Malaria case management
Plasmodium vivax malaria

A field guide

World Health Organization

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Abbreviations

3S	smart safety surveillance
ACT	artemisinin-based combination therapy
ADR	adverse drug reaction
AHA	acute haemolytic anaemia
CHW	community health worker
DALY	disability-adjusted life year
G6PD	glucose-6-phosphate dehydrogenase
ICER	incremental cost-effectiveness ratio
M&E	monitoring and evaluation
MMV	Medicines for Malaria Venture
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NMP	national malaria programme
PAVE	Partnership for Vivax Elimination
RDT	rapid diagnostic test
QA	quality assurance
QC	quality control
TRuST	Tafenoquine Roll-out Study
WHO	World Health Organization

Glossary

adherence*	Compliance with a regimen (chemoprophylaxis or treatment) or with procedures and practices prescribed by a health care worker
adverse drug reaction*	A response to a medicine that is harmful and unintended and that occurs at doses normally used in humans
artemisinin-based combination therapy*	A combination of an artemisinin derivative with a longer acting antimalarial drug that has a different mode of action
case, malaria*	Occurrence of malaria infection in a person in whom the presence of malaria parasites in the blood has been confirmed by a diagnostic test
case management*	Diagnosis, treatment, clinical care, counselling and follow-up of symptomatic malaria infections
cure, radical*	Elimination of both blood-stage and latent liver infection in cases of *Plasmodium vivax* and *P. ovale* spp. infection, thereby preventing relapses Note: The term is used only for *P. vivax* and *P. ovale* spp. infections to reflect the use of anti-hypnozoite medicines.
drug, schizontocidal*	A drug that kills schizonts, either in the liver or in the blood
erythrocytic cycle*	A portion of the life cycle of the malaria parasite from merozoite invasion of red blood cells to schizont rupture. The duration is approximately 24 hours in *P. knowlesi*, 48 hours in *P. falciparum*, *P. ovale* spp. and *P. vivax*, and 72 hours in *P. malariae*.
glucose-6-phosphate dehydrogenase deficiency	A genetic abnormality of glucose-6-phosphate dehydrogenase, an enzyme found in red blood cells that plays a critical role in protecting from oxidative damage. Although mostly asymptomatic, this deficiency can manifest clinically as (i) neonatal jaundice; (ii) acute haemolytic anaemia triggered by, for example, fava beans, infection or medicines (including primaquine and tafenoquine); and (iii) chronic non-spherocytic haemolytic anaemia, which is very rare.
haemoglobinuria	The presence of free haemoglobin in the urine, typically caused by the breakdown of red blood cells (haemolysis) and the subsequent release of haemoglobin into the bloodstream, which is then filtered by the kidneys leading to dark or reddish-brown (cola-coloured) urine
haemolysis	The rupture (or lysis) of red blood cells (erythrocytes), leading to the release of haemoglobin into the surrounding blood plasma. Haemolysis can take place within the blood vessels (intravascular haemolysis) or outside of them, primarily in the spleen or liver (extravascular haemolysis).
health care worker	Professional health care workers

hypnozoite*	Persistent liver-stage of *P. vivax* and *P. ovale* spp. malaria that remains dormant in host hepatocytes for variable periods, from three weeks to one year (exceptionally even longer), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse)
latent period*	For *P. vivax* and *P. ovale* spp. infections, the period between the primary infection and subsequent relapses. This stage is asymptomatic; parasites are absent from the bloodstream but present in hepatocytes.
malaria stratification*	Classification of geographical areas or localities according to epidemiological, ecological, social and economic determinants for the purpose of guiding malaria interventions
methaemoglobinaemia	A condition of elevated methaemoglobin in the blood, leading to reduced oxygen delivery to tissues and symptoms such as cyanosis, shortness of breath, headache, dizziness, nausea and poor muscle coordination
parasitaemia*	Presence of parasites in the blood Note: If this condition is not accompanied by symptoms of malaria, it is known as asymptomatic parasitaemia.
prequalification*	Process to ensure that health products are safe, appropriate and meet stringent quality standards for international procurement Note: Health products are prequalified by an assessment of product dossiers, inspection of manufacturing and testing sites, quality control testing in the case of vaccines and medicines, validation of the performance of diagnostic tests and verification that the products are suitable for use in the destination countries.
rapid diagnostic test*	Immunochromatographic lateral flow device for rapid detection of malaria parasite antigens
recrudescence*	Recurrence of asexual parasitaemia of the same genotype(s) that caused the original illness, due to incomplete clearance of asexual parasites after antimalarial treatment Note: Recrudescence is different from reinfection with a parasite of the same or different genotype(s) and relapse in *P. vivax* and *P. ovale* spp. infections.
recurrence*	Reappearance of asexual parasitaemia after treatment, due to recrudescence, relapse (in *P. vivax* and *P. ovale* spp. infections only) or a new infection
reinfection*	A new infection that follows a primary infection; can be distinguished from recrudescence by the parasite genotype, which is often (but not always) different from that which caused the initial infection

relapse*	Recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* spp. infections arising from hypnozoites Note: Relapse occurs when the blood-stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts. After an interval, generally from three weeks to one year, the hepatic schizonts rupture and liberate merozoites into the bloodstream.
schizont*	Stage of the malaria parasite in host liver cells (hepatic schizont) or red blood cells (erythrocytic schizont) that is undergoing nuclear division by schizogony and, consequently, has more than one nucleus
semi-quantitative G6PD test	A test used to measure glucose-6-phosphate dehydrogenase enzyme activity with fixed standard thresholds for deficient, intermediate and normal enzyme activity
treatment, anti-relapse*	Antimalarial treatment designed to kill hypnozoites and thereby prevent relapses or late primary infections with *P. vivax* or *P. ovale* spp.
treatment, radical*	Treatment to achieve complete cure Note: This applies only to *P. vivax* and *P. ovale* spp. infections and consists of the use of medicines that destroy both blood and liver stages of the parasite.

* Terms marked with an asterisk are derived from: WHO malaria terminology, third edition. Geneva: World Health Organization; 2025 (https://iris.who.int/bitstreams/dfcba4db-c691-4e58-9368-67d0c6ebcd49/download).

1. Background

Malaria is a life-threatening disease caused by protozoan parasites of the genus *Plasmodium*, transmitted to humans mainly through the bites of infected female *Anopheles* mosquitoes. Malaria affects populations in tropical and subtropical regions across the globe, placing an immense burden on public health systems. Despite significant advances in malaria control, the disease remains a major global health issue *(1)*. There are five species of *Plasmodium* that cause malaria in humans and represent a public health concern: *P. falciparum*, *P. vivax*, *P. ovale* spp., *P. malariae* and *P. knowlesi*.

P. vivax contributes substantially to the malaria burden outside of sub-Saharan Africa, being the dominant parasite in south and central America *(1)*. It also plays a significant role in malaria transmission across south-east Asia, India, Oceania, the eastern Mediterranean and the Horn of Africa.

Malaria caused by *P. vivax* and *P. ovale* spp. results in a latent liver-stage infection (hypnozoite), which can lead to recurrence of asexual parasitaemia (relapse) weeks, months or sometimes even years after the primary infection. Radical cure is required to eliminate both blood-stage and latent liver-stage infection, thereby curing acute malaria as well as preventing relapse. Radical cure is achieved through the administration of a schizontocide to clear the blood-stage infection and an 8-aminoquinoline to clear the hypnozoites, thereby preventing relapse.

Until November 2024, primaquine was the only anti-relapse therapy recommended by the World Health Organization (WHO). The main drawback with primaquine is the ability to adhere to treatment, which can span one, two or eight weeks, depending on the regimen being deployed.

WHO recommended tafenoquine in 2024 as an additional 8-aminoquinoline that can be deployed in specific situations as a replacement for primaquine. The main advantage of tafenoquine is the single-dose treatment, which overcomes the adherence challenges with primaquine. However, both primaquine and tafenoquine induce haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and a qualitative or semi-quantitative G6PD test is required to guide the selection of the most appropriate *P. vivax* case management pathway.

The availability of the new diagnostic tools and 8-aminoquinoline treatments in the updated *WHO guidelines for malaria*, published in November 2024 *(2)*, prompted the development of this field guide for *P. vivax* malaria case management. This document aligns with the updated recommendations and incorporates evidence and lessons learned from feasibility studies and pilot implementations to support countries in the timely implementation of the updated WHO recommendations.

1.1 Purpose, process, target audience and structure of the field guide

Purpose. The objective of this field guide is to provide planning and implementation field guidance on the management of *P. vivax* and *P. ovale* spp. malaria, aligned with the updated WHO recommendations. This content should be considered complementary to the *Malaria case management: operations manual (3)*.

Target audience. The field guide is intended for those involved in malaria control and elimination and the delivery of malaria services, including national malaria programme managers, health care providers in endemic areas, including doctors, nurses and other health care workers involved in the delivery of malaria case management, public health officials and policy-makers, and nongovernmental organizations and international partners supporting malaria programmes.

Structure of the field guide. Section 1 provides a brief background and context on *P. vivax* malaria and the implications of G6PD deficiency when using 8-aminoquinolines for radical cure. Section 2 summarizes the new WHO recommendations on *P. vivax* malaria case management, with useful information on the sourcing of quality-assured commodities. Section 3 is organized around a step-wise guide for the management of *P. vivax* malaria and offers practical advice on patient assessment and diagnosis, patient counselling, G6PD testing, the selection of the appropriate treatment options, advice on patient follow-up and monitoring for adverse drug reactions (ADRs). Section 4 presents the required steps at the national level for the planning and implementation of the new treatment policy, including the necessary supply management, training and capacity-building, supervision, community-based activities and delivery in emergency settings. Monitoring and evaluation (M&E) guidance, including example indicators and guidance on controlled deployment of tafenoquine, is provided in Section 5. Useful complementary resource materials are collated in the Annexes. The field guide also provides a wealth of figures, tables and boxes summarizing key information in quick overviews.

While this document focuses on *P. vivax* malaria case management, this guidance also applies to *P. ovale* spp. malaria as per the WHO guidelines for malaria *(2)*. If there are any differences between the species, these are specifically highlighted.

Process of development: A draft field guide was developed based on the November 2024 update to the *WHO guidelines for malaria (2)* regarding *P. vivax* malaria case management, which included new WHO recommendations on G6PD testing and amended treatment options for radical cure with primaquine and tafenoquine, as well as an up-to-date review of the available published literature on *P. vivax* case management.

The initial draft was shared for review and input with participants invited to the WHO technical consultation, held in Geneva, Switzerland, on 8–10 October 2024. Participants included multiple external stakeholders, including those from endemic countries, malaria experts, and public health professionals from Australia, Brazil, Cambodia, Colombia, Ethiopia, India, Indonesia, Lao People's Democratic Republic, Myanmar, Nigeria, Peru, Papua New Guinea, Thailand, Venezuela and Viet Nam, as well as financial and technical partners (FIND, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Medicines for Malaria Venture [MMV], PATH and Unitaid). In a collaborative effort, the document was shared with participants for a detailed chapter-wise review.

WHO processes were used to assess declared interests and to manage any conflicts of interest. No new WHO recommendations were formulated at the technical consultation; participants focused on developing implementation guidance based on evidence of pilot country experiences. All expert members were allowed to fully participate in the deliberations of the technical consultation, as none of the declared interests were considered to have a real or perceived conflict with respect to the objectives of the WHO technical consultation. The meeting report of the technical consultation is available upon request to the WHO Department of Malaria and Neglected Tropical Diseases.

Following the meeting, all feedback received at the WHO technical consultation was incorporated into the field guide, and the revised document was shared with the experts for a final round of review and comments. All feedback received on the advanced version of the document was used, at WHO's discretion, to inform the finalization of the field guide by the WHO Secretariat.

1.2 *P. vivax* life cycle

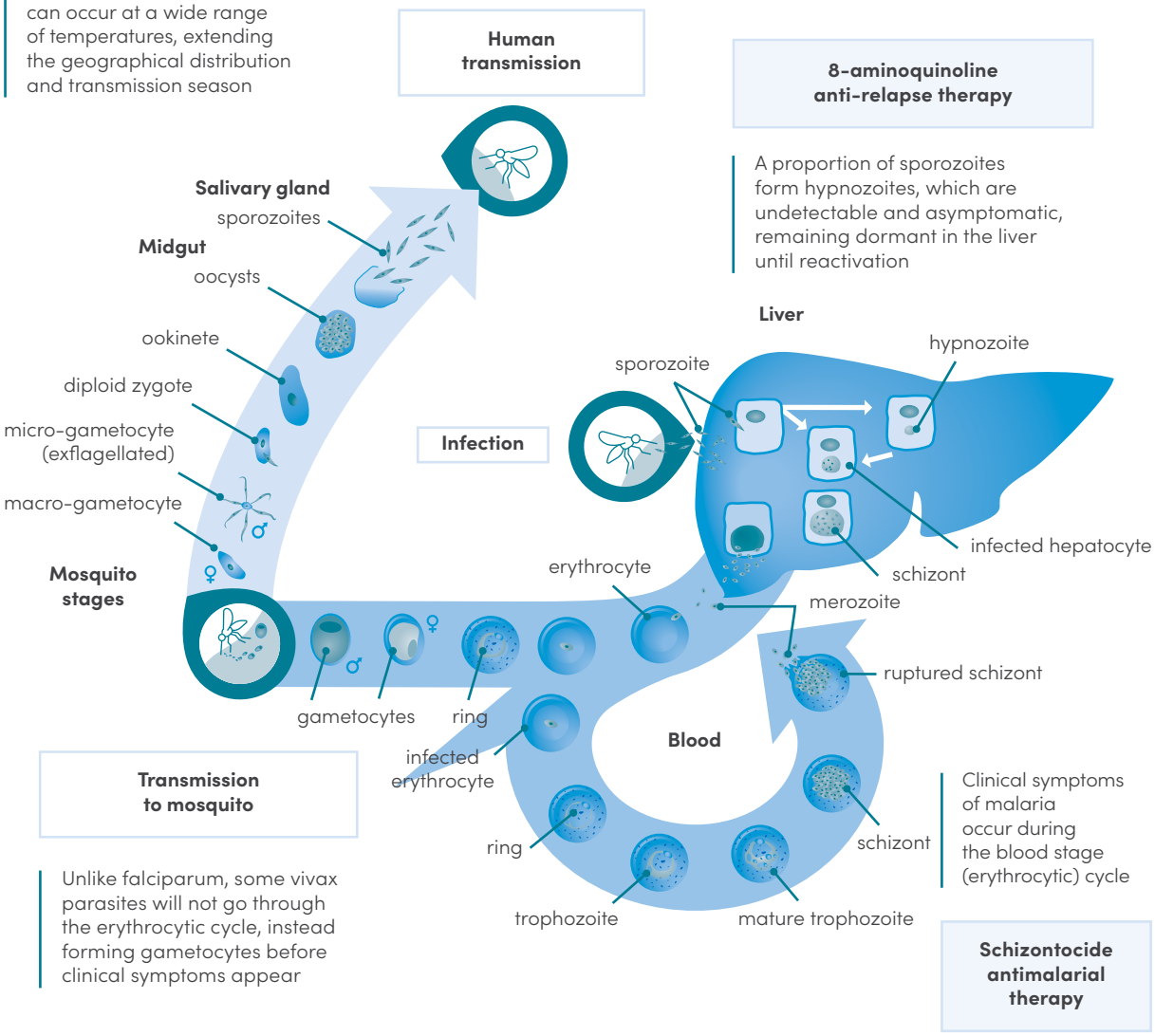
P. vivax presents unique challenges in malaria control and elimination due to the presence of a dormant liver stage (**hypnozoite**) that cause **relapses**, its capacity for transmission before clinical symptoms become evident, and its wide geographical distribution *(4)*. Additional information on *P. vivax* can be found through MMV's *P. vivax* information hub *(5)*.

The key stages of the *P. vivax* life cycle are described below and illustrated in Fig. 1, which also shows the schizontocidal medicines targeting parasite bloodstream stages and 8-aminoquinoline medicines targeting liver stages.

- **Infection.** The *P. vivax* life cycle begins when an infected female *Anopheles* mosquito bites a human, inoculating sporozoites into the person's bloodstream. Sporozoites travel to the liver and invade hepatocytes, where they either mature into schizonts, containing thousands of merozoites, or enter the hypnozoite stage.
- **Acute malaria.** Merozoites are released into the bloodstream from the hepatic schizonts and invade red blood cells, where they undergo asexual reproduction, forming trophozoites and schizonts and differentiating in gametocytes. The erythrocytic schizonts rupture, releasing more merozoites to infect new red blood cells. This erythrocytic cycle causes the clinical symptoms of malaria.
- **Relapse.** Some hypnozoites in the liver can reactivate later, maturing into schizonts and causing relapse. The relapse interval varies geographically, depending on factors such as the *P. vivax* strain, the number of sporozoites inoculated, the entomological inoculation rate, host immunity and the treatment administered. Relapse may occur as early as 16 days and as late as three years after the initial infection, even if the blood-stage infection was adequately treated *(6)*. Key characteristics of hypnozoites include the following:
    - o They cannot be directly diagnosed and do not cause signs or symptoms before reactivation.
    - o They are insensitive to schizontocidal antimalarial medicines such as chloroquine, artemisinin-based combination therapies (ACTs), and medicines that target active liver stages, such as atovaquone-proguanil and pyrimethamine.
    - o They enable the parasite to be reintroduced in areas where *P. vivax* has been previously eliminated through human migration, potentially causing outbreaks and re-establishment of transmission.
- **Transmission.** Some gametocytes are ingested when a mosquito bites an infected person. Compared to *P. falciparum* infections, the gametocytes are generated very soon in the course of a *P. vivax* infection, after the incubation period. Once ingested by a mosquito, male gametocytes fertilize female gametocytes and develop an ookinete and oocysts in the mosquito gut, containing thousands of sporozoites that migrate to the mosquito's salivary glands. When the mosquito bites a new human host, the malaria infection is transmitted from its salivary glands. Note that a single infectious bite can lead to multiple *P. vivax* relapses and onward transmission (Fig. 2).

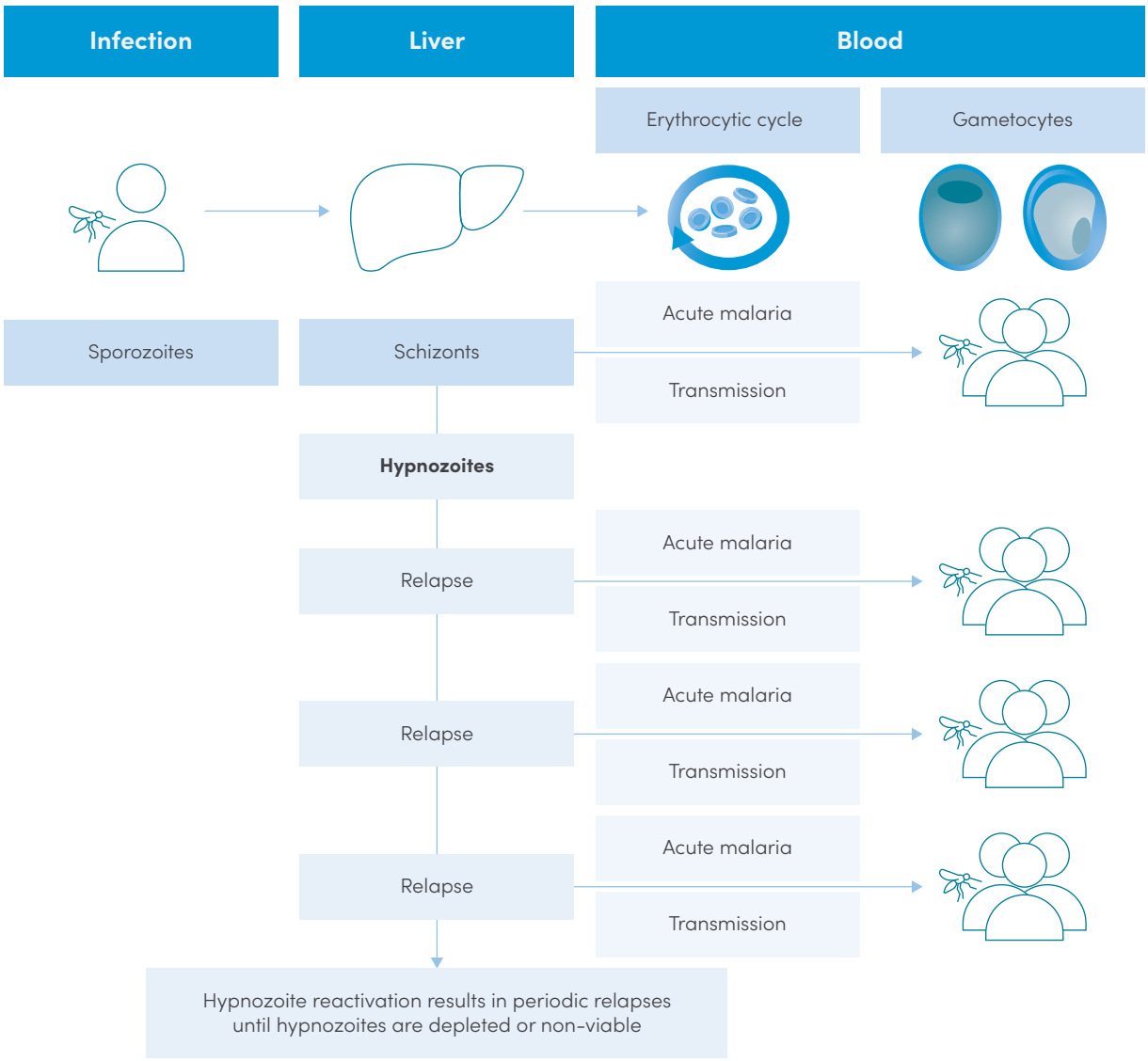
Fig. 1. *P. vivax* life cycle

The mosquito stages of vivax can occur at a wide range of temperatures, extending the geographical distribution and transmission season



Source: adapted with permission from Medicines for Malaria Venture (MMV).

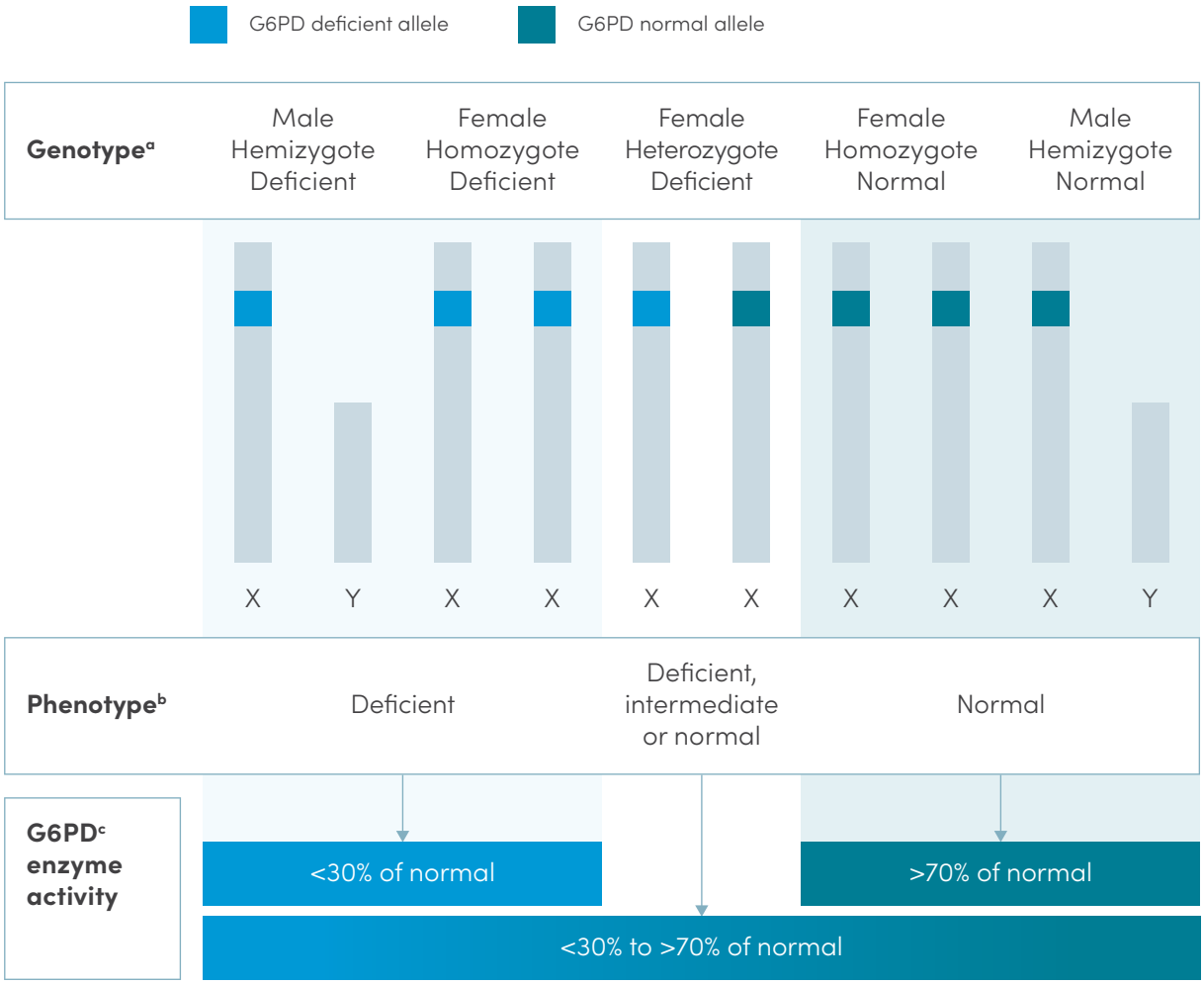
Fig. 2. A single infectious bite can lead to multiple *P. vivax* relapses and onward transmission



1.3 G6PD deficiency and clinical implications in malaria

G6PD deficiency. The G6PD enzyme plays an essential role in protecting red blood cells from oxidative damage by catalysing the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH), thereby supporting the detoxification of free radicals. G6PD enzyme deficiency is an X-linked genetic disorder that – as illustrated in Fig. 3 – expresses itself in different genotypes and phenotypes. This deficiency affects about 500 million people worldwide, with variable prevalence from less than 1% to more than 20% among males in different populations.

Fig. 3. G6PD genotype, phenotype and enzyme activity thresholds relevant for the treatment of *P. vivax* malaria



[a] Genotype refers to the genetic makeup of an organism – the specific set of genes it carries.

[b] Phenotype is the observable characteristics or traits of an organism.

[c] G6PD enzyme activity refers to the functional capacity of the G6PD enzyme to catalyse reactions in the pentose phosphate pathway, particularly the production of NADPH, which provides the cell with the capacity to protect itself from oxidative stressors.

Because the G6PD gene is X-linked, hemizygous males have only one copy of the G6PD gene and females have two copies of the G6PD gene. Heterozygous females have two different copies of the G6PD gene, homozygous females have two copies of the same G6PD gene. These different **genotypes** translate into different **phenotypes**: normal, deficient and intermediate. In the context of *P. vivax* malaria, thresholds for **G6PD enzyme activity** relative to the adjusted male median[1] are used to identify individuals at risk of haemolysis from the administration of 8-aminoquinolines.

- Individuals with **normal G6PD activity**, including male hemizygotes and female homozygotes, exhibit G6PD enzyme activity levels that are **at least 70% of normal activity**.

[1] The adjusted male median is a reference value representing the median G6PD enzyme activity among a population of G6PD normal healthy males. It is based on G6PD enzyme activity measurements obtained using the quantitative spectrophotometric reference assay normalized for haemoglobin and external temperature.

- Male hemizygotes and female homozygotes with clinically relevant **G6PD deficient** activity typically exhibit enzyme activity levels that are **below 30% of normal activity**.
- G6PD intermediate activity is **from 30% to 70% of normal activity** in heterozygous females. G6PD activity can **vary widely** in heterozygous females, ranging from levels similar to G6PD deficient hemizygous males (G6PD activity **below 30%** of normal) **to** normal levels (G6PD activity **at least 70% of normal**). This variability arises from Lyonization (X-chromosome inactivation), a process occurring during embryogenesis that leads to random inactivation of one of the two X chromosomes, generating a proportion of red blood cells expressing the deficient G6PD gene variant while others express the normal variant.

These clinically relevant G6PD enzyme thresholds are used to guide *P. vivax* radical cure and should not be confused with other values of G6PD enzyme activity proposed to classify genetic variants of G6PD deficiency in males.

Clinical implications of G6PD deficiency in malaria. If G6PD-dependent haemolysis is triggered following 8-aminoquinoline administration, it progresses rapidly. Its severity depends on the exposure levels to the medicine, the patient's G6PD enzyme activity, the G6PD deficient genetic variant, and the extent of oxidative stress triggered by the malaria infection itself.

G6PD-associated haemolysis can aggravate anaemia associated with clinical malaria. Once the oxidative stress is removed, depending on the extent of **acute haemolytic anaemia (AHA)** and bone marrow response, haemoglobin levels and haematocrit can recover without medical intervention in most cases.

If haemolysis is severe, it may become clinically evident as AHA. Based on data for primaquine, AHA typically occurs between day 2 and day 5 following administration of the medicine on day 1. To date, there have been no reports of AHA with tafenoquine, but it is assumed that the time course for AHA would be similar.

Typically, intravascular haemolysis leads to haemoglobinuria with "cola-coloured" or dark urine (see Fig. 4) and abdominal pain. Jaundice and pallor are also associated with haemolysis. Other symptoms include shortness of breath, dizziness, fever, severe fatigue, chest pain and low urine output. Rapid pulse, back pain, nausea and vomiting, heart failure and headache are also reported. In severe AHA cases, fluid support and blood transfusion may be needed urgently to ensure the patient´s survival (see Section 3.5).

The risk of drug-induced haemolysis can be managed by testing the patient for G6PD activity and dispensing the appropriate medicine and dose to ensure that G6PD enzyme levels are sufficient to protect erythrocytes from oxidative damage.

Fig. 4. Image of "cola-coloured" urine indicating haemoglobinuria

Source: photograph courtesy of M. Lacerda.

2. WHO recommendations

P. vivax malaria case management should be guided by the recommendations provided in the updated *WHO guidelines for malaria (2)*. Section 2.1 summarizes the current WHO recommendations on G6PD testing and the treatment of uncomplicated *P. vivax* malaria; Section 2.2 focuses on severe *P. vivax* malaria; and guidance on the sourcing of quality-assured medicines and tests is provided in Section 2.3.

2.1 Uncomplicated *P. vivax* and *P. ovale* spp. malaria

The current WHO recommendations on the management of *P. vivax* malaria are summarized below in three boxes for ease of understanding:

- Box 1. Treatment of blood-stage infections;
- Box 2. Testing for G6PD deficiency; and
- Box 3. Anti-relapse treatment.

Fig. 5 provides a summary overview of the different recommended treatment options based on the availability of G6PD testing.

Box 1. Treatment of blood-stage infections

Blood stage infection (2015)

In areas with **chloroquine-susceptible infections**, adults and children with uncomplicated *P. vivax*, *P. ovale* spp., *P. malariae* or *P. knowlesi* malaria should be treated with either an ACT or chloroquine.

In areas with **chloroquine-resistant infections**, adults and children with uncomplicated *P. vivax*, *P. ovale* spp., *P. malariae* or *P. knowlesi* malaria should be treated with an ACT.

Box 2. Testing for G6PD deficiency to guide the administration of 8-aminoquinolines, i.e., either primaquine or tafenoquine, for anti-relapse therapy

Blood stage infection (2024 – good practice statement)

The G6PD status of patients should be used to guide administration of either primaquine or tafenoquine for preventing relapse.

Qualitative near-patient G6PD tests (2024)

Qualitative near-patient tests for G6PD deficiency should be used to inform administration of specific treatment regimens to prevent relapses of *P. vivax* and *P. ovale* spp. G6PD non-deficient individuals can receive 0.5 mg/kg/day primaquine for 14 days or 0.5 mg/kg/day primaquine for 7 days.

- In males and females, < 30% of normal G6PD activity is considered deficient.
- In patients undergoing G6PD activity testing, near-patient qualitative tests for G6PD deficiency are considered highly accurate to distinguish G6PD above or below a threshold of 30% of normal G6PD activity.
- These tests cannot be used to identify females with intermediate G6PD deficiency (30–70% G6PD activity) due to a heterozygous genotype. Instead, females with G6PD activity in this intermediate range will be classified as normal with a qualitative test.

Semi-quantitative near-patient G6PD tests (2024)

Semi-quantitative near-patient tests with fixed standard thresholds for deficient, intermediate and normal G6PD activity should be used to inform administration of specific treatment regimens. The dose of 1 mg/kg/day primaquine for 7 days or single dose tafenoquine should only be given to those above the threshold that corresponds to > 70% of normal G6PD activity; and 0.5 mg/kg/day primaquine for 14 days or 0.5 mg/kg/day primaquine for 7 days can be given to those with a threshold that corresponds to > 30% of normal G6PD activity to prevent relapses of *P. vivax* and *P. ovale* spp.

- In males and females, < 30% of normal G6PD activity is considered deficient; females with G6PD activity between 30% and 70% due to a heterozygous genotype are considered to have intermediate G6PD activity and are also (but less so) at risk of haemolysis.
- In patients undergoing G6PD activity testing, near-patient semi-quantitative tests for G6PD deficiency with fixed thresholds corresponding to > 30% and < 70% of normal G6PD activity are considered highly accurate at a threshold of 30% of normal G6PD activity to indicate whether *P. vivax* and *P. ovale* spp. patients are G6PD deficient, and are considered accurate at a threshold of ≤ 70% activity to indicate whether *P. vivax* and *P. ovale* spp. patients are deficient or have intermediate G6PD activity.

Box 3. Anti-relapse treatment of *P. vivax* and *P. ovale* spp.

Tafenoquine as anti-relapse therapy (2024)

Tafenoquine is recommended as an alternative to primaquine (3.5 mg/kg total dose) for preventing relapses of *P. vivax* in patients ≥ 2 years of age, who have ≥ 70% G6PD activity and who receive chloroquine treatment.

- These recommendations pertain only to south America.
- Quantitative or semi-quantitative determination of G6PD activity must be done before tafenoquine administration.
- Tafenoquine is not recommended in pregnant and lactating women.
- Tafenoquine is not recommended in patients receiving ACTs for the treatment of *P. vivax*.
- Controlled deployment and/or further research is encouraged outside of south America, to generate evidence of the efficacy and safety of tafenoquine compared to primaquine as an anti-relapse treatment.
- No data are available comparing tafenoquine with primaquine given at a total dose of 7 mg/kg.

Primaquine as anti-relapse therapy (2024)

To prevent relapse, children and adults (except pregnant women, infants aged < 1 months and women breastfeeding infants aged < 1 months, and people with G6PD deficiency), primaquine should be given at a high total dose (7 mg/kg) at 0.5 mg/kg/day for 14 days or 1 mg/kg/day for 7 days for prevention of relapses in patients with uncomplicated *P. vivax* or *P. ovale* spp. malaria.

- The primaquine high dose (7 mg/kg) should be provided at 1 mg/kg/day for 7 days only to patients with ≥ 70% G6PD activity.
- National decisions regarding the two high-dose (7 mg/kg) primaquine regimens given over 7 or 14 days will be affected by the availability of G6PD semi-quantitative testing and capacity for supervised therapy.
- Evidence for the magnitude of benefit may vary geographically. Whether a high dose of primaquine 7 mg/kg is given in 14 days or 7 days, the absolute benefit of using the high primaquine total dose will vary according to the risk of recurrence in the population. The benefits are higher in Africa, south-east Asia and Oceania. However, in areas on the Indian subcontinent and in the Americas, where the absolute benefit of a total high dose of 7 mg/kg might be only marginally greater than that of 3.5 mg/kg, primaquine at a low 3.5 mg/kg total dose might be used.
- It should be emphasized that determination of G6PD status using an appropriate test is needed to guide the safe administration of primaquine (see Section 5.2.1.6 of the *WHO guidelines for malaria* on G6PD testing *[2]*).

Preventing relapse in people with G6PD deficiency (2015)

In people with G6PD deficiency, primaquine base at 0.75 mg/kg body weight once a week for 8 weeks can be given to prevent relapse, with close medical supervision for potential primaquine-induced haemolysis.

Preventing relapse in *P. vivax* or *P. ovale* spp. malaria (2015 – good practice statement)

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine should be based on an assessment of the risks and benefits of adding primaquine.

Pregnant and breastfeeding women (2015)

In women who are pregnant or breastfeeding, weekly chemoprophylaxis with chloroquine can be given until delivery and breastfeeding are completed, then, on the basis of G6PD status, primaquine can be given to prevent future relapse.

Wherever possible, the G6PD status of patients should be used to direct anti-relapse therapy with 8-aminoquinolines. Recognizing the challenges and programmatic risks associated with implementing these policies, countries should make progress in evaluating and piloting the introduction of G6PD tests to guide policy decisions on this matter.

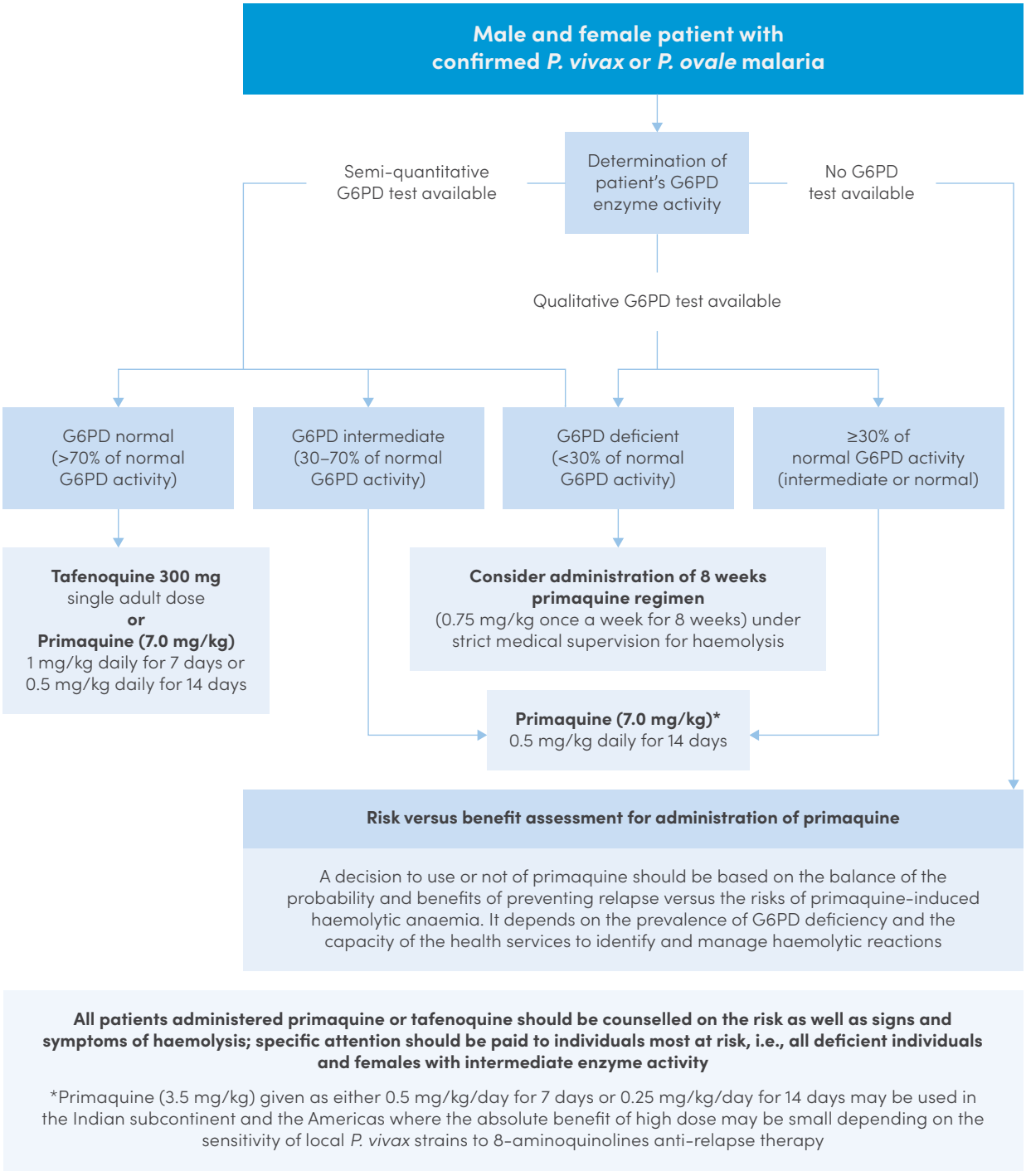
As shown in Fig. 5, neither the administration of single-dose **tafenoquine** nor the administration of **high-dose primaquine (7 mg/kg total dose) given as 1 mg/kg daily for 7 days** can be considered without prior semi-quantitative G6PD testing.

In settings where only qualitative G6PD testing is available, primaquine (7 mg/kg total dose) can be given as **0.5 mg/kg daily for 14 days** to patients with ≥ 30% of normal G6PD activity. This dosing regimen also applies to patients who are identified as intermediate with a semi-quantitative G6PD test.

For G6PD-deficient patients, weekly administration of primaquine can be considered with a dose of **0.75 mg/kg once a week for 8 weeks**; strict medical supervision for haemolysis is recommended.

Where G6PD testing is not available, a decision to administer primaquine should be based on a **risk–benefit assessment** conducted by the NMP at both the individual and population levels *(2)*. Box 4 lists key criteria to be considered, including relapse rates, *P. vivax* incidence rates, G6PD prevalence rates and health system factors. An algorithm for AHA management and monitoring for ADRs should be established. Comprehensive patient counselling should be provided on the signs and symptoms of primaquine-induced haemolysis and the required responses.

Fig. 5. Therapeutic pathways of *P. vivax* and *P. ovale* spp. anti-relapse treatment with 8-aminoquinolines in relation to G6PD testing



Source: WHO guidelines for malaria (2).

Box 4. Individual and public health risk of administering primaquine without G6PD testing

The **individual and public health risk** of administering primaquine without G6PD testing **may be greater than the benefits** in areas or populations with:

- low relapse rates;
- low *P. vivax* incidence rates; and
- high G6PD deficiency prevalence.

The **individual and public health risk** of administering primaquine without G6PD testing **may be less than the benefits** in areas or populations with:

- high relapse rates;
- high *P. vivax* incidence rates;
- absence of G6PD deficiency or very low G6PD deficiency prevalence rates;
- consistent access to patient counselling on the signs and symptoms of primaquine-induced haemolysis and appropriate action; and
- good access to the health care system and good capacity of health facilities to manage AHA, including blood transfusion services.

2.2 Severe *P. vivax* malaria

Although *P. vivax* malaria has a low case fatality rate in most patients, it can occasionally cause severe disease, as in *P. falciparum* malaria. 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 (see further details in Section 3.1). Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria. Following administration of parenteral artesunate, treatment should be completed with a full oral treatment course of an ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment should be given after recovery. Full details on the recommendations can be obtained in the *WHO guidelines for malaria (2)*.

2.3 Quality-approved medicines and tests

WHO recommends that only medicines of proven quality (that is, in line with international standards such as the International Pharmacopoeia) should be used for malaria treatment. WHO, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of antimalarial medicines based on their compliance with internationally recommended standards of manufacture and quality:

- The list of WHO-prequalified antimalarial medicines is regularly updated and can be accessed online *(7)*.
- Complementary information is available on the Global Fund's *List of malaria pharmaceutical products classified according to the Quality Assurance Policy*, which is also periodically updated and accessible online *(8)*. The list contains products that have been assessed under the Expert Review Panel mechanism – an independent advisory board that provides a service to procurement or

funding agencies to support time-limited procurement for antimalarial medicines that have not yet been prequalified by WHO.

Similar resources are available for rapid diagnostic tests (RDTs) for malaria and G6PD testing:

- WHO regularly updates its list of prequalified in vitro diagnostic products *(9)*.
- The Global Fund's list of malaria products classifies products according to its Quality Assurance Policy, which includes RDTs and G6PD tests that have been approved under the WHO Expert Review Panel for Diagnostics *(10)*.

3. Case management

Radical cure of *P. vivax* malaria requires elimination of both blood-stage parasites and dormant liver-stage hypnozoites. When the patient recognizes symptoms of malaria, treatment should be sought immediately, so that case management can be initiated without delay. The potential steps for case management (with cross-references to the corresponding sections in this field guide) are outlined in Table 1. These steps are not given in any specified order. The important goal is to ensure rapid diagnosis and prompt initiation of blood-stage treatment, while determining the best regimen option for anti-relapse treatment.

Table 1. Steps in *P. vivax* malaria case management

Task	Activities	Field guide cross-reference
Diagnosis	**Patient assessment and diagnosis of malaria**, including medical history and clinical assessment (Note: If severe malaria is suspected, immediate referral and treatment is required.) Parasitological confirmation of malaria using RDT or microscopy	Section 3.1
Blood-stage treatment	**Initiation of antimalarial treatment**, with either an ACT or chloroquine as per the national guidelines	Section 3.2
G6PD testing	**Pre-test patient counselling**, including the purpose of G6PD testing and importance of relapse prevention	Section 3.3.1
	Testing for the patient's G6PD status, considering the availability of different testing methods	Section 3.3.2
	Post-test patient counselling, including communication of the G6PD test result and explanation of the required treatment option, the importance of adherence to treatment, and when to return in case of ADRs	Section 3.3.1
Anti-relapse treatment	**Administration of appropriate anti-relapse treatment on the basis of G6PD test result** (8-aminoquinoline: either primaquine or tafenoquine)	Section 3.4
Follow-up	**ADRs** Mitigation, monitoring and management	Section 3.5
	Patient follow-up Timing and purposes	Section 3.6

3.1 Diagnosis

Clinical assessment of the patient. The clinical assessment of the patient should determine the severity of the disease by taking a medical history and performing a clinical examination, as well as obtaining the key information needed to direct appropriate therapy. Essential initial assessment criteria are listed in Table 2. At higher levels of the health care system, more comprehensive assessments will be conducted, according to normal clinical practice.

Table 2. Minimum essential assessments and key information required during initial patient assessment

History	Essential assessments	Key information
• Onset of fever, chills, headache, malaise • Any nausea or vomiting • Sweating or anorexia • Inability to drink • Travel history	• Physical examination • Diagnostic testing • Temperature • Hydration status • Pulse • Respiratory rate • Blood pressure • Anaemia[a]	• Age • Body weight • Pregnancy status • Breastfeeding status • Recent malaria history • Current medications

[a] Signs and symptoms include pallor, severe fatigue, jaundice (yellowing of the skin and eyes); assess haemoglobin levels if feasible using validated methods.

Parasitological confirmation of malaria. When a patient presents with suspected malaria, either light microscopy or specific RDTs can be used to diagnose clinical *P. vivax* malaria. For light microscopy, microscopists must be adequately trained and quality control (QC) procedures should be in place; WHO malaria microscopy standard operating procedures are available on the WHO website *(11)*. With regard to RDTs, a number of WHO-prequalified antigen-detecting products are commercially available and meet the required diagnostic performance criteria for the diagnosis of *P. vivax* malaria *(9)*.

Additional WHO guidance on selecting and procuring malaria RDTs can be found on the website *(12)*. There are currently no tests available to detect hypnozoite infection. However, serological markers of recent *P. vivax* infection are being investigated and developed.

Note that there are currently no RDTs that can specifically diagnose *P. ovale* spp. *(10)*. Diagnosis is to be done or confirmed by light microscopy.

Severe malaria. Although severe malaria is a rare complication of *P. vivax* malaria, it presents a medical emergency and requires immediate referral for appropriate treatment. All levels of the health care system, including the community level, should be trained to recognize severe disease and the criteria and process for referral in the given setting. The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disability and prevention of recrudescent infection. Management of severe malaria comprises clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care. Further details on the diagnosis and management of severe malaria can be found in the *WHO guidelines for malaria (2)*.

3.2 Blood-stage treatment: schizontocides

Either chloroquine or an ACT can be given to clear the blood-stage infection and treat acute malaria.

- **ACT.** As per WHO guidelines, ACTs can be used as the primary first-line treatment option for *P. vivax* in all settings and are recommended in areas where there is documented chloroquine resistance.
- **Chloroquine.** Chloroquine should only be used in areas where the parasites remain sensitive.

3.3 G6PD testing

3.3.1 Pre- and post-test patient counselling

Ensuring that patients are well informed about the benefits of radical cure and the required treatment protocol enhances adherence and empowers the patient to manage risk through early recognition and self-referral to mitigate ADRs. Counselling should be conducted throughout the entire consultation process.

Health care providers should have materials about G6PD deficiency and primaquine and tafenoquine ADRs available in the local language and in formats accessible to patients. These materials should enable clear and effective communication of the topics outlined in Box 5.

Box 5. Checklist for patient counselling

With adequate patient information materials, patients should be informed about the following:

Before performing the G6PD test (if applicable)

- ☐ Explain the purpose of the G6PD test and the benefits of primaquine or tafenoquine treatment.

Before assigning treatment

- ☐ Explain the reasons for administering primaquine or tafenoquine and the risk of repeated relapses without treatment.
- ☐ Enquire as to the patient's medical history of haemolysis.

After performing the G6PD test or where testing is not available

- ☐ Explain which treatment the patient will receive and why.
- ☐ For primaquine, reinforce the importance of adherence to the full treatment course.
- ☐ For high-dose primaquine, inform the patient of the risk of gastrointestinal adverse events and the importance of taking the medicine with food.
- ☐ Inform the patient of the risk of haemolytic anaemia and associated common symptoms (see Sections 1.3 and 3.5).
- ☐ Instruct the patient to monitor the colour of their urine.
- ☐ Instruct the patient to stop taking primaquine if their urine becomes dark (see Fig. 4).
- ☐ Inform the patient when and where to seek medical advice. Typically, AHA occurs between day 2 and day 5 following the administration of the medicine on day 1 (see Section 1.3).

Note that the aim of G6PD testing in the context of *P. vivax* radical cure is to determine the G6PD activity at that time point and to direct 8-aminoquinoline treatment accordingly; it does not provide a definitive diagnosis of G6PD deficiency, as the read-out may change in the same patient over time and this test does not replace a genetic diagnosis of G6PD deficiency. Moreover, definitive testing for G6PD deficiency should be done when individuals are in a healthy state. For this reason, especially in females, G6PD testing should be repeated each time radical cure is considered.

Based on the G6PD test results, or in the absence of G6PD testing, patients should understand the treatment options for *P. vivax* malaria and the risks associated with treatment, including ADRs and their mitigation, and what actions to take should these occur.

3.3.2 Testing for a patient's G6PD status

As illustrated in Fig. 5, there are presently two types of tests available to guide anti-relapse treatment: (i) qualitative tests; and (ii) near-patient quantitative or semi-quantitative tests. To ensure reliable G6PD testing, it is essential that proper QC and quality assurance (QA) methods be implemented.

Qualitative G6PD tests. Qualitative tests provide a binary read-out, i.e., G6PD deficient versus G6PD non-deficient. Tests are calibrated so that a G6PD deficient result is equivalent to < 30% of normal G6PD enzyme activity and G6PD non-deficient (usually referred to as "G6PD normal") is equivalent to ≥ 30% of normal G6PD enzyme activity. There are three main methods of qualitative testing; their use depends on the setting.

- **Lateral flow tests.** These near-patient tests are based on a cartridge holding reagents that react to G6PD enzyme activity in a blood sample. Results are presented as a G6PD deficient/normal colour change, which is read by the operator.
- **WST-8/1-methoxy phenazine methosulfate method.** This test is suitable for settings where there are laboratory facilities. The presence of NADPH – a product of G6PD activity – results in a strong orange colour, indicating normal G6PD activity; no colour indicates G6PD deficiency.
- **Fluorescent spot test.** The test evaluates NADPH fluorescence under UV light, indicating G6PD activity. An absence of fluorescence indicates G6PD deficiency.

Note that qualitative tests cannot be used to direct therapy with tafenoquine or primaquine at a dose of 1 mg/kg/day for 7 days. Moreover, qualitative tests will classify G6PD heterozygote females who have intermediate enzyme activity (≥ 30% to ≤ 70% of normal) as "G6PD normal", even though they may be at risk of drug-induced haemolysis.

In some countries, screening of newborns for G6PD deficiency has been introduced using qualitative methods and the G6PD status is recorded on a personal medical card. Though not ideal for individual case management, any available test could be used in population surveys to estimate the average prevalence of G6PD deficiency in males in that specific community.

Near-patient quantitative or semi-quantitative G6PD tests. With the semi-quantitative tests, the G6PD enzyme activity thresholds relevant for *P. vivax* case management are interpreted relative to population-based values in G6PD normal males, normalized for haemoglobin concentration, as shown in Box 6. Definitions used by the manufacturer

to define G6PD deficient, intermediate and normal ranges should be adhered to when using the test to inform treatment. Health care workers need to be well trained to understand the different categories and their importance for selecting an appropriate treatment option for a patient.

Box 6. G6PD enzyme activity thresholds relevant to *P. vivax* case management

- G6PD deficient — < 30% of normal G6PD enzyme activity
- G6PD intermediate — ≥ 30% to < 70% of normal G6PD enzyme activity
- G6PD normal — ≥ 70% of normal G6PD enzyme activity

Note that the first semi-quantitative near-patient G6PD test was prequalified by WHO in December 2024 *(10)*.[2] This test, comprising an analyser and test devices, is portable and easy to use in peripheral health care settings. A capillary (finger prick) or venous whole blood sample is needed, with the result becoming available within two minutes. Regular QC needs to be undertaken, e.g., when using the analyser for the first time, after having replaced its batteries or when unexpected test results are obtained.

QC and QA of G6PD tests. QC ensures that the test performance is accurate and reliable, while QA focuses on maintaining high standards in laboratory practice for continuous improvement. Both are essential for reliable results and should be included in annual NMP budgets.

- **Internal and external QC and calibration can be applied:**
  - **Internal QC and calibration.** Tests require specific internal QC measures and the specific manufacturer's guidelines should be followed. For example, calibration of the test might be needed, a separate purchase of controls might be required, or a specific frequency of QC might be applicable (e.g., weekly or prior to testing in low-frequency use scenarios). In addition to routine QC, specific situations might require an immediate internal QC check, such as during initial usage of the test analyser, when using each new batch of test kits, if there is evidence of non-reproducible results, after changing the battery in the analyser device, and following any damage or exposure to temperature extremes.
  - **External QC and calibration.** Third-party external calibration is necessary for certain devices, such as spectrophotometers, normally on a yearly basis.
- **Internal and external QA can be applied:**
  - **Internal QA.** Alongside device QC, end-user proficiency can be periodically assessed with user-quality assessments using specific controls, e.g., see PATH's *SD Biosensor STANDARD G6PD Test user competency assessment (14)*. Deficient, intermediate and normal controls have their own ranges of G6PD activity. Users must be able to obtain test results within these ranges of values. This can be done on a weekly or monthly basis or when users need more practice, such as in low transmission settings where there are low caseloads of *P. vivax* patients.
  - **External QA programme.** Referral laboratories providing confirmatory G6PD testing should engage in external QA programmes to uphold ISO/IEC 17025 standards. Normally, this should be done by large institutions only at the national or subnational level.

[2] Detailed information can be found in the product details on the WHO Prequalification website *(13)*.

Caveat regarding haemoglobin measurements. Some near-patient semi-quantitative G6PD tests may also provide a total haemoglobin level read-out on the device, but use of this result to diagnose anaemia should only be done if this is part of the intended use of the device. In the absence of a claim for the use of total haemoglobin to determine state of anaemia, the manufacturer is not required to provide evidence of the accuracy of results to national regulatory authorities or the WHO Prequalification Team; therefore, the accuracy of haemoglobin levels cannot be assured. Based on intended use and claims of the semi-quantitative G6PD tests currently prequalified by WHO,[3] if anaemia is suspected based on clinical assessment, then haemoglobin should be evaluated using alternative validated methods *(15)*.

3.4 Anti-relapse treatment: primaquine or tafenoquine

In placebo-controlled studies, primaquine and tafenoquine reduced the risk of *P. vivax* recurrence by around 70% versus chloroquine alone over at least six months following the initial infection *(16, 17)*.

The selection of the appropriate 8-aminoquinoline (i.e., either primaquine or tafenoquine) and treatment regimen to prevent *P. vivax* relapse should be guided by the patient's G6PD status and a number of other criteria, as listed below.

- **Primaquine.** The G6PD status of a patient determines the required dose and duration of the treatment. Adherence to the daily or weekly dose schedule is key to ensure efficacy and prevent *P. vivax* relapse. Strategies should be in place to encourage adherence to primaquine, including patient counselling and directly observed therapy where feasible. The following dosing regimens can be given depending on a patient's G6PD status and the setting; specific conditions are detailed in Section 2 and Fig. 5.
    - Patients who are G6PD **normal** (≥ 70% of normal G6PD activity): primaquine 7 mg/kg, given at 1 mg/kg daily for 7 days, or given at 0.5 mg/kg daily for 14 days.
    - Patients who are G6PD **normal** (≥ 70% of normal G6PD activity) or **intermediate** (≥ 30 to ≤ 70% of normal G6PD activity): primaquine 7 mg/kg, given at 0.5 mg/kg daily for 14 days.
    - Patients who are G6PD **deficient** (< 30% of normal G6PD activity): primaquine at 0.75 mg/kg once a week for 8 weeks.

    Note that primaquine should not be given to pregnant women, infants < 1 month of age and women breastfeeding infants < 1 month of age.

[3] The intended use of the STANDARD™ G6PD test and STANDARD™ G6PD Analyzer initially submitted for WHO prequalification assessment included a statement that "T-Hb results [...] are used to determine G6PD status and not state of anemia". The prequalified product #02GA11 does not provide a haemoglobin read-out.

- **Tafenoquine.** Tafenoquine is given as a single-dose treatment, facilitating direct observation of the full therapeutic dose and enhancing patient adherence. However, tafenoquine should only be used if the patient has ≥ 70% of normal G6PD activity, as determined by a quantitative or semi-quantitative G6PD test. Tafenoquine is available as a 150 mg tablet and as a 50 mg dispersible tablet. Adults, adolescents and children weighing > 35 kg should receive a single 300 mg dose on day 1 or day 2 of the three-day course of chloroquine. Children ≥ 2 years of age and weighing > 10 kg to ≤ 35 kg should be dosed with dispersible tablets as outlined in Table 3.

Table 3. Tafenoquine dose recommendations

Body weight (kg)	Total dose	Number of tablets
> 10 to ≤ 20	100 mg	Two 50 mg dispersible tablets
> 20 to ≤ 35	200 mg	Four 50 mg dispersible tablets
> 35	300 mg	Two 150 mg tablets

Note that tafenoquine is not recommended for pregnant or breastfeeding women and should only be used in children ≥ 2 years old with a body weight over 10 kg.

Selection of appropriate anti-relapse medicine. The selection of the appropriate 8-aminoquinoline for a given patient depends on schizontocidal treatment, pregnancy and breastfeeding status, patient age, the availability of G6PD testing and a patient's G6PD status.

- **Schizontocidal treatment.** Primaquine can be used with chloroquine or an ACT, whereas tafenoquine is currently recommended for use only with chloroquine.
- **Pregnancy status.** Neither primaquine nor tafenoquine can be given to pregnant women, as no data on fetal drug exposure are available and the medicine could potentially pose a risk to a G6PD deficient fetus.
- **Breastfeeding status.** Secretion of primaquine in breast milk is negligible. Primaquine can be given to women who have been breastfeeding for > 1 month without the requirement to test the infant for G6PD deficiency *(2)*. No clinical data are available on tafenoquine concentrations in breast milk.
- **Patient age.** Both primaquine and tafenoquine are available as adult and paediatric formulations. Primaquine is approved for use in children ≥ 1 month of age. Tafenoquine is approved for use in children ≥ 2 years of age with a body weight over 10 kg. Both 8-aminoquinolines can be used in adults.
- **G6PD testing.** A semi-quantitative test must be conducted to ensure ≥ 70% of normal G6PD activity before the administration of tafenoquine. Different primaquine regimens can be given based on the results of semi-quantitative or qualitative G6PD testing or in cases where no G6PD testing is available (see Fig. 5).
- **G6PD status.** Because of the risk of drug-induced haemolysis in G6PD deficient patients, G6PD testing should be performed before primaquine or tafenoquine administration (see Section 3.3) *(2)*. If G6PD testing is not available, certain primaquine regimens can be considered based on a risk–benefit assessment (see Fig. 5 and Box 4).

A summary overview of these factors is provided in Table 4.

Table 4. Summary of considerations for 8-aminoquinoline administration

Consideration	Primaquine	Tafenoquine
Schizontocidal treatment	Chloroquine or ACT	Chloroquine
Use in pregnant women	No	No
Use in breastfeeding women	≥ 1 month breastfeeding	No
Use in children[a]	≥ 1 month old	≥ 2 years old
Treatment regimen	7-day, 14-day or 8-week regimens	Single dose
G6PD testing	Different dosing regimens based on G6PD test availability (semi-quantitative or qualitative), or risk–benefit assessment if no G6PD testing is available. Semi-quantitative test required for high-dose primaquine: 1 mg/kg daily for 7 days can only be used in patients with ≥ 70% of normal G6PD activity.	Semi-quantitative test required: tafenoquine can only be used in patients with ≥ 70% of normal G6PD activity.

[a] There are limited data on the use of primaquine in young children and infants and on the use of tafenoquine in children < 16 years of age.

Note that in women who are pregnant or breastfeeding, weekly chemoprophylaxis with chloroquine (300 mg base) can be given until delivery and for the first month of breastfeeding. After breastfeeding for one month, based on G6PD status, primaquine can be given to prevent future relapses.

3.5 ADRs

Key ADRs associated with primaquine and tafenoquine. Comprehensive details of potential ADRs are provided in the relevant product data sheets for the medicines used in the case management of *P. vivax*. However, there are certain common and/or potentially serious ADRs relating to the use of primaquine and/or tafenoquine that require special attention; these are summarized in Box 7.

Box 7. Key ADRs associated with primaquine and tafenoquine

Drug-induced haemolysis

Dose-dependent drug-induced haemolysis in individuals with G6PD deficiency can be caused by both primaquine and tafenoquine.

- Clinical symptoms generally present at day 2–5 following the start of treatment.
- Health care workers and patients should be aware of the symptoms of haemolysis and the necessary action to take should these occur (Sections 1.3 and 3.3).

Abdominal pain, vomiting and other gastrointestinal symptoms are dose-related side-effects, particularly with higher doses of primaquine. These symptoms can be reduced in frequency and severity by taking the medicine with food.

Methaemoglobinaemia is a condition in which an abnormal amount of methaemoglobin is produced. Methaemoglobin cannot release oxygen effectively, leading to reduced oxygen delivery to tissues.

- Mild to moderate increases in methaemoglobin levels occur typically within hours of dosing, particularly with higher doses of primaquine.
- Most cases are asymptomatic, and severe and life-threatening methaemoglobinaemia is rare, so routine monitoring of methaemoglobin is not required.
- Clinical symptoms such as bluish discoloration of the skin and lips should prompt hospitalization for immediate assessment and supportive care with oxygen until resolution.

Monitoring and management of haemolysis. Drug-induced haemolysis clinically manifests normally between days 2 and 5 after the initiation of primaquine or tafenoquine on day 1. Signs and symptoms of drug-induced haemolysis are summarized below in Box 8.

Box 8. Checklist of symptoms of AHA

Key signs

- ☐ Pallor
- ☐ Dark (red or black) urine
- ☐ Jaundice (yellowing of the skin or eyes)

Other signs and symptoms

- ☐ Severe fatigue
- ☐ Fever
- ☐ Dizziness
- ☐ Breathlessness

When a patient presents with symptoms of AHA following 8-aminoquinoline administration, the patient should be managed as indicated below in Box 9.

Box 9. Checklist for the management of AHA

At all levels of the health system

- ☐ Stop administering primaquine.
- ☐ Give oral hydration.

In the community

- ☐ Refer the patient to the nearest facility with trained health care personnel and the required capacities.

Referral criteria and procedures will need to be tailored to the context and facilities available.

Lower referral level

- ☐ Make a clinical assessment; decide whether referral to a higher level facility is necessary.
- ☐ Determine haemoglobin levels[a], if available.
- ☐ Determine serum creatinine, if available.

Higher referral level

- ☐ Make a clinical assessment.
- ☐ Determine haemoglobin, serum creatinine and blood urea nitrogen.
- ☐ Give a blood transfusion, if necessary, as per standard clinical management protocols.
- ☐ Assess for acute kidney injury and manage as per standard clinical management protocols, which may include intravenous fluid support or potentially renal replacement therapy.

[a] Small declines in haemoglobin (10–20%) are common with malaria infection and with the initiation of antimalarial therapy. However, additional symptoms, such as dark urine, that are particularly aggravated at days 2–5 suggest drug-induced haemolysis.

Malaria microscopy is done to confirm parasite clearance and assess blood cell morphology, and laboratory tests should be done, including a full blood count and urinalysis, to assess causality and inform appropriate treatment. There are key clinical and laboratory findings for identifying G6PD-associated AHA (Box 10).

Box 10. Clinical and laboratory findings associated with G6PD-dependent AHA induced by 8-aminoquinolines

- G6PD deficient or intermediate enzyme activity
- Genetic confirmation of a G6PD deficient variant
- Rapid decline in haemoglobin within five days of treatment with primaquine or tafenoquine
- Intravascular haemolysis resulting in haemoglobinuria (and abdominal pain)
- Reticulocytosis around 4–7 days after onset of AHA
- Elevated lactate hydrogenase and unconjugated bilirubin
- Low or undetectable haptoglobin
- Methaemoglobinaemia (sometimes)
- Blood slides showing contracted erythrocytes, spherocytes
- The presence of Heinz bodies with supravital staining with methyl violet, and highly specific hemi-ghosts (bite cells) on blood slides
- Negative direct antiglobulin (Coombs test); a positive test would indicate an immunological etiology.

If G6PD-associated AHA is confirmed, treatment will depend on the severity of haemolysis and other underlying risk factors.

- Haemoglobin levels guide the clinical management, taking into consideration the patient's clinical condition, physiological state and specific risk factors. In general, blood transfusion is considered when haemoglobin levels drop to below 7 g/dL in otherwise stable patients but may be considered at 8–9 g/dL in patients who are at risk of complications, such as in older adults, children, pregnant women, and those with pre-existing cardiovascular disease or respiratory distress.
- An adequate fluid and hydroelectrolytic balance should be maintained to prevent acute kidney injury and pulmonary oedema, both of which are potential complications of AHA.
- Acute kidney injury may require renal replacement therapy, requiring facilities for haemodialysis.

Attributing the AHA to drug treatment requires a case investigation, considering the timing of treatment and the exclusion of other potential causes. An example of the process used in the Tafenoquine Roll-out Study (TRuST) feasibility study in Brazil is available in Annex 1.

3.6 Patient follow-up

Post-treatment follow-up of patients should be incorporated into the routine clinical follow-up as per national treatment guidelines. The feasibility of patient follow-up will depend on the country context. The goal of follow-up is to monitor adherence to treatment and occurrence of ADRs. Assuming that treatment is initiated and supervised on day 1, follow-up could:

- support **adherence** to the required primaquine dosing at all or some time points, as feasible in the intended area of implementation, on **days 2–7 or days 2–14** for daily primaquine, depending on the treatment duration, or weekly in **weeks 2–8** with weekly primaquine;
- assess **symptoms of haemolysis** on **days 3–5** for tafenoquine or primaquine and in each week of treatment for weekly primaquine;
- confirm **clinical cure** or clearance of blood-stage infection on **day 28**; and
- assess **prevention of recurrence** at a point **after day 28**, depending on the relapse periodicity and feasibility of following patients.

The follow-up visits are opportunities for patient counselling and community sensitization, supported by educational materials, and may be encouraged through SMS reminders, support from community health workers (CHWs), and transport fees to overcome economic barriers to return visits.

4. Planning and implementation

Update of national documents. The initial key step to drive treatment policy change within a country is to update the national treatment guidelines, in line with the WHO guidelines on the management of *P. vivax* malaria *(2)*. The relevant case management updates should also be included in the national malaria strategic plan and malaria annual operational plans.

Countries should also ensure that the medicines and G6PD tests have the necessary national regulatory approval and are included in the National Essential Medicines List and the Essential Diagnostics List, respectively. Depending on the country, there may also be a need to update national health regulations to allow specific health care workers to perform diagnostics, such as malaria RDTs and G6PD tests to guide anti-relapse treatment.

A well developed strategy and national plan ensure that *P. vivax* case management implementation is effective and sustainable, and addresses the country-specific context and requirements. The national strategy will guide decision-making and planning to implement the new national treatment policies and goals.

Situational analysis. A situational analysis at national and subnational levels should be undertaken to facilitate adoption and implementation. Areas to be evaluated include the epidemiology of *P. vivax* malaria, prevalence and distribution of G6PD deficiency, and health care system readiness to adequately deploy anti-relapse treatment, among others.

Further information and guidance can be found in the WHO publication *Service availability and readiness assessment (SARA): an annual monitoring system for service delivery: reference manual (18)*.

National implementation strategy. The programmatic objectives and implementation scenarios will need to be integrated into the broader malaria case management implementation plans, which determine who, what, where, how and when the policy should be deployed within each implementation scenario.

A costed integrated implementation plan should be developed and used for resource mobilization. Engagement with relevant stakeholders is essential to ensure that resource needs are adequately catered for. The detailed budget should outline all expected costs related to the intervention, considering direct costs (e.g., procurement of antimalarial medicines, diagnostic tests and required consumables) and indirect costs (e.g., training of health personnel, supervision and monitoring systems).

Note that feasibility and pilot studies assess how new tools, such as G6PD testing and the introduction of tafenoquine and primaquine, can be integrated into routine health services under real-world conditions. Practical challenges can be identified and addressed, such as health worker training needs, supply chain requirements, patient adherence and community acceptance. Such studies also afford the opportunity to test operational protocols and safety monitoring systems and inform cost-effectiveness analyses. By generating contextual evidence and engaging stakeholders, pilot study experiences can support effective, scalable and appropriate roll-out of radical cure strategies. Examples of such studies, lessons learned and cost-effectiveness evaluations are provided in Annex 2, Annex 3 and Annex 4, respectively.

4.1 Supply chain management

Effective supply chain management ensures that essential malaria commodities, including medicines, malaria RDTs and G6PD tests (analysers, test devices and controls), and sufficient ancillary items (such as gloves, alcohol swabs, waste containers, sample collectors, etc.) are available in the right quantities, at the right time, at the right place. The aim is to ensure uninterrupted access while minimizing wastage.

Proper storage of the commodities is essential to ensure their quality, efficacy and availability when needed. Particular attention should be paid to ensuring that the latest manufacturers' recommendations on both shelf life and storage conditions are followed. As there are substantial shelf-life differences between 8-aminoquinoline medicines, G6PD tests and QC kits (see Annex 5), procurement and dissemination of individual commodities need to be carefully planned and potentially staggered accordingly. A comprehensive supply chain management plan involves optimal coordination of procurement, distribution, storage and monitoring of malaria-related supplies, considering their individual shelf lives and storage requirements.

Accurate quantification is essential to prevent overstocking (which may lead to wastage) or understocking (which may cause stockouts, hinder programmatic activities, and negatively impact patients' trust in the health system). NMPs, in collaboration with the central medical stores, will have tools for quantification, usually based on consumption or morbidity methods, and access to the key epidemiological data for the national context. The quantification of commodities should be integrated in national supply chain management and aligned with the national policy, guided by the new *P. vivax* malaria case management guidelines. Specific considerations for the quantification of required medicines and tests for *P. vivax* case management apply; a corresponding overview is provided in Annex 5.

4.2 Training and capacity-building

Effective implementation of the *P. vivax* treatment algorithm requires workforce training, practical support and integration of new skills into daily routines. Regular refresher courses, supportive supervision and supportive learning environments are key for maintaining health care provider confidence and competence.

Training materials. Standardized training materials, including job aids and flow charts, are needed, which can be developed from materials already available in the country. The specific training materials required will depend on the implementation strategy. Annex 6 provides an overview of training, with examples of the typical range of training materials needed for implementation of *P. vivax* radical cure with semi-quantitative G6PD testing, primaquine and tafenoquine.

Case management. Training for *P. vivax* malaria case management should be integrated into the national case management training strategy, including the use of cascade training methodologies. The goals of the training package are to:

- ensure a comprehensive understanding of the importance of proper G6PD testing and *P. vivax* radical cure for both the individual patients as well as the communities in which they live;
- demonstrate full competency in performing G6PD testing, and using and interpreting the G6PD test results to guide treatment that is appropriate for the country or specific setting;

- demonstrate full competency in dispensing *P. vivax* treatment including radical cure;
- minimize risks by providing appropriate patient counselling and follow-up;
- identify ADRs and take appropriate action in terms of referral and reporting;
- ensure comprehensive understanding of the need for regular QC of G6PD tests and the importance of correct storage conditions for both medicines and tests; and
- support stock management, record keeping and reporting.

G6PD testing. Specific training will be required on performing the G6PD test and interpreting its results in view of patient counselling and treatment provision, guided by the specific manufacturer's instructions for use. Additional G6PD diagnostic test resources are available from the G6PD Operational Research Community of Practice *(19)*; these include training videos on thematic areas: e.g., collecting blood from the finger, taking blood from the tube, capillary blood procedure and printer connection. A general outline for G6PD test training is provided in Annex 6, and an example video on G6PD testing can be found on the MMV YouTube channel *(20)*.

Pharmacovigilance. Pharmacovigilance involves detecting, reporting, assessing, understanding and preventing ADRs and other related problems. Pharmacovigilance of the medicines used for *P. vivax* radical cure should be well incorporated into the overall pharmacovigilance system in the country.

WHO provides guidance on establishing and strengthening pharmacovigilance *(21)*, and has developed and introduced various tools and techniques for each stage, with further tools in development *(22)*. The consolidated WHO guidance and information on pharmacovigilance is available online *(21)*; further information on the implementation of a framework for pharmacovigilance of tafenoquine and primaquine is available in Annex 7.

Safety of medical devices. Feedback on the safety, quality and performance of medical devices, such as RDTs and G6PD tests, is also an important requirement for ensuring patient safety. Any problems or adverse events related to WHO-recommended medical devices should be reported to WHO. More details can be found on the WHO Regulation and Prequalification website *(23)*.

4.3 Supportive supervision and mentoring

Supervision of *P. vivax* case management should be integrated into supervision of quality of care in health facilities, including diagnosis of *P. vivax*, G6PD testing, and radical cure with primaquine and tafenoquine.

The aim of supportive supervision is to ensure the safe and effective deployment of anti-relapse therapies. For supervisors to provide effective on-the-job training to health workers, they must be well informed about the specific protocols for G6PD testing and treatment, use standardized procedures, and be capable of delivering high-quality, context-sensitive training and supervision *(24)*.

Based on the experiences from early adoption countries, supervision should focus on the following key elements:

- **correct performance and interpretation of G6PD tests**, with clear protocols for patient classification and follow-up and the specific changes to *P. vivax* malaria case management;
- **eligibility assessment and treatment decision-making**, considering factors such as age, breastfeeding status and pregnancy status in addition to G6PD test results;
- **counselling skills**, including communicating the rationale for testing, the importance of adherence and potential ADRs;
- **accurate documentation and reporting**, including recording of G6PD test results, treatment decisions and patient outcomes to support adherence to protocols and pharmacovigilance; and
- **use of job aids and decision support tools**, which improve health worker confidence and reduce clinical errors.

To identify supervision needs, consider:

- the scope of changes introduced relative to current practice;
- the need for training in supportive supervision techniques, observation and performance of G6PD testing, including problem-solving, adult training techniques, time management, two-way communication, and skills in coaching and mentoring;
- use of supervision reports to tailor support and address common themes and challenges; and
- develop tools for competency evaluation of supervisors and refresher training.

4.4 Community-based activities

Community engagement. Community engagement is necessary to raise awareness of *P. vivax* malaria and encourage health-seeking behaviours. With the implementation of near-patient G6PD testing, it is key to sufficiently address any fears or stigma regarding testing. Furthermore, the lack of familiarity with tafenoquine as a new treatment option needs to be managed to increase acceptability. It is, therefore, important to develop a comprehensive community awareness and behaviour change communication programme to accompany *P. vivax* radical cure implementation.

Non-health personnel can provide channels for delivering health education messages and can work in partnership with health providers, for example, via school children to their families or faith-based organizations. For any activity conducted within the community, it is important to consult, involve and collaborate with multiple stakeholders at the local level.

CHWs. CHWs and volunteers have been successfully deployed to deliver health education initiatives within their communities but must receive adequate training to build capacity and expertise. Where CHWs are involved, their training content should be simple, using clear, accessible language. Visual aids, practical demonstrations and interactive activities can enhance understanding and retention. Regular opportunities for training and skill development as well as monitoring are needed to enhance community acceptance. Consideration must also be given to the motivation and retention of trained CHWs and volunteers. It is important to recognize the contribution of these individuals.

Further general information is available in the WHO publications *Community engagement: a health promotion guide for universal health coverage in the hands of the people (25)* and *WHO guideline on health policy and system support to optimize community health worker programmes (26)*.

4.5 Emergency settings

Humanitarian emergencies often create conditions that disrupt routine health services while simultaneously increasing the risk of malaria transmission. The new *P. vivax* malaria treatment options present specific additional challenges for the management of *P. vivax* malaria in emergency settings, given the need for G6PD testing and the new tafenoquine and primaquine treatment options. The WHO field manual on malaria control in emergencies *(2025)* provides operational-level guidance for delivering malaria services during crises *(27)*. More general information is available in the WHO *Emergency response framework (28)*.

5. Monitoring and evaluation

Monitoring refers to the regular collection and analysis of data to ensure that a programme is running effectively and to make adjustments where needed. Evaluation is a more in-depth review, conducted at specific intervals or for specific purposes, that examines the longer term results and impacts of an intervention. Preparing a robust M&E system should commence prior to implementation, and activities should be well integrated into the overall performance framework for monitoring and evaluating malaria case management services.

5.1 Key indicators

For the implementation of *P. vivax* radical cure and near-patient G6PD testing, a structured approach to M&E should be adopted, building on indicators already existing within the health management information system. All indicators should be aligned with existing national indicators on case management. Examples of indicators for monitoring *P. vivax* case management are given in Tables 5 and 6, listed by the following categories:

- **input indicators:** the resources invested in a malaria programme to achieve its objectives, including financial, human and material inputs;
- **process indicators:** activities carried out to transform inputs into outputs;
- **output indicators:** the direct results of delivering services or interventions;
- **outcome indicators:** the short- to medium-term changes generated by programme implementation; and
- **impact indicators:** the disease burden, namely malaria morbidity and mortality, aligned with the programme objectives.

The most relevant indicators will depend on the programmatic objectives and implementation strategy.

Table 5. Examples of input, process and output indicators for *P. vivax* case management

Input indicators		
Health system capacity	Number of: • health care facilities at each level • health care workers at each level • laboratory technicians at each level	Assess: health system facilities and human resources
Commodities supply chain	Number of: • G6PD tests procured • G6PD QC kits procured • chloroquine tablets procured • ACT tablets procured • primaquine tablets procured • tafenoquine tablets procured	Assess: quantification and procurement
Process indicators		
Health system capacity	Number of: • staff trained in performing G6PD tests and radical cure at each level	Assess: training for radical cure and G6PD testing according to plans
Commodities supply chain	Number of: • essential commodities for G6PD testing and radical cure distributed to target health facilities in the previous three months	Assess: distribution and supply management
Output indicators		
Health system readiness	Number of: • G6PD tests performed and radical cure dispensed at each level	Evaluate: services delivered for G6PD testing and radical cure
Commodities availability	Proportion of health care facilities with: • no stockouts of essential commodities for G6PD testing and radical cure in the previous three months	Evaluate: supply chain management

Table 6. Examples of outcome and impact indicators for *P. vivax* case management

Outcome indicators: routine data collection		
Health system demand	Proportion of: • *P. vivax* diagnostic tests performed	Assess: *P. vivax* diagnostic
Quality of care	Proportion of *P. vivax* cases with: • correct radical cure dispensed according to G6PD tests results	Assess: adherence to guidelines on G6PD testing and radical cure
Safety and tolerability	Proportion of *P. vivax* cases presenting after radical cure with: • haemolysis • gastrointestinal ADRs • methaemoglobinaemia • hospitalization for AHA	Review: adherence to guideline on safety monitoring
Impact indicators: routine data analysis		
Disease burden	Changes over time in reporting of: • *P. vivax* test positivity rate • *P. vivax* cases	Assess: impact against programme objectives
Risk–benefit	Changes over time in: • hospitalizations for *P. vivax* malaria or ADRs due to radical cure	Assess: impact against programme objective

5.2 Controlled deployment of tafenoquine

In all regions treating blood-stage *P. vivax* infections with chloroquine, early deployment of tafenoquine can be undertaken in a controlled manner through a **careful, phased and monitored** introduction to ensure safe and effective use while simultaneously introducing the necessary capacities for G6PD testing.

Key components include:

- **national registration** of tafenoquine and semi-quantitative G6PD test(s) and **policy updates;**
- **step-wise roll-out:** implementing tafenoquine and G6PD testing in selected regions, municipalities or specific malaria foci, ensuring feasibility and operational capacity before national scale-up;
- **safety monitoring:** establishing robust pharmacovigilance systems to monitor adverse events, especially possible drug-induced haemolysis in individuals treated for malaria, as well as monitoring the use of G6PD testing and correct interpretation by end-users;

- **capacity-building:** training health care workers on G6PD testing, tafenoquine and high-dose primaquine administration, establishing a referral network for haemolysis management and patient counselling; and
- **data collection:** gathering real-world evidence on safety, effectiveness and feasibility to inform broader implementation.

Controlled deployment will minimize potential risks, facilitate the effectiveness of the interventions and optimize resources for broader adoption across the region.

A minimum set of parameters should be monitored, documented and evaluated. Therefore, any form of controlled deployment should incorporate M&E systems for the collection data on the impact, effectiveness and safety of tafenoquine.

This evidence, systematically collected and collated, will contribute to the revision and update of the current WHO recommendation on tafenoquine as an anti-relapse treatment alternative to primaquine.

Examples of key parameters to monitor include:

- assessment of treatment success: patient follow-up on pre-determined days (see Section 3.6) and documentation of the number of recurrences over time;
- tolerability of tafenoquine compared to primaquine;
- detection of ADRs: patient follow-up on pre-determined days (see Section 3.6) and documentation of the number and severity of ADRs, particularly drug-induced haemolysis, abdominal pain, vomiting and other gastrointestinal symptoms, and methaemoglobinaemia (see also Section 3.5, Box 7);
- number of malaria cases/hospital admissions/deaths;
- number of patients requiring blood transfusion following administration of 8-aminoquinolines;
- documentation of medical errors, such as incorrect treatment for specific patient characteristics (e.g., pregnancy or breastfeeding status, G6PD enzyme activity, age), dosing errors (e.g., age, weight), etc.;
- documentation of diagnostic errors, such as incorrect G6PD test use, incorrect interpretation of test result, issues with QA of the G6PD test, etc.; and
- stockouts of required commodities.

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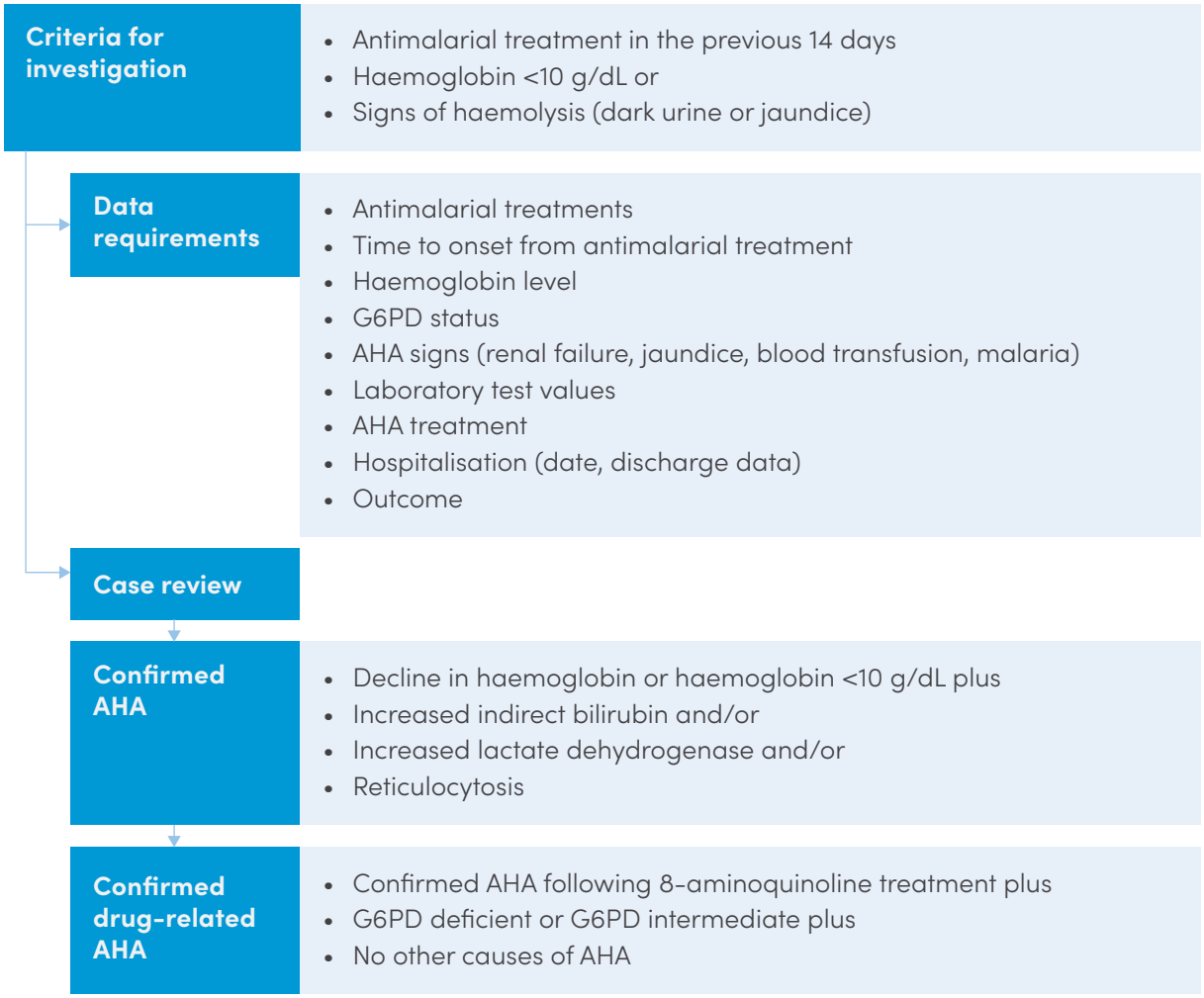
Annex 1. AHA case investigation

To accurately assess the risks of primaquine and tafenoquine, it is important to conduct a thorough case investigation of any suspected cases of G6PD-associated AHA (Fig. A.1.1) *(1, 2)*. This process is required to attribute causality to treatment as opposed to *P. vivax* infection or other causes. This information is important for directing appropriate mitigation and for pharmacovigilance. The flow chart in Fig. A1.1 outlines the criteria used to identify cases of G6PD-related, drug-induced AHA during the TRuST study conducted in Brazil, based on well established criteria *(1, 2)*.

Fig. A1.1. Procedures and data requirements for AHA case investigation (Brazil)



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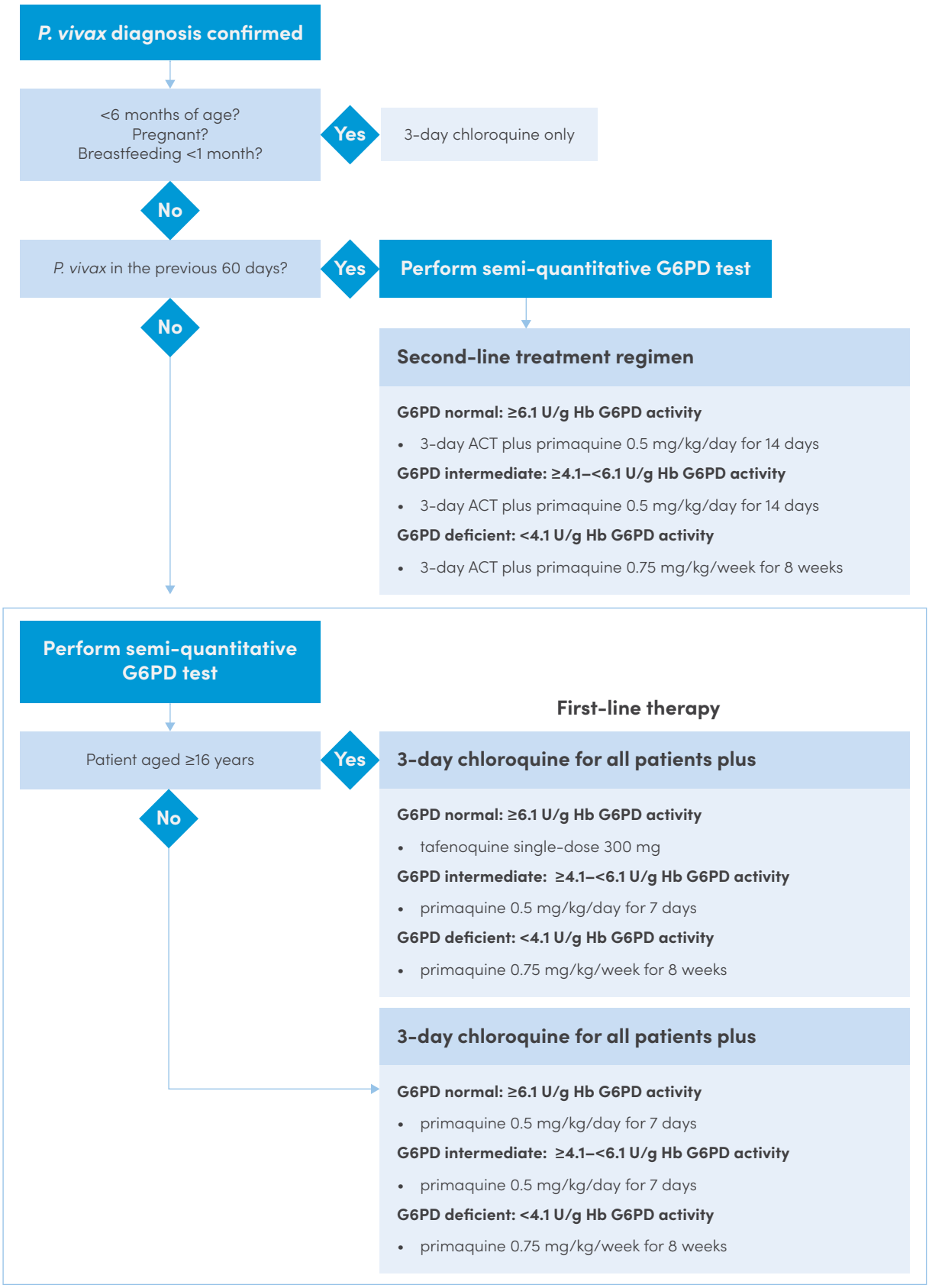
Annex 2. Feasibility studies and pilot implementations

This Annex provides information on the feasibility studies and pilot implementations in Brazil, Indonesia and Papua New Guinea, Peru and Thailand.

Brazil. TRuST was the first real-world observational study evaluating the feasibility of providing relapse-prevention treatment for *P. vivax* malaria using tafenoquine or primaquine following near-patient G6PD testing (Fig. A2.1) *(1)*. Co-sponsored by the Brazilian Ministry of Health and MMV, the study took place in Manaus, Amazonas, and Porto Velho, Rondônia *(1–3)*. A short film showcasing the implementation of TRuST in Brazil is available on the MMV YouTube channel *(4)*.

Fig. A2.1. Treatment algorithm for the TRuST study in Brazil



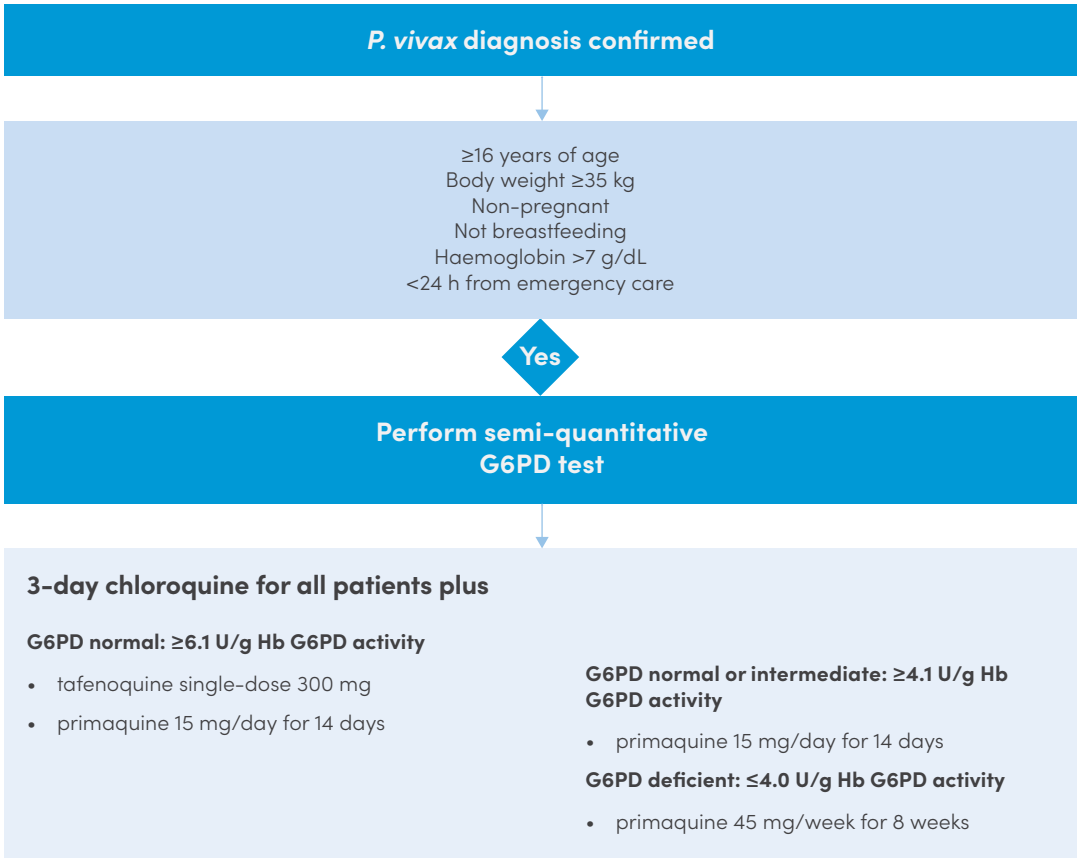
Indonesia and Papua New Guinea. As part of the Partnership for Vivax Elimination (PAVE), the Menzies School of Health Research and the Burnet Institute are conducting feasibility studies in Indonesia and Papua New Guinea to assess the safety, feasibility and cost-effectiveness of a high-dose primaquine regimen for treating *P. vivax* malaria. Known as the SCOPE study (short-course primaquine for the radical cure of *P. vivax*), the research focuses on providing near-patient G6PD testing and using a shorter seven-day treatment regimen (Table A2.1). These studies, supported by Unitaid, aim to generate evidence that will guide national policy-makers in Indonesia, Papua New Guinea, and potentially other regions to adopt these strategies, helping to reduce the burden of *P. vivax* malaria. WHO has emphasized the need for further evidence on the safety of high-dose primaquine, and these studies seek to address that gap (information provided by MMV).

Table A2.1. Primaquine regimens used in the SCOPE study

G6PD activity	Primaquine regimen
Normal (> 70% of normal G6PD activity)	1 mg/kg daily for 7 days Age > 6 months and > 5 kg in Indonesia Age > 1 year in Papua New Guinea
Intermediate (30–70% of normal G6PD activity)	0.5 mg/kg for 14 days Age > 6 months and > 5 kg in Indonesia Age > 1 year in Papua New Guinea
Deficient (< 30% of normal G6PD activity)	0.75 mg/kg weekly for 8 weeks Age > 6 months and > 5 kg in Indonesia Age > 1 year in Papua New Guinea

Peru. PAVE Peru is a 25-month feasibility study in Loreto, Peru, which began in April 2023. Conducted under PAVE, with funding from Unitaid and sponsored by MMV, the study aims to assess the feasibility, acceptability and cost of administering primaquine or tafenoquine after G6PD testing under real-world conditions (Fig. A2.2). The study includes both quantitative and qualitative components and will also assess the effectiveness of training delivered. The research is led by Universidad Peruana Cayetano Heredia. Loreto, Peru's largest department, covers nearly one third of the country and is sparsely populated due to its remote location in the Amazon Basin. In 2020, the department accounted for 84% of Peru's 15 822 reported malaria cases. The treatment algorithm applied in PAVE Peru is shown in Fig. A2.2 (information provided by MMV).

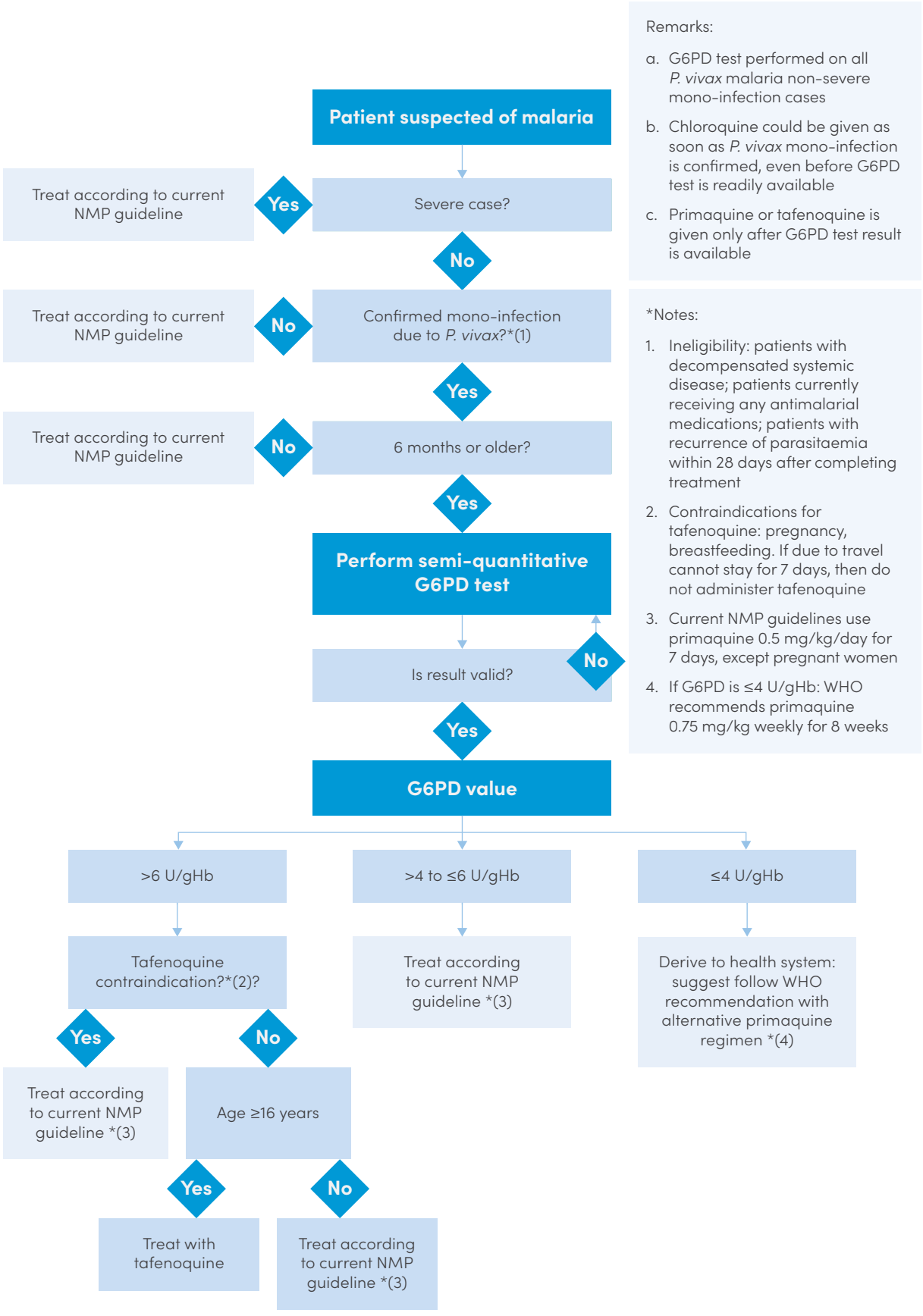
Fig. A2.2. PAVE Peru treatment algorithm



Thailand. The ARCTIC (Assessing Radical Cure Treatment in Routine Care) study assessed the feasibility of using G6PD testing and radical cure treatment with tafenoquine or primaquine for *P. vivax* malaria in Thailand's public health system (Fig. A2.3) *(5)*. Conducted in Mae Hong Son and Yala provinces, where *P. vivax* is prevalent, this study was the first in the Asia-Pacific region to evaluate single-dose tafenoquine in routine care. The study had two phases: phase 1 (September–December 2022) in five hospitals, followed by phase 2 (January–August 2023), which expanded to four additional malaria clinics. The study was led by Thailand's Ministry of Public Health, with support from MMV.

A short film introducing the ARCTIC feasibility study in Thailand is available on the MMV YouTube channel *(6)*.

Fig. A2.3. Treatment algorithm for the ARCTIC study in Thailand



Remarks:

a. G6PD test performed on all *P. vivax* malaria non-severe mono-infection cases
b. Chloroquine could be given as soon as *P. vivax* mono-infection is confirmed, even before G6PD test is readily available
c. Primaquine or tafenoquine is given only after G6PD test result is available

*Notes:

1. Ineligibility: patients with decompensated systemic disease; patients currently receiving any antimalarial medications; patients with recurrence of parasitaemia within 28 days after completing treatment
2. Contraindications for tafenoquine: pregnancy, breastfeeding. If due to travel cannot stay for 7 days, then do not administer tafenoquine
3. Current NMP guidelines use primaquine 0.5 mg/kg/day for 7 days, except pregnant women
4. If G6PD is ≤4 U/gHb: WHO recommends primaquine 0.75 mg/kg weekly for 8 weeks

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Annex 3. Lessons learned from pilot implementations

PAVE was launched in July 2021 as an umbrella initiative consolidating key *P. vivax* access work led by PATH and MMV. The initiative supported countries in adopting new and existing tools and approaches to achieve universal access to the best clinical practices for *P. vivax* case management and to accelerate *P. vivax* elimination through:

- working with NMPs to identify optimal radical cure tool options and strategies for their given contexts to achieve higher patient coverage;
- generating and making available high-quality evidence on *P. vivax* case management that can be considered by national governments in making policy decisions and guiding implementation; and
- advancing the development of quality-assured medicines and diagnostics for *P. vivax*.

PAVE is supporting feasibility studies providing appropriate radical cure (primaquine or tafenoquine) following G6PD testing in Brazil, Ethiopia, Indonesia, Papua New Guinea, Peru, Thailand and Viet Nam, and pilot implementations of near-patient G6PD testing in Cambodia, Colombia, Guatemala, Honduras, India, Lao People's Democratic Republic, Pakistan and Panama. Key observations from these experiences have been collated into the following document: *Lessons learned from operational research: key considerations for introducing new radical cure tools for P. vivax malaria (1)* and are summarized in Box A3.1 *(2)*. Case studies are outlined in Box A3.2.

Box A3.1. Summary experiences of the PAVE project

Integration with existing systems. Introducing new tools such as G6PD semi-quantitative testing, tafenoquine and different primaquine regimens requires seamless integration with existing health systems. This involves ensuring compatibility with the existing diagnostic and treatment frameworks, while also addressing any policy gaps or barriers at different levels.

Cost reduction through strategic deployment. Costs can be minimized by deploying G6PD tests to high-caseload areas and ensuring efficient procurement practices, such as checking expiry dates and using multilateral procurement channels to avoid markups.

Using established resources. PAVE has developed resources for training, QA and operational research. These resources are available through the *P. vivax* information hub *(3)*.

Quality training is essential. Effective training for malaria workers is key, given the complexity of G6PD tests and their interpretation compared to malaria RDTs. Training should include a practical element with participants having "hands-on" use of the tools, followed by proficiency assessments to ensure that health care workers are able to provide patients with good quality care. A low trainee-to-trainer ratio (4:1 or 5:1) and dedicated training time are recommended. Monitoring the effectiveness of training by recording practical and theory post-test assessment results on a programme monitoring database can help identify who needs to be re-trained immediately and where supervision should be initially targeted.

Supervision maintains quality. Post-training supervision is vital to maintain high-quality patient care, especially in areas where G6PD tests are new or infrequently used and during the first 6–9 months following implementation. Integrating G6PD testing oversight into ongoing supervision activities, creating new checklists and conducting regular proficiency assessments help to sustain competent use. Where feasible, supervision reports should be included in the programme monitoring database, enabling the NMP to continually assess where supervision is most needed.

Pharmacovigilance systems. Effective pharmacovigilance is important to maintain trust in the health system and should be incorporated into malaria case management.

Box A3.2. Case studies of *P. vivax* radical cure pilot implementation

***P. vivax* radical cure implementation, Brazil**

Pilot studies were conducted in the Brazilian Amazon to inform national roll-out within the Brazilian national health system.

- **SAFEPRIM** evaluated the operational feasibility of near-patient semi-quantitative G6PD testing prior to primaquine administration. Conducted between mid-January 2020 and December 2020, the study indicated that the test was feasible and well accepted by health care providers and patients *(4)*.
- **TRuST** examined the operational feasibility of a revised treatment algorithm for *P. vivax* radical cure including near-patient semi-quantitative G6PD testing prior to primaquine or tafenoquine *(5, 6)*. The study was conducted between September 2021 and August 2022, with implementation across higher/medium-level health care facilities in phase 1 and lower level health facilities in phase 2. There was high adherence to the treatment algorithm across the health system levels, and treatment was shown to be effective, supporting national adoption.
- A parallel qualitative study (**QualiTRuST**) considered health care provider perceptions of training for the semi-quantitative G6PD test and tafenoquine, the results of which were used to develop a training framework to support national adoption *(7, 8)*.

***P. vivax* radical cure implementation, Thailand**

ARCTIC was an operational feasibility study examining the real-world use of near-patient G6PD testing and appropriate radical cure treatment with tafenoquine or primaquine within Thailand's public health system *(9)*. This was the first feasibility study to use single-dose tafenoquine in routine care in the Asia-Pacific region. The study was conducted in Mae Hong Son and Yala provinces, which have high rates of *P. vivax* malaria. The study was conducted in two phases. The first phase took place in five hospitals from September to December 2022. After an interim review by an Independent Study Oversight Committee, phase two was approved and ran from January to August 2023. Phase two continued in the original five hospitals and expanded to include four malaria clinics. Semi-quantitative G6PD testing and radical cure with tafenoquine or primaquine was found to be highly feasible and supported roll-out to control a *P. vivax* outbreak along the Thailand–Myanmar border *(9)*.

***P. vivax* radical cure implementation, Cambodia**

Cambodia has implemented G6PD testing and radical cure with primaquine at the health centre level *(10–15)*. The country has an extensive network of 2548 village malaria workers and 275 mobile malaria workers covering most rural villages in malaria-endemic areas. *P. vivax* malaria patients identified by these community-based volunteers are referred to health centres for G6PD testing and radical cure treatment. Both village malaria workers and mobile malaria workers supervise radical cure, monitor clinical recovery, check urine colour for signs of haemolysis, ensure adherence on days 3, 7 and 14, and report patient outcomes. However, referral completion rates were suboptimal *(10)*. A study conducted in the Kravanh district demonstrated the feasibility of village malaria workers and mobile malaria workers undertaking near-patient G6PD testing within the community, given regular supervision, support and coordination from the health centre *(12)*. This provides a potential model for roll-out to remote and hard-to-reach populations *(10)*.

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Annex 4. Cost-effectiveness

In a particular setting, *P. vivax* radical cure and G6PD testing need to be operationally feasible and have a positive risk–benefit assessment both clinically and epidemiologically. If these criteria are met, then cost-effectiveness should be considered.

Key aspects driving direct costs to the health system are provided in Table A4.1. In addition, there will be indirect costs including lost productivity, transportation expenses and increased vulnerability to other illnesses, among others. There will also be costs of continued *P. vivax* transmission in the community.

Table A4.1. Key components of the direct costs of *P. vivax* radical cure for cost-effectiveness assessments

Costs of suboptimal treatment, including poor adherence to primaquine
• Mortality
• Morbidity
• Acute and chronic anaemia
• Hospitalization
• Relapse(s) treatment and adverse outcomes
Costs of inadequate G6PD testing
• Mortality from AHA
• Morbidity from AHA
• Hospitalization from AHA
Costs of optimal treatment
• Antimalarial medicines
• Malaria diagnostics
• G6PD test
• Training, supervision and M&E
• Data management
• QC and QA of RDTs and G6PD tests

Box A4.1 gives examples of cost-effectiveness evaluations undertaken in Brazil, Lao People's Democratic Republic and along the Thailand–Myanmar border.

Box A4.1. Examples of cost-effectiveness evaluations

Cost-effectiveness of semi-quantitative G6PD testing and primaquine in Brazil

An analysis of real-life data indicated high cost-effectiveness for semi-quantitative G6PD testing prior to administering primaquine within Brazil's public health system *(1)*. The incremental cost-effectiveness ratio (ICER) of G6PD screening versus primaquine administration without prior G6PD testing was US$ 495 per primaquine-related hospitalization avoided – equivalent to 7.3% of one Brazilian GDP per capita (US$ 6822).

Cost-effectiveness of semi-quantitative G6PD testing and tafenoquine in Brazil

The cost-effectiveness of *P. vivax* radical cure with G6PD semi-quantitative testing prior to administering tafenoquine in Brazil was evaluated using a transmission model *(2)*. Tafenoquine treatment was compared to seven-day primaquine (0.5 mg/kg/day) without G6PD testing. Scenarios considered tafenoquine use in adults only or in children over 2 years of age and assumed primaquine adherence rates between 30% and 90%. In all cases, tafenoquine administration following semi-quantitative G6PD testing was highly cost-effective with ICERs between 1.9% and 23.5% of the willingness-to-pay threshold. Notably, cost-effectiveness was demonstrated even at high rates of primaquine adherence, partly because of primaquine-related AHA hospitalizations and mortality in the absence of G6PD testing.

Cost-effectiveness of semi-quantitative G6PD testing in Lao People's Democratic Republic

A decision-tree modelling study evaluated the cost-effectiveness of unsupervised versus supervised primaquine with or without G6PD testing at a typical health facility *(3)*. The ICERs were US$ 96.72 for the G6PD test with the unsupervised primaquine strategy and US$ 184.86 for the G6PD test with the supervised primaquine strategy. Both ICERs were lower than the GDP per capita in the country. Sensitivity analysis revealed that low adherence to the 14-day primaquine regimen reduced the cost-effectiveness of both G6PD test strategies. Furthermore, the lower the number of *P. vivax* cases reported at a health facility, the higher the ICER. The expected budget requirement would be US$ 0.5 million if the G6PD test roll-out was selectively implemented based on the number of *P. vivax* cases reported at health facilities.

Thailand–Myanmar border cost-effectiveness analysis and online tool

A decision-tree model was developed comparing G6PD testing followed by primaquine, chloroquine alone, or primaquine without G6PD testing *(4)*. Compared to using chloroquine alone, the screening strategy had similar costs but averted 0.026 disability-adjusted life years (DALYs) per primary infection in males and 0.024 DALYs in females. Compared to administering primaquine without G6PD screening, the screening strategy offered modest cost savings while averting 0.011 DALYs in males and 0.004 DALYs in females. Probabilistic sensitivity analyses showed with over 75% certainty that G6PD testing was cost-effective at a willingness-to-pay threshold of US$ 500, which is well below Myanmar's per capita GDP benchmark *(4)*. The decision tree has been developed into an online tool for evaluating cost-effectiveness of G6PD near-patient tests *(5)*.

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Annex 5. Quantification

Specific requirements apply for the quantification of *P. vivax* malaria case management commodities in line with the updated treatment guidelines. Parameters for consideration and example calculations are provided in this Annex, subdivided by medicines and G6PD testing.

Note that there are substantial differences between 8-aminoquinoline medicines, G6PD tests and QC kits in terms of shelf life,[1] and procurement and dissemination of individual commodities need to be planned for and potentially staggered accordingly. Moreover, when introducing the new treatment options, the expected increase in health seeking and demand from planned **social and behaviour change communication campaigns** should be taken into account. In addition, sufficient **buffer stock** of all required commodities should be factored in to account for loss, theft, damage, unexpected supply gaps, and so on.

Medicines. The addition of tafenoquine to the menu of treatment options for *P. vivax* malaria case management will affect the quantification of the required mix of primaquine, chloroquine and ACTs, considering expected prevalences of different G6PD enzyme activity levels among patients in the intended area of use. Only patients with normal G6PD enzyme activity can be treated with tafenoquine or primaquine at a dose of 1 mg/kg daily for 7 days; intermediate patients will still need to be treated with primaquine 0.5 mg/kg daily for 14 days and deficient patients for 8 weeks with a weekly dose of 0.75 mg/kg body weight. Current recommendations are for tafenoquine to be administered with chloroquine, while primaquine can be administered with chloroquine or an ACT as per national treatment guidelines (Table A5.1). Table A5.1 illustrates the required combinations of tafenoquine or primaquine with chloroquine or ACTs depending on the G6PD enzyme activity only; additional factors for consideration, such as patient age or haemoglobin restrictions, and other factors that inform treatment decision-making (Section 3) are not included.

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[1] Example shelf lives of commodities currently prequalified by WHO:

- Primaquine (phosphate), 15 mg film-coated tablet: shelf life **24 months** *(1, 2)*.
- Tafenoquine. While adult and child formulations differ in their recommended shelf lives, the recommended storage conditions are the same, i.e., do not store above 30°C:
  - Tafenoquine 150 mg film-coated tablets: shelf life **60 months** *(3)*.
  - Tafenoquine 50 mg dispersible tablets: shelf life **24 months** *(4)*.
- SD Biosensor G6PD test. To perform the G6PD test, a handheld analyser is required, in which test devices are inserted; the shelf life of these test devices is **18 months**. Regular QC (e.g., when using the analyser for the first time, after having replaced batteries, when unexpected test results are obtained, etc.) needs to be performed to ensure the accuracy of the G6PD test, with the required controls having a shelf life of **12 months**. Note: The test kit should be stored at 2–30°C out of direct sunlight for the duration of its shelf life; it may be stored in a refrigerator at 2–8°C but should not be frozen *(5)*.

Table A5.1. Quantifying medicines for *P. vivax* malaria case management: illustrative mix of schizontocides and 8-aminoquinolines treatment options to cover different G6PD enzyme activity levels

Enzyme activity (percentage of normal G6PD enzyme activity)	Tafenoquine	Primaquine		
		1 mg/kg daily for 7 days	0.5 mg/kg daily for 14 days	0.75 mg/kg weekly for 8 weeks
G6PD normal (≥ 70%)	Chloroquine	Chloroquine or ACT	Chloroquine or ACT	
G6PD intermediate (≥ 30% to < 70%)			Chloroquine or ACT	
G6PD deficient (< 30%)				Chloroquine or ACT

In cases where the new primaquine dosing scheme of 1 mg/kg daily for 7 days is applied to G6PD normal patients, different age patterns and available product strengths need to be accounted for to obtain the required target dose (see Table A5.2). In Table A5.2, fields marked in grey reflect dosing with multiples of 15 mg tablets without the need to split the tablet. When 15 mg tablets are scored, half tablets can be considered to obtain the desired target dose. Besides the quality-assessed 15 mg tablets currently available on the market, primaquine products with 2.5mg and 5mg tablet strengths are now WHO prequalified *(6)*; WHO regularly updates the list of prequalified products with new product entries *(7)*.

Table A5.2. Primaquine target doses

Patient body weight (kg)	1 mg base/kg body weight daily for 7 days	0.5 mg base/kg body weight daily for 14 days	0.75 mg base/kg body weight weekly for 8 weeks
5	5.00	2.50	3.75
6	6.00	3.00	4.50
7	7.00	3.50	5.25
8	8.00	4.00	6.00
9	9.00	4.50	6.75
10	10.00	5.00	7.50
11	11.00	5.50	8.25
12	12.00	6.00	9.00
13	13.00	6.50	9.75
14	14.00	7.00	10.50
15	15.00	7.50	11.25
16	16.00	8.00	12.00
17	17.00	8.50	12.75
18	18.00	9.00	13.50

Patient body weight (kg)	1 mg base/kg body weight daily for 7 days	0.5 mg base/kg body weight daily for 14 days	0.75 mg base/kg body weight weekly for 8 weeks
19	19.00	9.50	14.25
20	20.00	10.00	15.00
21	21.00	10.50	15.75
22	22.00	11.00	16.50
23	23.00	11.50	17.25
24	24.00	12.00	18.00
25	25.00	12.50	18.75
26	26.00	13.00	19.50
27	27.00	13.50	20.25
28	28.00	14.00	21.00
29	29.00	14.50	21.75
30	30.00	15.00	22.50
31	31.00	15.50	23.25
32	32.00	16.00	24.00
33	33.00	16.50	24.75
34	34.00	17.00	25.50
35	35.00	17.50	26.25
36	36.00	18.00	27.00
37	37.00	18.50	27.75
38	38.00	19.00	28.50
39	39.00	19.50	29.25
40	40.00	20.00	30.00
41	41.00	20.50	30.75
42	42.00	21.00	31.50
43	43.00	21.50	32.25
44	44.00	22.00	33.00
45	45.00	22.50	33.75
46	46.00	23.00	34.50
47	47.00	23.50	35.25
48	48.00	24.00	36.00
49	49.00	24.50	36.75
50	50.00	25.00	37.50
51	51.00	25.50	38.25
52	52.00	26.00	39.00
53	53.00	26.50	39.75

Patient body weight (kg)	1 mg base/kg body weight daily for 7 days	0.5 mg base/kg body weight daily for 14 days	0.75 mg base/kg body weight weekly for 8 weeks
54	54.00	27.00	40.50
55	55.00	27.50	41.25
56	56.00	28.00	42.00
57	57.00	28.50	42.75
58	58.00	29.00	43.50
59	59.00	29.50	44.25
60	60.00	30.00	45.00
61	61.00	30.50	45.75
62	62.00	31.00	46.50
63	63.00	31.50	47.25
64	64.00	32.00	48.00
65	65.00	32.50	48.75
66	66.00	33.00	49.50
67	67.00	33.50	50.25
68	68.00	34.00	51.00
69	69.00	34.50	51.75
70	70.00	35.00	52.50
71	71.00	35.50	53.25
72	72.00	36.00	54.00
73	73.00	36.50	54.75
74	74.00	37.00	55.50
75	75.00	37.50	56.25
76	76.00	38.00	57.00
77	77.00	38.50	57.75
78	78.00	39.00	58.50
79	79.00	39.50	59.25
80	80.00	40.00	60.00
81	81.00	40.50	60.75
82	82.00	41.00	61.50
83	83.00	41.50	62.25
84	84.00	42.00	63.00
85	85.00	42.50	63.75
86	86.00	43.00	64.50
87	87.00	43.50	65.25
88	88.00	44.00	66.00

Patient body weight (kg)	1 mg base/kg body weight daily for 7 days	0.5 mg base/kg body weight daily for 14 days	0.75 mg base/kg body weight weekly for 8 weeks
89	89.00	44.50	66.75
90	90.00	45.00	67.50
91	91.00	45.50	68.25
92	92.00	46.00	69.00
93	93.00	46.50	69.75
94	94.00	47.00	70.50
95	95.00	47.50	71.25
96	96.00	48.00	72.00
97	97.00	48.50	72.75
98	98.00	49.00	73.50
99	99.00	49.50	74.25
100	100.00	50.00	75.00

Table A5.3 summarizes aspects to be considered for the quantification of schizontocides and 8-aminoquinolines; Box A5.1 provides an example forecasting of tafenoquine adult and paediatric formulations; Table A5.4 shows an example of a forecasting tool developed by MMV.

Table A5.3. Additional considerations for the quantification of medicines

Item	Considerations
8-amino-quinolines	• **G6PD prevalence.** Tafenoquine and primaquine 1 mg/kg/day for 7 days cannot be given to patients with < 70% of normal G6PD activity; accordingly, other treatment alternatives need to be quantified for individuals with deficient or intermediate levels of G6PD activity. • **Availability of G6PD analysers.** The number of G6PD analysers and their distribution in different health facilities will impact the quantification and distribution of tafenoquine and primaquine required in the specific settings. • **Tafenoquine.** The implementation of tafenoquine will decrease the need for primaquine. However, even in areas where tafenoquine is fully implemented, primaquine is still required to treat patients with < 70% of normal G6PD activity. Corresponding quantifications need to consider *P. vivax* prevalence and prevalences of G6PD normal, intermediate and deficient enzyme activity in patients. • **Primaquine.** The addition of tafenoquine to the menu of treatment options will decrease the need for primaquine. The change to a different primaquine dose scheme and treatment duration may alter the number of strengths/packs required. Note: At present, only 15 mg tablets are WHO-prequalified, but 2.5 mg, 5.0 mg and 7.5 mg tablets are currently under assessment by the WHO Prequalification Team; evaluation results are updated regularly on the website of the WHO Prequalification Team *(7)*. • **Formulation.** Adult versus required paediatric dosages/formulations of primaquine and tafenoquine need to be quantified separately (see Section 3.4). While primaquine can be given to children ≥ 1 month old, tafenoquine can only be given to children ≥ 2 years old. • **Pregnancy.** Neither primaquine nor tafenoquine can be given to pregnant women. • **Breastfeeding.** Primaquine (but not tafenoquine) can be given to women who have been breastfeeding for > 1 month. • **Shelf life.** There are differences in the shelf life of 8-aminoquinoline adult versus paediatric formulations (see Section 3.4).
Schizontocides	Consider adjustments in needs for schizontocides: • **Tafenoquine** is currently approved for use with **chloroquine** only. • **Primaquine** can be administered with **either chloroquine or an ACT.** For ACT quantification based on consumption and morbidity methods, see Step 2 of the WHO publication *Good procurement practices for artemisinin-based antimalarial medicines (8)*.
Second-line treatment	Quantify second-line treatment for *P. vivax* according to the 8-aminoquinoline regimen. The introduction and scale-up of effective anti-relapse therapy will reduce the need for second-line treatment.
G6PD testing method	Quantify medicine needs in line with G6PD testing availability: Semi-quantitative G6PD testing is mandatory before tafenoquine or primaquine 1 mg/kg/day for 7 days, while other primaquine regimens can be given following semi-quantitative or qualitative testing or in some circumstances without G6PD testing based on a risk–benefit assessment (see Sections 2.1 and 3.3, and Fig. 5)

Box A5.1. Example forecasting of tafenoquine requirements

Tafenoquine regular tablets (300 mg adult dose corresponds to two regular tablets of 150 mg):

A. **Number of confirmed *P. vivax* cases** (in patients > 35 kg; approximately 12 years old) seeking treatment in health facilities, **excluding** breastfeeding and pregnant women, as they cannot be treated with tafenoquine.

B. Estimated percentage of the *P. vivax* caseload that is likely to have **access to G6PD testing**. (G6PD testing is mandatory before tafenoquine administration and only G6PD normal patients can receive tafenoquine.)

C. **Estimated prevalence of G6PD deficient and G6PD intermediate** patients, as they cannot be treated with tafenoquine. These patients need to be treated with primaquine (daily or weekly dose, as appropriate – see Section 2).

=> Requirement for tafenoquine doses (300 mg) = A x B x (1 – C)

Tafenoquine dispersible tablets (50 mg):

D. **Number of confirmed *P. vivax* cases** weighing 10–35 kg (older than 2 years) seeking treatment in health facilities. (Tafenoquine cannot be used in children under the age of 2 years.)

=> Requirement for tafenoquine blister strips (50 mg x 3 tablets) = D x B x (1 – C)

Source: adapted from the document *Lessons learned from operational research: key considerations for introducing new radical cure tools for* P. vivax *malaria (9).*

Table A5.4. Example tafenoquine forecasting tool developed by MMV

	Estimated values	Calculations/assumptions
Age distribution		
Adults	70%	Adult/adolescent/child ratio varies by country/ region
Adolescents (12 yrs – 16 yrs)	10%	
Paediatrics aged > 2 yrs – < 12 yrs	18%	
Paediatrics < 2 yrs	2%	
Sex		
Males	60%	
Females	40%	1 - Males
Non-pregnant/ breastfeeding	85%	
G6PD activity		
G6PDd	7%	
G6PDi	10%	

	Estimated values	Calculations/assumptions
TQ eligible		
Males (adults/ adolescents/ paediatrics)	83%	1 - (G6PDd + G6PDi)
Females (adults/ adolescents)	71%	Non-pregnant/BF x (1 - (G6PDd + G6PDi))
Girls	83%	1 - (G6PDd + G6PDi)
TQ by adults/paediatric tablets		
Adult tablets (adult/ adolescents)	**62%**	((Adults + Adolescents) x Males x Eligible males)) + ((Adults + Adolescents) x Females x Eligible females))
Paediatric	**15%**	(Paediatrics x Males x Eligible males) + (Paediatrics x Females x Eligible girls)
TQ doses/quantities		
Vivax patients	20,000	
Access to G6PD testing	90%	NB: G6PD testing is mandatory before TQ
Adult doses	11,235	Vivax patients * Access to G6PD testing * Adult tablets
Paediatric doses	2,689	Vivax patients * Access to G6PD testing * Paediatric tablets
Buffer stocks	25%	
Minimum stocks per HF		
Total quantity (incl. buffer)		
Adult doses (1 box = 1 dose)	14,044	
Paediatric doses	3,362	
Paediatric boxes (30 blisters of 3 tabs)	112	Paediatric doses/30
PQ doses (TQ for G6PDn)		
PQ daily for G6PDi	1,800	Vivax patients x Access to G6PD Dx x G6PDi
PQ weekly for G6PDd	1,260	Vivax patients x Access to G6PD Dx x G6PDd
Legend		Update values to country context
		Automatic calculations

PQ: primaquine; TQ: tafenoquine.

G6PD testing. Semi-quantitative G6PD testing is a new intervention and quantification tools are currently under development.[2] The implementation process for tafenoquine and high-dose primaquine is a new, controlled, gradual process, and the calculation of G6PD tests should be based on both historical morbidity data and a component of minimum stock by level according to risk/stratification and health infrastructure. Box A5.2 provides an overview of parameters for consideration when quantifying requirements for commodities related to semi-quantitative G6PD testing, and Box A5.3 shows a worked example for an individual health facility. It is also critical to consider and plan for the storage requirements for the tests and controls (see above). Typically, if ambient temperatures exceed 30°C, refrigerated storage will be required on-site. Furthermore, shelf life (see above) may be shorter compared to malaria RDTs, and supply chains must be able to support more frequent re-stocking to avoid stockouts.

Box A5.2. G6PD testing – factors to be considered for quantification

Implementation sites

- ☐ G6PD deficiency prevalence in the intended area of use
- ☐ Number of G6PD testing implementation sites
- ☐ Number of points of care per implementation sites
- ☐ *P. vivax* prevalence
- ☐ Caseload in implementation area/health facility: expected number of patients to be tested (including breastfeeding woman and their infants; excluding the estimated number of pregnant women). Consider possible referrals from areas where G6PD testing is not (yet) implemented.
- ☐ Average family size (G6PD testing household members of confirmed *P. vivax* patients)

Note: Neither primaquine nor tafenoquine can be given to **pregnant women**; accordingly, G6PD testing is not required for pregnant women, and the number of expected pregnancies should be considered for the intended area of implementation.

Commodities

- ☐ **G6PD analyser** in line with planned number of G6PD implementation sites/number of points of care of implementation sites. Facilities with a high caseload might require more than one analyser. If outreach campaigns are planned, analyser requirements need to be increased accordingly.
- ☐ **G6PD control kits** (one box contains e.g., 10 high and 10 low controls) in line with number of implementation sites/points of care
  G6PD test devices. Consider the availability of different box sizes (e.g., 10 or 25 test strips) to be quantified in line with areas of expected high and low testing rates. Keep in mind that a split of box content for use at different points of care might not be possible, as boxes contain a specific code chip that must be used with the analyser. In addition, adequately quantify the G6PD test devices/strips needed for QC: Consider that for each round of QC, two test devices/strips, four blood transfer devices and two extraction buffers are required (covering high and low controls, respectively) – see Section 3.3.

[2] Semi-quantitative G6PD testing is mandatory only before the administration of tafenoquine or primaquine 1 mg/kg/day for 7 days, while other primaquine regimens can be given following semi-quantitative or qualitative testing or in some circumstances without G6PD testing based on a risk–benefit assessment (see Sections 2.1 and 3.3, and Fig. 5).

- ☐ **Auxiliary items – for sample testing and QC,** e.g., gloves, alcohol swabs, sharps boxes, etc.
  Consider availability of **extra blood transfer devices.** (The number of blood transfer devices in the product boxes does not necessarily allow for any mistakes during the testing process. Based on pilot project experiences, it is advisable to quantify for spare blood transfer devices.)
  Ensure sufficient amounts of **spare batteries** for analysers.
  Consider potentially required **cold storage** and the need for refrigerators depending on test and control storage requirements in the planned implementation settings.
- ☐ **Buffer stocks** added as needed to each of the items above, considering particularly G6PD analysers (in case of breakage/loss) and test devices (e.g., for repeat tests in the field if the test fails or the test delivers unexpected or unreliable results). Consider a buffer of, e.g., 20%/25%/30%.

Note: Longer **shelf life** and small **box size** are important parameters for reducing **wastage** *(10)*. For instance, G6PD tests are available on the market in packs of 10 and 25; the 10-test pack can help reduce wastage in areas where low rates of G6PD testing are expected.

Materials required for training/refresher training

- ☐ Number of training sites
- ☐ Training of trainers: number of trainers to be trained
- ☐ Training of health providers: number of health providers to be trained
- ☐ Number of proficiency assessments, e.g., one after training, one after refresher training
- ☐ Number of analysers for training sites
- ☐ Number of test devices/strips for training and appropriate storage facilities
- ☐ Number of control sets for training and appropriate storage facilities
- ☐ Auxiliary items for training (see list above)

Note: Requirements per trainee: at least two test devices and two control sets per training/refresher training, i.e., four test devices and eight blood transfer devices per trainee. Requirements for proficiency assessments to be added.

Box A5.3. Example quantification of G6PD tests required at a health facility

Assumption: a community records an average of 10 *P. vivax* patients per year. Analyser, test devices/strips and QC kits need can be calculated as follows:

G6PD analysers

Average caseload is low; testing is conducted by a limited number of health care workers: one analyser is required for the selected community.

Test kits

A. Average number of tests to be performed: 10 tests for 10 patients

B. Buffer: 30% (to account for possible mistakes, damage, breakage, and reserve in case of need to run control samples)

10 x 1.3 = 13 test strips required

A box of testing equipment comprises, e.g., one coding chip, 25 test strips, 50 blood transfer devices, 25 tubes containing extraction buffer solution. Accordingly, to test 13 samples, one box of equipment is required.

Control kits

A box contains, e.g., 10 low controls and 10 high controls for use throughout the one year; accordingly, one box is required.

Ancillary items

Do not forget to quantify for ancillary materials (including cold storage, depending on requirements of tests and controls – see list above), including buffer stock.

Source: adapted from the document *Providing G6PD test to health facilities for* Plasmodium vivax *radical cure.* National Institute of Malariology – Parasitology – Entomology. Hanoi, 1/2022 *(11)*.

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Annex 6. Training materials

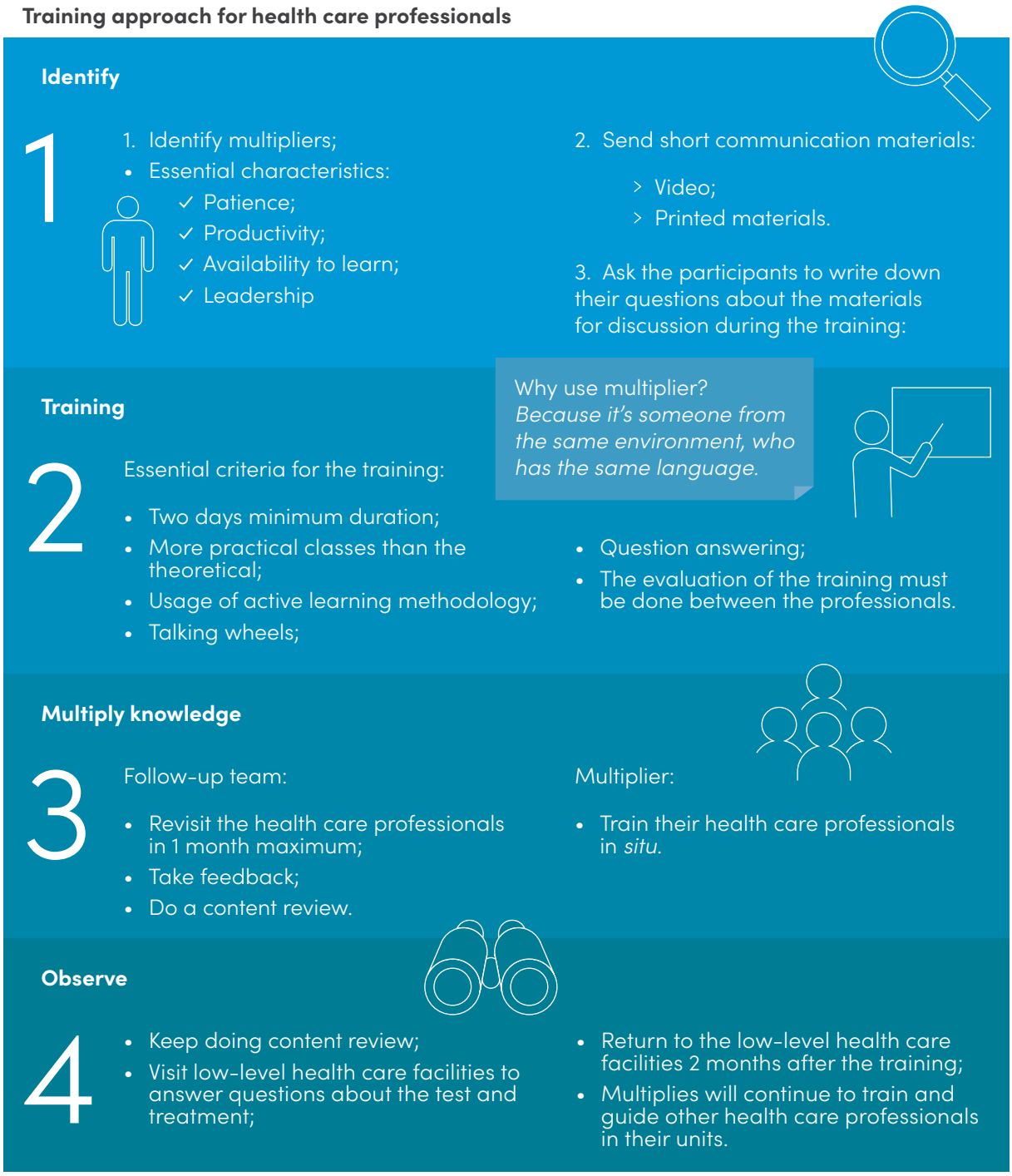
Table A6.1 presents a general guide to the training requirements for performing semi-quantitative G6PD tests. Fig. A6.1 displays an example training framework. Table A6.2 provides an overview of the training materials needed to implement *P. vivax* radical cure with G6PD testing, primaquine and tafenoquine, including links to materials.

Table A6.1. General guide to training for performing semi-quantitative G6PD tests

Section	Content
Introduction to G6PD deficiency	• Overview of G6PD deficiency, its clinical significance, and the associated health risks, prevalence in the country (map if available) • Importance of near-patient G6PD testing before administration of primaquine or tafenoquine • Populations at higher risk for G6PD deficiency and indications for testing
Understanding the test	• Overview of the test including its components • How the test works • Advantages of using the test, rapid results, ease of use, portability • Use of the test to direct treatment options for patients • The test identifies patients at risk of AHA based on G6PD enzyme activity; it does not provide a diagnosis of G6PD deficiency. • The test may not be valid following recent blood transfusion.
Sample collection and handling	• Step-by-step guide for blood sample collection: o use of lancets for safe and hygienic blood sampling o collection of the required blood volume • Safety measures during sample collection (gloves, alcohol swabs) • Proper disposal of sharps and biohazardous materials
Performing the test	• Step-by step procedure for running the specific test, including: o device set-up o blood sampling o sample preparation o sample analysis o results display
Interpreting results	• Understanding how the results should be used to direct therapy
Patient counselling	• Pre-test and post-test patient counselling • Advising patients about how their results affect their treatment
Reporting and documentation	• How to record the results in the patient records
Device maintenance and QC	• Correct storage, cleaning and maintenance procedures • Running QC tests, frequency and methods

Section	Content
Troubleshooting common issues	• Dealing with errors, malfunctions and issues in obtaining samples
Practicals and case studies	• Hands-on training for participants • Case studies highlighting the risks and benefits of G6PD testing
Assessment	• Confirmation of understanding through quizzes and performance assessments tailored to background knowledge and education

Fig. A6.1. Training framework developed during pilot implementation in Brazil



Source: Santos et al. 2024 (reproduced under a CC BY license) *(1)*.

Table A6.2. Training materials to support *P. vivax* radical cure

Resource	Tools
Training manuals and guides	• **Standard operating procedures:** detailed step-by-step instructions on conducting the G6PD tests and administering treatment • **User manuals:** manufacturer's guides for the G6PD testing devices • **Clinical guidelines:** details of the diagnosis and treatment of *P. vivax* malaria • **Treatment algorithm:** visual summary of the clinical pathway and case management
Educational resources	• **Training packages:** modular packages containing individual sessions on different aspects required for the new case management pathway (e.g., the training package developed by PAVE Peru *(2)* or the PAVE training package to train health workers on near-patient G6PD testing and the use of tafenoquine and primaquine for preventing *P. vivax* malaria relapses *(3)*, which includes links to Training of Trainers materials and a video on how to use a G6PD test) • **Job aids:** laminated cards including the key steps and important reminders for easy reference during G6PD testing and treatment, including recognizing ADRs and the required actions, e.g., job aids used in the Peru PAVE project for G6PD semi-quantitative tests and treatment *(4)* and QC for semi-quantitative G6PD test *(5)* • **Dose reminders:** laminated cards outlining antimalarial doses • **FAQs and troubleshooting guides:** addressing common issues and questions that might arise during G6PD testing
Visual aids	• **Instructional videos:** demonstrations of the *P. vivax* life cycle, G6PD testing procedure (e.g., PAVE video on how to use a specific semi-quantitative test *[3]*), interpretation of results, administration of treatment and ADRs • **Posters and diagrams:** illustrating the *P. vivax* life cycle, testing process, sample handling and key aspects of treatment, including the symptoms of haemolysis • **Flow charts:** simplified flow charts outlining the treatment algorithm and decision-making process based on G6PD test results • **Flip charts for patient counselling:** e.g., from PAVE Peru Project for vivax malaria, semi-quantitative testing and treatment *(6)* • **Comic book for patient education:** e.g., from PAVE Peru *(7)*, or from the TRuST study in Brazil – an illustrated comic-style book to help patients understand G6PD testing and new treatments for *P. vivax* malaria *(8)* • **Video for patient education:** e.g., from PAVE Peru *(9)*

Resource	Tools
Hands-on training materials	• **Practice materials for qualitative G6PD tests:** e.g., the WHO publication *How to use a G6PD rapid diagnostic test (for detecting glucose-6-phosphate dehydrogenase deficiency): a guide for training at health facility level (10)* • Practical exercises for semi-quantitative G6PD tests, e.g., video on how to use the G6PD test *(3)* • **Case studies:** real-world scenarios for trainees to practice decision-making and apply their knowledge • **Role-playing exercises:** interactive sessions for trainees to practice patient communication and counselling on the G6PD test and ADRs
Assessment tools	• **Competency checklists:** lists of skills and procedures for which trainees must demonstrate proficiency (SD Biosensor STANDARD G6PD Test user competency assessment *[11]*) • **Quizzes and exams:** written assessments to test knowledge on G6PD deficiency, *P. vivax* malaria, treatment protocols and ADRs • **Practical exams:** hands-on test where trainees perform the G6PD test and explain the process to assess competence
Reference materials	• **Scientific articles:** research papers on G6PD deficiency and *P. vivax* malaria case management for deeper understanding • **National treatment protocols:** guidelines and considerations for treatment to support compliance with national policies
Support materials	• **Help desk information:** contact details for technical support • **Peer support networks:** information on local or online communities where health workers can share experiences and seek advice
Digital tools	• **E-learning platforms:** online courses and webinars for remote training and continuous education • **Mobile materials:** instructional materials on G6PD test procedures, treatment protocols, and patient management available through social media apps

Additional training materials and useful reading from the pilot and implementation projects include:

- **training and resources (*P. vivax* information hub)** – a library of PAVE resources with tools and training kits relevant for the *P. vivax* malaria research community *(12)*;
- **G6PD testing and primaquine/tafenoquine treatment talking points for *P. vivax* malaria patients** – an illustrated set of talking points developed during the TRuST study in Brazil to assist health workers in understanding G6PD deficiency, G6PD testing and the risks associated with treatment *(13)*; and
- **TRuST study resources, Brazil** – other resources from the TRuST study available in Portuguese *(14)*.

More specific information for qualitative and semi-quantitative G6PD tests can be found on the associated PATH web page *(15)*, which lists general G6PD test resources (e.g., target product profiles, protocols, counselling), training materials (e.g., on semi-quantitative and fluorescent spot tests) and QA materials. Additional G6PD testing resources include the following:

- ***P. vivax* tool brief: point-of-care G6PD diagnostics** *(16)*. This brief provides an overview of near-patient G6PD testing, explaining its importance, classification, available tests and adoption considerations, targeting malaria programme staff and implementers seeking high-level knowledge.
- **G6PD diagnostic test webinar resources (PATH).** PATH has developed a webinar series on technical, clinical and operational considerations for near-patient G6PD tests and testing, specifically as it pertains to informing *P. vivax* case management. The webinars are available through the G6PD Operational Research Community of Practice *(17)* or the PATH YouTube channel *(18)*.

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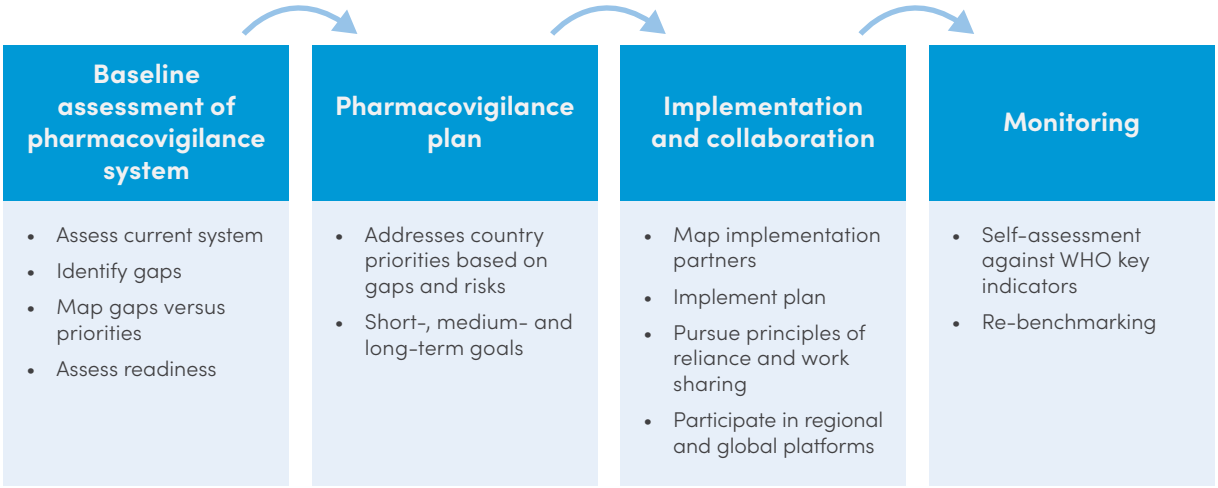
Annex 7. Implementation framework for pharmacovigilance of tafenoquine and primaquine

Pharmacovigilance activities with tafenoquine and primaquine are needed to inform risk–benefit assessments of *P. vivax* radical cure. An implementation framework will be necessary to assess, plan, implement and monitor the pharmacovigilance system (Fig. A7.1).

Fig. A7.1. Implementation framework for pharmacovigilance

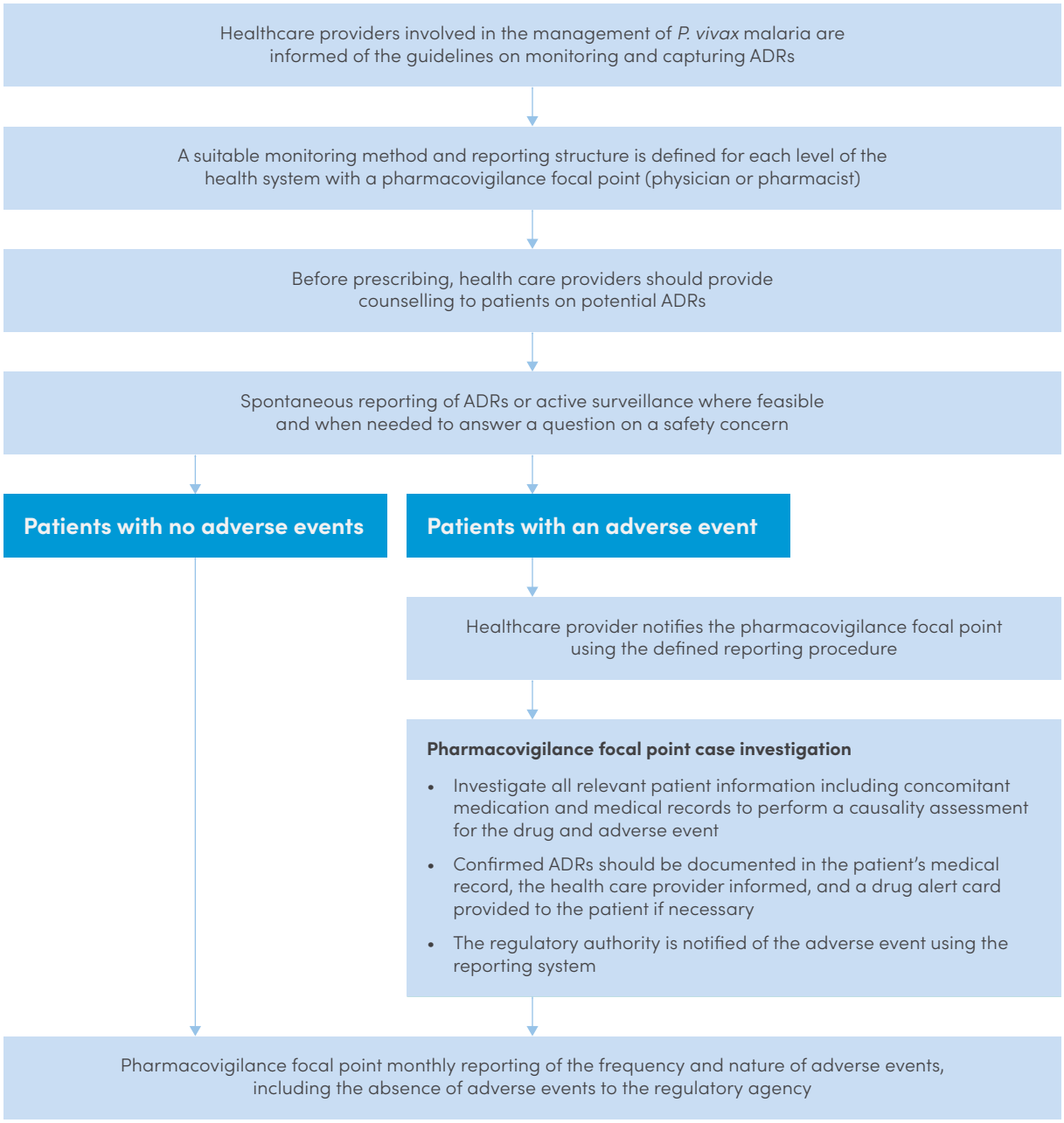


A baseline assessment should be conducted to assess preparedness using WHO pharmacovigilance indicators *(1, 2)*. Using this assessment, a step-wise workplan can be developed to address any gaps in the system. The workplan should cover the following areas:

- infrastructure and framework;
- pharmacovigilance tools, such as VigiMobile, VigiFlow, VigiLyze;
- risk management plans;
- qualitative and quantitative aspects of data, including roles and systems for data management;
- data analysis, signal generation and validation processes;
- mechanisms for use of local data and analyses;
- mechanisms and protocols for data sharing; and
- structures to enable collaboration between pharmacovigilance centres and the health system engaged in *P. vivax* malaria case management.

The final system should be simple enough to describe in a flow chart, such as the example in Fig. A7.2 *(1)*, and adaptable to all levels of the health system that are involved in *P. vivax* malaria case management. The use of communication technologies and different innovations in mobile and satellite telephony should be considered, especially considering that the greatest burden of disease occurs in dispersed populations.

Fig. A7.2. Example operational flow chart for pharmacovigilance of *P. vivax* radical cure



Implementation of the plan will require collaboration with stakeholders and can benefit from following the principles of work sharing and reliance. Participation in regional and global platforms would also be beneficial to all countries that are implementing *P. vivax* radical cure. WHO guidance for pharmacovigilance includes consolidated resources for pharmacovigilance strategies, guidance, protocols and publications *(3)*. In addition, the Uppsala Monitoring Centre (https://who-umc.org/) provides a range of services and tools to support drug safety monitoring and pharmacovigilance, and maintains VigiBase – a database of semi-structured detailed individual case safety reports on ADRs. Safety information for medical devices, including in vitro diagnostics, is available through the WHO Regulation and Prequalification department *(4)*.

Infrastructure upgrades may be required if system strengthening is necessary. Pharmacovigilance training will be needed for all those involved in the monitoring, reporting, investigation and analysis of ADRs associated with *P. vivax* malaria case management. WHO and the International Society of Pharmacovigilance have developed the WHO-ISoP pharmacovigilance curriculum, which can be used by anyone who needs to plan and conduct training courses in pharmacovigilance *(5)*. An M&E structure should also be established using key pharmacovigilance indicators and benchmarking using WHO pharmacovigilance indicators *(1, 2)*.

Lessons learned. A proof of concept study evaluating the WHO smart safety surveillance (3S) project was conducted in Armenia, Brazil, Ethiopia, India, Peru and Thailand directed at three priority products. This study included tafenoquine in Brazil, Ethiopia, Peru and Thailand, but as the medicine was not yet available, a proxy assessment was done using primaquine (Box A7.1) *(6)*. This study was used to inform the WHO "SMART" Pharmacovigilance Strategy *(7)*.

Box A7.1. Piloting principles of the WHO "SMART" Pharmacovigilance Strategy within the 3S framework to prepare for the introduction of tafenoquine

The WHO 3S project included tafenoquine in Brazil, Ethiopia, Peru and Thailand, but as the medicine was not yet available, a proxy assessment was done using primaquine *(6)*. A baseline assessment of countries participating in the pilot identified gaps in pharmacovigilance preparedness, which were used to develop a workplan. Pharmacovigilance activities included investing in active surveillance methods in Brazil and Peru, strengthening collaboration with national pharmacovigilance centres and NMPs, using primaquine as a proxy, and conducting joint assessment of risk minimization plans as a work sharing exercise in the Asian region. The impact was measured by comparing pre- and post-3S-intervention outcomes, including the number and quality of reports (completeness scores) in the WHO global database of individual case safety reports, VigiBase, and the number of structural indicators met. The implementation period ranged from nine to 18 months, starting in March 2018 and ending in May 2020. The results showed various improvements in ADR reporting and report quality, increased capacity for signal detection and evaluation, and an improved capacity to assess risk management plans following the implementation of 3S principles. Continued monitoring is important to ensure the sustainability of the current 3S project's gains and successes.

The lessons learned from the 3S pilot project were as follows:

1. Prioritize products based on the potential risks and data needs.
2. Promote work sharing among different regulatory authorities to enhance efficiency, reduce resource burdens, and speed up decision-making, particularly for safety concerns around medicines.
3. Rely on the work conducted by a trusted regulatory body for decision-making. Reliance is especially valuable for countries with limited resources, enabling them to benefit from the expertise and regulatory infrastructure of more established authorities.
4. Embed the regulatory body in the pharmacovigilance system.
5. Adopt a step-wise approach.

The use of mobile and digital communication technologies is a key opportunity, especially considering that the greatest burden of disease occurs in dispersed populations. Acceptability of SMS as a tool for malaria treatment adherence was evaluated in the Brazilian Amazon as part of a multicomponent strategy using the mHealth platform (Box A7.2) *(8)*.

Box A7.2. A multicomponent strategy to strengthen pharmacovigilance in Brazil

The 3S approach deployed multicomponent, patient-centred interventions to improve adherence and strengthen pharmacovigilance *(8)*, including:

- educational materials for counselling and identifying warning signs of haemolytic anaemia;
- SMS treatment reminders through an mHealth component; and
- follow-up phone surveys three days post-treatment via a web-based platform linked to the malaria information system.

Adherence was assessed using the Morisky Medication Adherence Scale, and self-reported adverse events were collected through a structured questionnaire and reported to the Brazilian Health Regulatory Agency. Educational materials reached 5594 patients, 1512 joined the mHealth component, a total of 7323 SMS reminders were sent and 1062 patients completed follow-up surveys. Most patients (95.9%) followed the regimen of chloroquine and primaquine 0.5 mg/kg/day for 7 days. Adherence to the regimen was high (93.3%), and 95.2% of patients reported at least one adverse event, with headache, appetite loss, and nausea being the most common. A small percentage (5.4%) reported symptoms of haemolytic anaemia, and three patients were diagnosed with G6PD deficiency and recovered after hospital treatment. The strategy improved treatment adherence and enhanced safety surveillance in real-world settings. Active monitoring via phone surveys reduced underreporting of ADRs, offering a low-cost, scalable solution to support malaria control efforts.

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For further information please contact:

World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland
Email: GMPinfo@who.int

9789240120815