop diagnostic methods that:

- more readily detect parasites in a clinical setting (with a sensitivity of 25 parasites/ $\mu$ L of blood); and
- can detect submicroscopic, asymptomatic infections in elimination settings, where it is critical to detect all infections.

### 3.1.3 DIAGNOSIS OF *P. VIVAX* LIVER-STAGE INFECTIONS

Liver-stage infections (hypnozoites) cannot be detected using current diagnostic methods. Research is needed to develop tools that will enable the presence of hypnozoites to be detected, to:

- better define the prevalence of *P. vivax* in populations and the challenge presented to control and elimination programmes; and
- assess the efficacy of drugs against the liver stage of *P. vivax* malaria.

### 3.1.4 DIAGNOSIS OF G6PD DEFICIENCY

Patients who are G6PD deficient are prone to haemolysis when administered primaquine. Currently available and validated methods of testing for G6PD deficiency are not applicable for routine use in field settings, because they either require laboratories and skilled staff, or are prohibitively expensive. Research is needed to:

- develop a test for G6PD deficiency that can be used where patients seek treatment;
- define the limitations of such testing for females heterozygous for G6PD deficiency; and
- define the extent to which primaquine can be safely administered in the absence of G6PD testing, taking into account the prevalence of G6PD deficiency and the ability to monitor signs of haemolysis.

### 3.1.5 TREATMENT OF HYPNOZOITES

The only drug available for preventing relapses, primaquine, causes mild to severe haemolysis in patients with G6PD deficiency. Primaquine requires a 14-day treatment course to which patients may not adhere, and the drug is not recommended in population groups that are most susceptible to the consequences of repeated relapses (pregnant women and infants). Primaquine has mainly been tested alongside chloroquine, and the two drugs appear to have a synergistic effect for radical cure.

The development of a drug against the liver stage that is effective and does not have significant side-effects would greatly enhance the effectiveness of *P. vivax* treatment. Research is needed on:

- strategies to increase compliance with primaquine treatment;
- the efficacy and safety of different doses and treatment courses of primaquine, to determine whether treatment courses can be safely shortened to increase compliance;
- the efficacy and safety of primaquine in children aged <5 years;
- the efficacy and safety of primaquine when co-administered with existing or new ACTs; and
- the development of a safe, single-dose treatment for liver stages that can be used by all population groups (tafenoquine is a single-dose treatment but also confers a risk of haemolysis).

### 3.1.6 PREVENTING RELAPSE WITHOUT PRIMAQUINE

Pregnant or lactating women, infants and G6PD-deficient patients have no access to primaquine for preventing relapse. Patients with CYP2D6 mutations do not respond to primaquine. Research is needed to validate and optimize regimens of suppressive chemoprophylaxis with chloroquine, mefloquine, atovaquone-proguanil or other therapeutic agents.

### 3.1.7 DEVELOPMENT OF A VACCINE

The only *P. vivax* vaccine currently undergoing clinical development targets the interaction between *P. vivax* Duffy binding protein and the human red blood cell Duffy antigen. There has been limited progress in the development of a vaccine against pre-erythrocytic stages, or a transmission-blocking vaccine based on the sexual stage Pvs25. A continuing priority is further development of potential *P. vivax* vaccines, as articulated in the updated *Malaria vaccine technology roadmap* (72).

## 3.2 BIOLOGY AND EPIDEMIOLOGY OF *P. VIVAX* MALARIA

A better understanding of the biology and epidemiology of *P. vivax* malaria is critical to developing new tools, and understanding which strategies for the control and elimination will be most effective.

### 3.2.1 BIOLOGY

Improved knowledge of the biology and pathophysiology of *P. vivax* malaria would facilitate the development of improved diagnostic tools, new medicines and vaccines. Research is needed on:

- how *P. vivax* invades reticulocytes and how it remodels the red cell membrane following invasion – this would greatly facilitate the identification of novel vaccine candidate antigens as well as potential new drugs;
- the mechanism of relapse;
- the mechanisms through which *P. vivax* triggers severe disease, such as the relative contributions to pathogenesis of extravascular sequestration (as in the spleen and bone marrow) and inflammation, along with the possible roles of comorbidities in exacerbating illness; and
- affordable and practical methods for laboratory culture of blood-stage or liver-stage parasites – to facilitate the development of new diagnostic tools, medicines and vaccines. These methods should permit full maturation, especially of hypnozoites, to yield invasive merozoites.

### 3.2.2 EPIDEMIOLOGY

A better understanding of the epidemiology of *P. vivax* malaria is needed so that strategies for its control and elimination can be more effectively planned and monitored. Areas that need to be researched are the:

- global extent of *P. vivax* infection, morbidity, severe disease and mortality, and the characteristics of populations most at risk, including the role of Duffy negativity – this may include the use of PCR to more accurately determine the prevalence of submicroscopic *P. vivax* infections and the association between *P. vivax* and severe disease;
- contribution of hypnozoites (versus new mosquito-borne infections) to the incidence of clinical cases in strains of *P. vivax* with varying incubation periods, latency and relapse periodicity;
- contribution of low-density infections to transmission of disease;
- prevalence of G6PD deficiency (and other risk factors for adverse events after treatment with primaquine); and
- incidence of adverse events associated with primaquine treatment.

## 4. DEVELOPING THE RESPONSE TO *P. VIVAX*

Since 2000, a substantial expansion of malaria intervention coverage has contributed to unprecedented decreases in malaria morbidity and mortality globally (9). A critical stage has now been reached in which the world can build on the gains achieved and accelerate progress towards elimination. The *Global Technical Strategy for Malaria 2016–2030* (73), sets ambitious targets to eliminate malaria in 35 countries by 2030, and reduce case incidence and mortality rates by 90%. *P. vivax* malaria represents a major challenge to achieving these targets, since it is responsible for about half the cases of malaria outside Africa and it predominates in countries approaching elimination.

A compelling response to *P. vivax* malaria therefore needs to be developed globally and at the national level. This will require the following:

- **A recognition that *P. vivax* malaria control and elimination requires additional specific measures.** Such measures include:
  - targeting outdoor-biting and outdoor-resting mosquitoes where they represent the main source of transmission;
  - ensuring that microscopic services are able to detect low-density *P. vivax* infections, or that bivalent RDTs are used in areas where *P. falciparum* and *P. vivax* coexist;
  - where appropriate, testing of all patients for G6PD deficiency before administration of primaquine;
  - treating both blood and liver stages of *P. vivax* malaria; and
  - establishing surveillance and monitoring systems that can report on *P. vivax*-specific interventions and their impact.
- ***P. vivax* research to be prioritized so that new tools and strategies can augment existing control efforts.** There is an urgent need to:
  - develop vector-control interventions that target outdoor-biting and outdoor-resting mosquitoes;
  - develop diagnostic methods that more readily detect parasites in a clinical setting, including submicroscopic asymptomatic infections and liver-stage infections;
  - develop a test for G6PD deficiency that can be used where patients seek treatment;

- develop a drug against the liver stage that is effective, does not have significant side-effects and can be used by all population groups; and
  - better define the global extent of *P. vivax* infection, morbidity, severe disease and mortality and associated risk factors, to facilitate effective programme planning.
- **Appropriate levels of investment by endemic countries and donor agencies to develop and implement the additional tools and strategies required.** Malaria interventions are highly cost effective, and provide one of the highest returns on investment in public health; they help to alleviate poverty, improve equity and contribute to overall development. International donors and domestic governments need to be persuaded to invest in the additional measures required for *P. vivax* malaria control, and to continue investment even when malaria is reduced to low levels or eliminated.
  - ***P. vivax* to be adequately reflected in global, regional and national plans for malaria control and elimination.** The implementation of such plans should be monitored at regular intervals through *P. vivax*-specific indicators on programme coverage and disease incidence.
  - **Public awareness, community inclusion and multisectoral engagement in planning and implementation.** Close collaboration with community leaders and nongovernmental implementing partners is essential to increase the acceptance and uptake of strategies. Integrated, people-centred health services should be planned in coordination with communities and health-care providers in the public and private sectors. Malaria interventions cannot succeed unless communities adopt guidance on the use of prevention tools and recommended therapies. Well-planned public health communication and behavioural change programmes are essential for informing affected communities about the benefits, and correct use, of malaria prevention tools.
  - **Political commitment to ensure that the poorest and most marginalized populations have access to services.** In many endemic countries the rural poor, migrant populations (e.g. those who travel for seasonal work) and other marginalized groups have both the highest risks associated with *P. vivax* infection and disease, and the least access to effective preventive and curative services. Investments in new tools and in programme implementation will have little effect unless there is commitment to remove the barriers that affected populations face in accessing appropriate preventive and curative interventions. Populations living in remote or hard-to-reach areas and with limited access to health facilities may sometimes be supported only through community-based approaches, often in partnership with nongovernmental implementing partners.

Recent progress in reducing malaria globally has shown that, with adequate investments and the right mix of strategies, remarkable progress can be made in defeating malaria. If programmes to fight *P. vivax* are made a priority, along with investment in new tools, the door will be opened to a more rapid achievement of malaria elimination in many parts of the world, and to the multiple health and economic benefits that will ensue.

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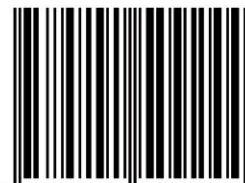
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