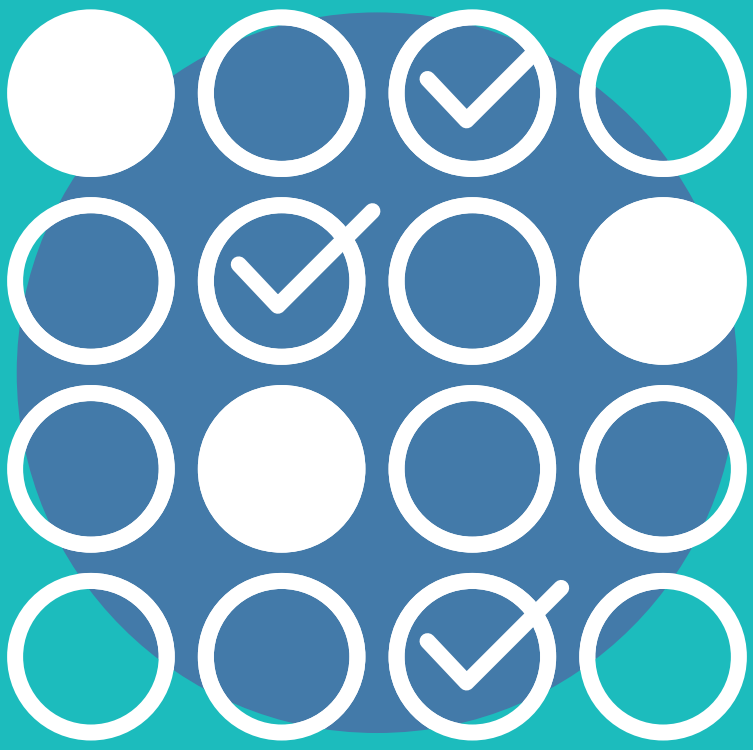
# Diagnostic tests for detecting the risk of *Plasmodium vivax* relapse

## Preferred product characteristics



World Health Organization

# Diagnostic tests for detecting the risk of *Plasmodium vivax* relapse

## Preferred product characteristics

World Health Organization

Diagnostic tests for detecting risk of *Plasmodium vivax* relapse: preferred product characteristics

ISBN 978-92-4-008984-6 (electronic version)
ISBN 978-92-4-008985-3 (print version)



**Suggested citation**. Diagnostic tests for detecting risk of *Plasmodium vivax* relapse: preferred product characteristics. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at https://iris.who.int/.

# Contents

# Acknowledgements

The World Health Organization (WHO) would like to thank the many individuals who contributed to the development of this document.

This document was prepared by Jane Cunningham (WHO Epidemic and Pandemic Preparedness), Lindsey Wu (WHO Global Malaria Programme), under the leadership of Daniel Ngamije (Director, WHO Global Malaria Programme), and with support from Rosalind Howes (FIND, Switzerland) and Leanne Robinson (Burnet Institute, Australia), with review by and contributions from the scientific development committee on tests for detecting the risk of *P. vivax* relapse.

Members of the scientific development committee included: James Beeson (Burnet Institute, Australia); Jane Carlton (New York University, United State of America); Elliot Cowan (Partners in Diagnostics, United States of America); Gonzalo Domingo (PATH, United States of America); Chris Drakeley (London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland); Rosalind Howes (FIND, Switzerland); Stephen Karl (Institute of Medical Research, Papua New Guinea); Moses Laman (Institute of Medical Research, Papua New Guinea); Patrick Lammie (Task Force for Global Health, United States of America); Leanne Robinson (Burnet Institute, Australia); Ivo Mueller (Walter and Eliza Hall Institute of Medical Research, Australia); Isaac Quaye (Regent University College of Science and Technology, Ghana); Hernando A Del Portillo (ISGlobal, Spain); Aungkana Saejeng (Regional Office of Disease Prevention and Control, Thailand); Nguyen Quang Thieu (National Institute of Malariology, Parasitology and Entomology, Viet Nam); Giselle Maria Rachid Viana (Evandro Chagas Institute, Ministry of Health, Brazil); and Michael White (Institut Pasteur, France).

WHO would like to thank the experts and observers who participated in the technical consultation meetings on 21 and 23 March 2023. WHO also thanks the organizations and individuals who provided input through the public consultation on the draft document, which was open from 31 July to 31 August 2023.

This work was supported by the Bill & Melinda Gates Foundation.

# Abbreviations

| | |
|---|---|
| G6PD | glucose-6-phosphate dehydrogenase |
| GTS | *Global technical strategy for malaria 2016–2030* |
| IFU | instructions for use |
| POC | point-of-care |
| PPC | preferred product characteristics |
| RDT | rapid diagnostic test |
| TPP | target product profile |
| WHO | World Health Organization |

# Overview

The *Global technical strategy for malaria 2016–2030* (GTS) (*1*) seeks to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threat of drug and insecticide resistance. It encourages innovation and the development of new tools, technologies, and strategies (collectively referred to as "interventions") to maintain progress in malaria control and to further advance towards elimination. To accelerate implementation of the GTS, the World Health Organization's (WHO) Global Malaria Programme conducted a review of its guidelines and guidance development processes to ensure transparency, consistency, efficiency, and predictability. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve WHO's communication on identified public health needs and to encourage and facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;
- stimulate the development of relevant new products to meet those needs; and
- facilitate the timely, effective assessment of new products, and the formulation of WHO recommendations and prequalification listings.

# Terminology

**Preferred product characteristics (PPCs)** are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers including researchers, regulatory agencies, procurement agencies, and funders of research and development. PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve public health impact.

**Target product profiles (TPPs)** in the context of public health are used to set research and development targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process.

# 1. Background

Relapsing malaria is a mosquito-borne parasitic infection caused by two species of human parasites, *Plasmodium vivax* and two subspecies of *P. ovale*. *P. vivax* malaria is endemic in all WHO Regions except the European Region, with an estimated 6.9 million clinical cases in 2022 (*2*). *P. vivax* is a target that is integral to malaria elimination efforts, but it remains a substantial cause of morbidity and contributor to childhood mortality in endemic regions. *P. ovale* is a sporadic infection in Africa, South-East Asia and the Western Pacific with a very limited clinical burden (*3*).

The WHO Global Malaria Programme and other organizations and stakeholders have called for the global reduction of malaria burden towards eventual malaria elimination *(1,4)*. As the major relapsing malaria species, *P. vivax* presents a major challenge to achieving these targets. About one third of the global population is still at risk of contracting *P. vivax* malaria (*5*). The formation of dormant hypnozoites by *P. vivax* means that tailored and sustained interventions are required to control the burden of this species, and the impact of these interventions is slower than it is for *P. falciparum*. Therefore, as transmission declines in co-endemic areas, *P. vivax* becomes the main source of clinical malaria, and foci of stable (high) *P. vivax* transmission can persist even when *P. falciparum* is nearing elimination.

Around 85% of *P. vivax* clinical/blood-stage infections are due to reactivation of latent parasites, rather than newly transmitted infections *(6,7)*. While less often associated with acute illness, continued relapses are a cause of chronic anaemia *(8)* and have been shown to be associated with an excess in morbidity and mortality *(9)*. In addition to diagnostic tools that can detect the acute, erythrocytic phase of *P. vivax*, new tools are needed to detect dormant infections before they reactivate and contribute to morbidity and onward transmission.

To help guide research and development efforts and assist donors, technical agencies and ministries of health to select products that best respond to public health needs, the WHO Global Malaria Programme, with input from a PPC development group made up of clinicians, public health experts and laboratory scientists, has developed two PPCs for tests to detect risk of *P. vivax* relapse. These tools are expected to improve screening, use of radical cure and case management among high-risk populations. These tools are also aimed at supporting population-level risk stratification for the targeting of interventions and monitoring and evaluation of ongoing elimination programmes.

The PPCs submitted for public consultation describe two types of tests to detect risk of *P. vivax* relapse:

- The first (PPC 1) is a point-of-care (POC) test to identify individuals at risk of *P. vivax* relapse to guide radical cure and case management. This is based on the detection of analytes indicative of hypnozoite carriage and/or current sequestered infection and/or recent (blood-borne) infection with *P. vivax*.
- The second (PPC 2) is a laboratory-based test to identify communities or individuals at risk of *P. vivax* relapse. Unlike the POC test (PPC 1), this test will be used to screen large numbers of individuals simultaneously as part of surveillance and/or monitoring activities related to *P. vivax* control and elimination.

## 1.1 Natural history of *P. vivax* infection

The distinguishing feature of *P. vivax* malaria is its establishment of a latent infection in the liver within a couple of days of infection. After sporozoite invasion of the hepatocyte, the parasite undergoes rapid transformation either into a quickly developing, metabolically active liver merozoite or into a developmentally arrested (called "dormant" hereafter) hypnozoite. Microscopy and antigen-detecting rapid diagnostic tests (RDTs) detect only parasites or their antigens, respectively, that are released into the blood stream (erythrocytic phase); therefore, these diagnostic methods cannot detect the presence of hypnozoites. The dormant hypnozoites are refractory to the radical cure drugs that kill active liver-stage infection (atovaquone, proguanil, pyrimethamine) and blood-stage infection. The triggers for hypnozoite reactivation and re-establishment of blood parasitaemia remain unclear. However, *P. falciparum* infection is one condition that appears to be involved. Both species are transmitted by the same mosquitoes, and individuals who have been exposed to *P. falciparum*-carrying mosquitoes in the previous 3–4 weeks are also at high risk of having encountered *P. vivax*-infected mosquitoes. This co-exposure means that *P. falciparum* cases have a much higher risk of carrying hypnozoites compared to the general population *(10,11)*.

While relapse patterns are vivax strain specific and hence vary by geography, epidemiological studies have shown that most clinical relapses occur within two years, and rarely after four years. In the tropics, relapses tend to occur at shorter intervals, with a first relapse coming within a few weeks to six months after the primary blood-stage infection for tropical and subtropical strains. Subsequent relapses tend to be more frequent. The proportion of *P. vivax* infections leading to relapses is also highly variable, determined in part by sporozoite inoculum and immunity *(12)*. On rare occasion, all the sporozoites invading a liver become hypnozoites and none form the liver schizonts that directly progress to blood infection and febrile illness (called *P. vivax hibernans*, which is currently limited to the Korean Peninsula).

The relapsing pattern of *P. vivax* and gametocyte production are key determinants of transmission for this parasite. Unlike *P. falciparum,* which can sustain a chronic blood-stage infection by repeatedly changing the surface coat of blood merozoites to avoid the host immune response, a blood-stage infection of *P. vivax* has no comparable immunological escape mechanism and is therefore vulnerable to immune suppression and clearance. Regular relapses are thus required for the maintenance of chronic *P. vivax* infection.

## 1.2 Public health response and key challenges

A 2015 WHO monograph, *Confronting* P. vivax *malaria (13)*, outlined key gaps in the toolbox against *P. vivax* malaria, many of which remain despite increased efforts to develop *P. vivax*-specific tools to address them. These gaps include the following:

- A lack of vector control tools to target outdoor biting/resting mosquitoes, which often transmit *P. vivax*.
- A greater proportion of *P. vivax* infections may be missed by current case management diagnostic tools, even if a patient presents with symptoms, due to the lower number of parasites typically circulating in the blood compared to *P. falciparum*.

- The majority of *P. vivax* transmission is due to asymptomatic infections (low-density blood-stage or sequestered infections in the blood or bone marrow, for example). New strategies and tools are needed to identify blood-stage infections and safely treat asymptomatic/afebrile carriers if *P. vivax* transmission is to be reduced expeditiously in line with national and regional targets.
- Detection of latent *P. vivax* infection: As described above, the dormant liver stage infections of *P. vivax* cannot be directly detected, and there is a large reservoir of people who are infected but unaware of their condition.
- Suboptimal *P. vivax* radical cure treatment regimens: Treatment currently requires a seven- or 14-day course of primaquine to treat a dormant infection, although one-day tafenoquine is now registered in several countries and is in pilot implementation. In the absence of effective radical cure treatment, people are at risk of multiple clinical relapses and the associated morbidity and mortality in young children.
- Affordable, accurate and near-patient tests for glucose-6-phosphate dehydrogenase (G6PD) deficiency to stratify which persons are at risk for clinically significant 8-aminoquinoline-induced haemolysis. WHO recently developed TPPs for tests of G6PD activity to support safe and effective anti-relapse therapy for *P. vivax (12*). Furthermore, at least one G6PD diagnostic is being evaluated in operational research studies to guide the use of tafenoquine or high-dose primaquine.

Since 2015, it has been recognized that *P. vivax* causes cryptic, asexual infections in a person's spleen and bone marrow, posing additional challenges. Specifically, *P. vivax* seems to take advantage of the splenic reservoir of immature reticulocytes, and most of the life cycle can take place in the spleen *(14,15)*. Bone marrow infections are associated with dyserythropoiesis and inefficient erythropoiesis *(16)*. Although many of these infections are associated with (very) low-density blood-borne parasitaemia, some are undetectable even by highly sensitive PCR *(14,15)*. Tests that could identify this hidden reservoir could also provide a proxy for probable hypnozoite carriage and risk of *P. vivax* relapse.

In essence, implementation of health-setting-appropriate and sufficiently sensitive tests for both blood-stage and latent *P. vivax,* combined with G6PD activity tests, is a prerequisite to ensure the most effective use of novel antimalarial drugs against *P. vivax* malaria (e.g. tafenoquine) beyond treatment of acute symptomatic/ febrile patients.

## 1.3 Available diagnostic tools for detecting clinical vivax infection

WHO currently requires that RDTs targeting detection of *P. vivax* achieve a panel detection score[1] of ≥ 75% at 200 parasites/µL, based on the independent laboratory evaluation conducted as a component of the WHO prequalification process *(17,18)*. This requirement ensures that RDTs will detect the majority of *P. vivax* clinical (symptomatic) infections, but the proportion of infections that are missed depends very much on the local epidemiology; compared to *P. falciparum,* a greater

1 The panel detection score was developed to reflect both product sensitivity and reproducibility. It requires four tests, two from each of two manufacturing lots, against the same sample (at 200 parasites/µL) to be positive to register as "detecting" the sample and quantifies the percentage of samples the product detected.

proportion of *P. vivax* cases are missed using this threshold *(19)*. The pyrogenic threshold for *P. vivax* may be below 200 parasites/µL *(20)*, a level at which current RDTs may show reduced sensitivity. The ability of commercial RDTs to meet this target of 200 parasites/µL has increased significantly over the past 15 years, but more data are still needed, particularly for RDTs targeting *P. vivax*-specific lactate dehydrogenase *(18,21)*. Due to these real or possibly perceived limitations, some countries, particularly in South and Central America, continue to rely on microscopy. Improving the sensitivity of RDTs for *P. vivax* is an ongoing research and development priority, with new assays targeting the lower limits of the pyrogenic threshold. Molecular assays are currently in development for use in POC settings, but for now remain laboratory platforms primarily used for high-throughput surveillance or research applications.

More sensitive tests for *P. vivax* will improve diagnosis of blood-stage infection and may help to detect some cryptic *P. vivax* infections in the spleen and bone marrow. However, there remains a lack of tests to detect latent infection/hypnozoites of *P. vivax* that result in relapse.

## 1.4 Current landscape of tests to detect the risk of *P. vivax* relapse or hypnozoite carriage

As described above, there is a public health need for tests that can identify individuals with viable hypnozoites who are at increased risk of *P. vivax* relapse and represent a potential source of onward transmission. There are no commercial assays that detect hypnozoites or cryptic/sequestered infections; however, there are antibody-detecting assays (lateral-flow RDTs, indirect immunofluorescence or enzyme-linked immunosorbent assays) often used in blood donor screening, which can detect past exposure. These commercial assays are not specific to *P. vivax* and may detect historic infections, whereas the primary interest lies in detecting and treating infections acquired in the preceding 6–9 months, when tropical and subtropical *P. vivax* strains are expected to relapse. Research and development efforts are under way, such as for direct detection of biomarkers of viable hypnozoites but have not been successful so far. Methods to detect *P. vivax* hypnozoite-derived exosomes are in the early biomarker discovery stage *(22)*. Indirect measures, such as detection of short-lived (6–9 months) immunological responses to *P. vivax* blood-stage antigens, however, have achieved proof of principle to detect recent *P. vivax* infection which may have a high likelihood of relapse *(23-25)*.

# 2. WHO strategic goals for tests for *P. vivax* relapse

WHO envisions two major public health value propositions for *P. vivax* relapse assays.

### 2.1 Use case 1: diagnosing risk of relapse to guide radical cure

- 1a: Screening and radical cure for high-risk communities in areas targeted for elimination.
- 1b: Improving acute case management by providing targeted radical cure after *P. falciparum* infection to prevent potential *P. vivax* relapses triggered by the *P. falciparum* infection or coinfection; by detecting patients who are likely to also carry hypnozoites at the time that the acute *P. falciparum* infection is diagnosed, targeted treatment can be offered to prevent these relapses.
- 1c: Prevention of reintroduction by screening travellers/migrants for hypnozoite carriage/risk of relapse (serological/hypnozoite-guided terminal prophylaxis); identifying individuals at risk of relapse and subsequent reintroduction of *P. vivax* into elimination areas could be averted through screening and treatment.

Use case 1 is of relevance to national malaria control programmes engaged in *P. vivax* elimination. Detection and treatment of those persons with hypnozoites, sequestered infection or a recent *P. vivax* infection as a proxy for the extant *P. vivax* infectious reservoir should reduce the time to elimination and will likely prove cost-effective compared to a longer elimination tail *(7)*. A test detecting relapse risk (by detecting recent *P. vivax* exposure, sequestered infection or direct evidence of hypnozoite carriage) would prove valuable in proactive or reactive testing, particularly in remote settings, to detect those subjects who are likely to harbour hypnozoites. Anyone who is positive could be treated with safe and effective radical cure, thereby both protecting the individual from the impact of future relapses and reducing the overall community-level parasite reservoir.

In regions with significant co-endemicity of *P. vivax* and *P. falciparum*, many studies have shown that patients with *P. falciparum* have a higher risk of subsequent *P. vivax* clinical episodes *(11)*. This suggests that empiric radical cure may be beneficial to individuals with any type of malaria in co-endemic settings. However, due to concerns with 8-aminoquinoline safety, many *P. vivax*-endemic countries are reluctant to consider presumptive/empiric radical cure for *P. vivax*. Confirmation of recent *P. vivax* infection would therefore be a prerequisite for determining the appropriateness of radical cure in non-*P. vivax* clinical cases. This is particularly important in regions with low *P. vivax* endemicity, where persons with confirmed *P. falciparum* infection are a recognized high-risk population, warranting additional testing for risk of *P. vivax* relapse as a more informed approach over empiric *P. vivax* radical cure with no knowledge of the patient's *P. vivax* status.

A POC test for relapse risk would be preferred over a benchtop test for use case 1 scenarios, as it would enable diagnosis and treatment in a single contact. A higher throughput benchtop version would greatly increase the logistical complexity of any screen and treat intervention, leading to loss to follow-up. The test procedures will also need to be such that minimal operator input is needed, while the test performance (sensitivity/specificity) will need to be adequate to justify a screen and

treat intervention. Test throughput can be modest, but should be scalable, if needed. In general, a lateral-flow test/RDT format, as used for malaria antigen testing, can be seen as an example (but not limiting) of an adequate POC test that satisfies the aforementioned criteria.

## 2.2 Use case 2: population-based screening to identify recent *P. vivax* infections/hypnozoite carriage for programmatic applications

- 2a: Risk stratification and subsequent targeting of interventions
- 2b: Monitoring and evaluation of ongoing elimination programmes

These use cases would be relevant to national malaria programmes in both near- and post-elimination settings. Such an assay could assist in guiding, monitoring and evaluating the progress of elimination activities by stratifying areas according to the likelihood of continued local transmission (pre-elimination) and/or confirming the (continued) absence of local transmission (post-local elimination). Use case 2 would require a higher throughput assay, making more centralized use economical. The test would also be expected to generally exhibit advanced clinical performance, and, for use in monitoring and evaluation scenarios, the test should allow for electronic data storage and transmission. Although using a high-throughput laboratory-based assay for a screen and treat intervention may be feasible in some settings, it would make the intervention much more logistically difficult to implement than with a POC test.

The PPCs for risk of *P. vivax* relapse tests well suited to these use case scenarios (see Table 1) are described in this PPC document (sections 3 and 4).

**Table 1. Overview of use scenarios for test to detect risk of *P. vivax* relapse**

| Use scenario | Screen and radical cure | Improve acute case management in *P. falciparum* and *P. vivax* endemic areas | Screen travellers/ migrants entering countries to prevent reintroduction | Risk stratification (+/- document absence of transmission) | Monitoring and evaluation |
|---|---|---|---|---|---|
| **Problem addressed** | Identifies individuals at risk of *P. vivax* relapse | Identifies individuals at risk of *P. vivax* relapse | Contributes to prevention of reintroduction | Identifies where, and at what level, transmission is occurring | Determines the impact of an intervention, either new or established |
| **Target population** | High-risk communities targeted for elimination | *P. falciparum* confirmed cases likely to carry hypnozoites | Travellers/migrants | Risk populations | Communities in areas with ongoing elimination programmes |
| **Action taken based on result** | G6PD test, followed by appropriate 8-aminoquinoline regimen | Artemisinin-based combination therapy + G6PD test, followed by appropriate 8-aminoquinoline regimen | G6PD test, followed by appropriate 8-aminoquinoline regimen | Mapping of risk to guide interventions, e.g. mass drug administration | Reporting on impact, informing policy |
| **Operational use of implementation** | Village | Village | Ports of entry | National, subnational, district | Subnational, district |
| **Transmission level** | Low to approaching zero transmission | Low transmission | Zero transmission | Moderate to very low transmission | Low to approaching zero transmission |
| **Requires POC testing** | Yes | Yes | Yes | No | No |

*Source:* Table adapted from *(26)*.

# 3. PPC 1: point-of-care test to detect risk of *P. vivax* relapse

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **1. General requirements** | | | |
| **1.1 Intended use** | To identify individuals at risk of *P. vivax* relapse based on detection of analyte(s) indicative of *P. vivax* hypnozoite carriage and/or current sequestered infection and/or recent (blood-borne) infection with *P. vivax* | Emerging data show that, in infectious individuals who may carry a high risk of relapse, *P. vivax* parasites can be sequestered in sites of erythropoiesis (bone marrow, spleen and liver) and may be difficult to detect *(14,15)*.<br><br>"Recent infection" could refer to the preceding nine-month window, based on available data from human infection studies and epidemiological studies *(10)*.<br><br>The test is designed to be conducted at the point of contact with a patient (in a facility or in the community) or a community member (e.g. during a campaign-style intervention). The rapid turnaround time to result allows for a "screen and treat" approach. | |
| **1.2 Targeted population** | All individuals living in or returning from travel to *P. vivax*-endemic settings where the transmission level ranges from low to elimination, and who are suspected of having latent or sequestered *P. vivax* infection | A "screen and treat" approach will be applied for those identified to be at risk of *P. vivax* relapse: if this test is positive, then it may inform radical cure treatment in line with WHO or national treatment guidelines. | |
| **1.3 Lowest infrastructure level** | Test design and procedure allow for use in "low-infrastructure" conditions (Level 0); no cold chain, and minimal or no additional laboratory equipment or technical accessories are required. | See Annex 1. Definition of health system infrastructure levels. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **1.4 Lowest level user** | The test can be reliably performed by health personnel or community health workers. | The test would ideally be usable by the level of health workers currently performing malaria testing. | |
| **1.5 Test training requirements** | ≤ 1 day with instructions for use (IFU) and a quick reference guide | Training requirements will vary according to the test format and experience of the user. Consider options for smartphone application(s) to ensure ongoing compliance and up-to-date training. | |
| **2. Design** | | | |
| **2.1 Portability** | All supplies required for sample collection and testing procedures packaged with the test (e.g. lancet, alcohol swabs, etc.)<br><br>If the test set-up requires an instrument, it should be easily portable (handheld or on desktop, weight < 3 kg), and no special transport conditions should be required (temperature, humidity, vibration, etc.). | Single-use test packs may be useful and help to reduce wastage in low transmission and elimination settings. | |
| **2.2 Instrument / power requirements, if applicable** | Battery- or solar power-operated; no additional equipment (e.g. micropipettes, vortex, etc.) should be required beyond the diagnostic instrument. | May use rechargeable batteries; may also have the capacity to be powered by the mains supply in addition to portable options. | |
| **2.3 Sample type / collection** | Fresh capillary blood from finger sticks and venous blood, or other non-invasive/minimally invasive biological samples collected according to routine procedures | Non-invasive or minimally invasive samples might include saliva, urine, volatile organic compounds, etc. Use of anti-coagulants with samples is acceptable. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **2.4 Test procedure** | Sample preparation steps should be limited in number and straightforward to perform; ideally, the procedure should be a single step.<br><br>Transfer of sample specimen to the testing device either directly or by use of a device provided with the kit (e.g. inverted cup, transfer loop, autofill pipette, etc.) | Example of sample preparation could be one preset dilution or a reagent mixing step. The test procedure should tolerate a short time lapse between sample collection and testing. | |
| **2.5 Sample volume** | A volume of sample that can be obtained in a non-invasive/minimally invasive way in all age groups | For example, in the case of a finger-prick sample, the acceptable volume would be < 50 µL (equivalent to approximately one drop). | |
| **2.6 Target analyte** | Marker or combination of markers identifying individuals at risk of *P. vivax* relapse | Risk of relapse may be determined by detecting analytes that indicate (directly and/or indirectly) hypnozoite carriage:<br><br>1. Direct evidence: hypnozoite metabolic markers or other direct indicator.<br><br>2. Proxy indicator: immunological biomarker profiles against *P. vivax* to reflect acute or recently cured blood-stage infection (e.g. in the last nine months, comparable to observed relapse patterns); a multiplexed approach assessing several markers may enhance clinical diagnostic performance.<br><br>3. Proxy indicator: detection of acute sequestered *P. vivax* infection (e.g. spleen, bone marrow) not detectable by current antigen-based RDTs or by microscopy.<br><br>Proxy indicator 3 may be insufficiently sensitive and may need to be combined with evidence from proxy 1 or proxy 2. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **2.7 Detection** | Unambiguous test interpretation | For example, via high-contrast test line detected with the naked eye or, if required, using an instrument; indoor and outdoor reading of a signal that provides a "yes/no" qualitative or a quantitative result. | |
| **2.8 Quality control** | Built-in process control indicator (test control) | Tests will need to be manufactured under stringent conditions (i.e. ISO 13485:2016); the test is not dependent on positive analyte controls being used for quality control by the user. | |
| **2.9 Supplies needed** | Reagents and supplies included in the kit are associated with minimal import restrictions. | Preferably animal-free, no bovine serum albumin (BSA), and no Triton X-100, for example. | |
| **2.10 Safety** | Safe for both patient and user; does not expose them to any unnecessary risks; and normal use does not create any additional hazards to the operator when observing universal blood safety precautions. | For example, in the case of finger-stick sampling, an auto-retracting sterile lancet should be provided. | |
| **3. Performance** | | | |
| **3.1 Species differentiation** | Ideally detects *P. vivax* only | Interference with other *Plasmodium* species may be acceptable given the low *P. vivax* endemicity in the intended use settings where mixed-species infections may be present. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **3.2 Diagnostic / clinical sensitivity** | > 80% sensitivity to detect a future relapse event | Diagnosis in this use case informs treatment decisions, so test performance metrics relate to the detection of individual-level risk of relapse. Tests should aim to reduce over-treatment (relative to the only currently available option of mass drug administration), while maintaining a public health and individual clinical benefit. [a]<br><br>The reference is the occurrence of a *P. vivax* relapse in the months following testing. Successfully detecting all blood-stage relapses is challenging and a high-sensitivity assay (e.g. PCR) should be used to repeatedly test individuals with high regularity. Well characterized bio-banked samples with accompanying meta-data (including clinical histories and infection status by PCR) could be used to assess diagnostic performance. | Results from recent field studies and modelling have assessed the trade-off (in terms of diagnostic sensitivity, specificity and over-treatment) between different mass test and treat strategies and mass drug administration *(24,25)*.<br><br>WHO encourages development of open biobanks that would facilitate research and development of tests designed to meet PPC targets. |
| **3.3 Diagnostic / clinical specificity** | > 90% specificity to detect a future relapse event | Same comments as above | Same comments as above |
| **3.4 Time to results** | < 30 minutes | < 30 minutes if multiple samples can be run in parallel; < 60 minutes may be acceptable. | |
| **3.5 Throughput** | ≥ 4 tests / hour / operator | | |
| **3.6 Target shelf life / storage conditions** | ≥ 18 months at ≥ 35 °C and 90% relative humidity, and able to support short periods of thermal stress | Requirements relate to test kits (i.e. consumables) that are used in the field. | |
| **3.7 Ease of use** | Maximum of one timed step; three or fewer user steps; IFUs should include a diagram of the method and results interpretation; must be usable in an unprotected external environment. | | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **3.8 Ease of results interpretation** | Interpreted using the unaided eye or an automated readout that is visible in full sunlight | | |
| **3.9 Operating temperature** | 15 °C to 40 °C | Operating temperature conditions should be adapted to the use case and to local conditions in the settings of intended use (likely at least up to 40 °C and 90% relative humidity). | |
| **4. Product configuration** | | | |
| **4.1 Service and support** | None required | If an instrument is required, its useful lifetime may be limited in terms of the number of use events or months/years of use (as indicated by the IFU or internal instrument internal display).<br><br>Initial lifetime calibration should be done at the time of manufacture and/or the instrument automatically self-calibrates without user input. | |
| **4.2 Waste disposal** | Does not include material that cannot be disposed of in normal laboratory biohazard or general waste streams | Ideally, consumables should be made from renewable or biodegradable materials. | |
| **4.3 Labelling and instructions for use (IFUs)** | Compliance required per stringent regulatory authority and WHO Prequalification guidance; product insert should be available in the relevant local language(s) and include IFUs for the test. | WHO Prequalification label/IFU guidance should be applied, regardless of whether the test is WHO-prequalified or not. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **5. Price and registration** | | | |
| **5.1 Target pricing per test** | End-user price point of US$ 2 or less<br><br>Pricing shall ensure affordability in settings of need, but not at a detriment to test performance. | Price points shown are for consumables only (i.e. no additional equipment costs associated with a laboratory-based test) and are estimates provided by the PPC development group; detailed business/return on investment case and cost of goods sold analyses will be required for proposed designs.<br><br>Reduction of relapse episodes justifies a higher price point than what is recommended for an antigen-detecting *P. vivax* RDT. | |
| **5.2 Capital cost, if applicable** | Modest (≤ US$ 2000) to zero, based on purchase commitment | If applicable, the preference would be to use an existing standard platform as opposed to a single-use laboratory platform. | |
| **5.3 Product registration (i.e. substantiation to regulatory body of product claims)** | Registration required for export from country of origin<br>• WHO prequalification if/once pathway is established<br>• Country-level registration (if required/applicable for target countries) | | |

Note:

[a] In low transmission settings, the positive predictive value of these tests may still to be low. Programmes may need to assess the risk–benefit on a case-by-case basis to balance public health value and clinical benefit to the individual.

# 4. PPC 2: laboratory-based test to detect risk of *P. vivax* relapse

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **1. General requirements** | | | |
| **1.1 Intended use** | Test to identify communities or individuals at risk of *P. vivax* relapse based on detection of analyte(s) indicative of *P. vivax* hypnozoite carriage and/or current sequestered infection and/or recent (blood-borne) infection with *P. vivax*<br><br>Unlike the POC test (see PPC 1), this test will be used to screen large numbers of individuals simultaneously as part of surveillance and/or monitoring activities related to *P. vivax* control and elimination. | Emerging data show that, in infectious individuals who may carry a high risk of relapse, *P. vivax* parasites can be sequestered in sites of erythropoiesis (bone marrow, spleen and liver) and may be difficult to detect. *(14,15)*.<br><br>"Recent infection" could refer to the preceding nine-month window, based on available data from human infection studies and epidemiological studies *(10)*.<br><br>The test is designed to be conducted as a centralized laboratory-based test and could be used in the context of a "screen and treat" application. The test allows for collection and transportation of samples to a central laboratory for final analysis and is suitable for medium- to high-throughput testing. | |
| **1.2 Targeted population** | All individuals living in or returning from travel to *P. vivax* endemic settings where the transmission level ranges from low to elimination, and who are suspected of having latent or sequestered *P. vivax* infection | A "screen and treat" approach may be applied for individuals identified to be at risk of *P. vivax* relapse, if follow-up is feasible in the context of use. If the test is positive, then it may inform radical cure treatment in line with WHO or national treatment guidelines for acute *P. vivax* infection. | |
| **1.3 Lowest infrastructure level** | Test use features allow for application in "limited infrastructure" conditions (Level 1); test use may require electricity and cold chain for transport and storage of reagents. | See Annex 1. Definition of health system infrastructure levels. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **1.4 Lowest level user** | The test may require trained laboratory professionals. | | |
| **1.5 Test training requirements** | ≤ 2 days of training to perform the test | | |
| **2. Design** | | | |
| **2.1 Portability** | No restrictions on portability, but should be feasible to ensure safe and practical delivery to and set-up in intended-use laboratory settings | Use in mobile laboratories could be envisioned and would be an ideal characteristic in terms of expanding its usability. | |
| **2.2 Power requirements** | Mains power<br><br>(local 100–240 V alternating current (AC), 50 or 60 Hz mains power) | Ideally also compatible with direct-current (DC) local supplies such as solar and other renewable power sources or an external uninterruptable power supply. | |
| **2.3 Maintenance and calibration** | Periodic maintenance and calibration of any instrumentation should be minimized. | If specialized services are needed but not locally available, an alternative mechanism of timely support must be provided.<br><br>Device self-monitoring /alerts on the need for calibration. | |
| **2.4 Sample type / collection** | Capillary blood from finger sticks and venous blood, or non-invasive/ minimally invasive biological samples collected according to routine procedures<br><br>Samples should be amenable to transport under ambient conditions and to short-term storage. | Non-invasive or minimally invasive samples might include saliva, urine, volatile organic compounds, etc. Use of anti-coagulants with samples is acceptable. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **2.5 Sample preparation / test procedure** | Sample preparation steps should be limited in number and compatible with medium- to high-throughput use. | | |
| **2.6 Sample volume** | A volume of sample that can be obtained in a non-invasive/minimally invasive way in all age groups | For example, in the case of a finger-prick sample, the acceptable volume would be < 50 µL (equivalent to approximately one drop. | |
| **2.7 Target analyte** | Marker or combination of markers identifying individuals at risk of *P. vivax* relapse | Risk of relapse may be determined through detection of analytes that indicate (directly and/or indirectly) hypnozoite carriage:<br>1. Direct evidence: hypnozoite metabolic markers or other direct indicator.<br>2. Proxy indicator: immunological biomarker profiles against *P. vivax* to reflect acute or recently cured blood-stage infection (e.g. in the last nine months, comparable to observed relapse patterns); a multiplexed approach assessing several markers may enhance clinical diagnostic performance.<br>3. Proxy indicator: detection of acute sequestered *P. vivax* infection (e.g. spleen, bone marrow) not detectable by current antigen-based RDTs or by microscopy.<br>Proxy indicator 3 may be insufficiently sensitive and may need to be combined with evidence from proxy 1 or proxy 2. | |
| **2.8 Type of analysis and detection** | Quantitative or semi-quantitative analysis generating signal outputs that may be detectable by an instrument | Choice and benefits of quantitative vs. semi-quantitative type of analysis may depend on the exact nature of the targets measured. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **2.9 Result output** | Results may be quantitative or semi-quantitative, but should allow for actionable outputs such as relapse risk stratification. | Same as above | |
| **2.10 Quality control** | Built-in process control indicator (test control) and positive analyte controls could be provided to enable users to perform quality controls. | | |
| **2.11 Supplies needed** | Reagents and supplies included in kit associated with minimal import restrictions | Preferably animal-free, no bovine serum albumin (BSA), and no Triton X-100, for example | |
| **2.12 Safety** | Safe for both the patient and user; does not expose them to any unnecessary risks; normal use does not create any additional hazards to the operator when observing universal blood safety precautions. | For example, in the case of finger-prick sampling, an auto-retracting sterile lancet should be used. | |
| **3. Performance** | | | |
| **3.1 Species differentiation** | Ideally detects *P. vivax* only | Interference with other *Plasmodium* species may be acceptable given the low *P. vivax* endemicity in the intended-use settings where mixed-species infections may be present. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **3.2 Diagnostic / clinical sensitivity** | > 80% sensitivity to detect a future relapse event | Test performance may be expected to outperform the PPC 1 POC test given the higher investment costs, but as test results are primarily to inform population-level risk levels, rather than individual treatment decisions (though both uses could be envisaged), less stringent performance may be acceptable.<br><br>The reference is the occurrence of a *P. vivax* relapse in the months following testing. Successfully detecting all blood-stage relapses is challenging and a high-sensitivity assay (e.g. PCR) should be used to repeatedly test individuals with high regularity. Well characterized bio-banked samples with accompanying metadata (clinical histories and infection status by PCR) could be used to assess diagnostic performance. | Results from recent field studies and modelling have assessed the trade-off (in terms of diagnostic sensitivity, specificity and over-treatment) between different mass test and treat strategies and mass drug administration *(24,25)*.<br><br>WHO encourages development of open biobanks that would facilitate research and development of tests designed to meet PPC targets. |
| **3.3 Diagnostic / clinical specificity** | > 90% specificity to detect a future relapse event | Same comments as above | Same comments as above |
| **3.4 Time to results** | < 4 hours to developed test result for a batch run of > 90 specimens, including sample preparation time | Time to result is less critical (compared to PPC 1), but operator time spent on a batch run should be minimized. | |
| **3.5 Result stability** | Test outcome (per batch run) should be automatically stored in the device, for > 1000 tests. | Ability to interpret and store final test results in a computer-aided manner not constrained by timed steps will help greatly in resource-constrained settings. | |
| **3.6 Throughput** | Minimum capacity of > 90 specimens per batch run (can be run with fewer), and ability to run two batches per eight hours | Must also be able to label/track individual specimens from accession to results | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **3. Target shelf life / storage conditions** | ≥ 18 months, 15 °C to 35 °C, 75% relative humidity, though storage at 4 °C to -20 °C acceptable for reagents; reagents need to withstand temperature excursion to 45 °C for two weeks without effect on shelf life. | Requirements are related to test kits that are used in the field, including specimen collection.<br>Note: The consumables required for laboratory-based testing procedures may or may not require a cold chain. | |
| **3.8 Ease of use** | Five or fewer timed steps; ≤ 15 user steps; IFU should include a diagram of the method and results interpretation. | | |
| **3.9 Ease of results interpretation** | Results can be interpreted by a suitable instrument. | | |
| **3.10 Operating temperature** | 15 °C to 35 °C; if in-device temperature compensation is required, it will be automatic. | | |
| **4. Product configuration** | | | |
| **4.1 Service and support** | Maintenance/technical support must be available from the manufacturer for the region of use (equipment and/or procedures). | | |
| **4.2 Waste disposal** | Does not include material that cannot be disposed of in normal laboratory biohazard waste streams | Ideally, consumables will be made from renewable or biodegradable materials. | |
| **4.3 Labelling and instructions for use (IFUs)** | Compliance required per stringent regulatory authority and WHO Prequalification guidance; product insert should be available in relevant local language(s) and should include IFUs for the test. | WHO Prequalification label/IFU guidance should be applied, regardless of whether the test is WHO-prequalified or not. | |

| | Characteristics | Background | Additional notes |
|---|---|---|---|
| **5. Price and registration** | | | |
| **5.1 Target pricing per test** | End-user price point of US$ 2 or less<br><br>Pricing shall ensure affordability in settings of need, but not at a detriment to test performance. | Price points shown are for consumables only (i.e. no additional equipment costs associated with a laboratory-based test) and are estimates provided by the PPC development group; detailed business/return on investment case and cost of goods sold analyses will be required for proposed designs. | |
| **5.2 Capital cost** | Multi-use/standard platform pricing should aim for < US$ 15 000. | Use of a standard platform as opposed to a single-use laboratory platform may constitute an advantage to the user. | |
| **5.3 Product registration (i.e. substantiation to regulatory body of product claims)** | Registration required for export from the country of origin<br>• WHO prequalification if/once pathway is established<br>• Country-level registration (if required/applicable for target countries) | | |

.

# References


1. Global technical strategy for malaria 2016–2030, 2021 update. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/342995, accessed 20 October 2023).

2. World malaria report 2023. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374472, accessed 25 January 2024).

3. Mahittikorn A, Masangkay FR, Kotepui KU, De Jesus Milanez G, Kotepui M. Comparison of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* infections by a meta-analysis approach. Sci Rep. 2021;11(1):6409. doi:10.1038/s41598-021-85398-w.

4. Malaria eradication: benefits, future scenarios and feasibility: a report of the Strategic Advisory Group on Malaria Eradication. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/331795, accessed 20 October 2023).

5. Battle KE, Lucas TCD, Nguyen M, Howes RE, Nandi AK, Twohig KA, et al. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-17: a spatial and temporal modelling study. Lancet. 2019; 394:332-3. doi.org/10.1016/S0140-6736(19)31096-7.

6. Robinson LJ, Wampfler R, Betuela I, Karl S, White MT, Li Wai Suen CSN, et al. Strategies for understanding and reducing the *Plasmodium vivax* and *Plasmodium ovale* hypnozoite reservoir in Papua New Guinean children: a randomized placebo-controlled trial and mathematical model. PLoS Med. 2015;12(10):e1001891. doi:10.1371/journal.pmed.1001891.

7. Commons RJ, Simpson JA, Watson J, White NJ, Price RN. Estimating the proportion of *Plasmodium vivax* recurrences caused by relapse: a systematic review and meta-analysis. Am J Trop Med Hyg. 2020; 103(3):1094–9. doi:10.4269/ajtmh.20-0186.

8. Douglas NM, Anstey NM, Buffet PA, Poespoprodjo JR, Yeo TW, White NJ, et al. The anaemia of *Plasmodium vivax* malaria. Malar J. 2012;11:135. doi:10.1186/1475-2875-11-135.

9. Dini S, Douglas NM, Poespoprodjo JR, Kenangalem E, Sugiarto P, Plumb ID, et al. The risk of morbidity and mortality following recurrent malaria in Papua, Indonesia: a retrospective cohort study. BMC Med. 2020;18:28. doi:10.1186/s12916-020-1497-0.

10. White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. Malar J. 2011;10:297. doi.10.1186/1475-2875-10-297.

11. Commons RJ, Simpson JA, Thriemer K, Hossain MS, Douglas NM, Humphreys GS, et al. Risk of *Plasmodium vivax* parasitaemia after *Plasmodium falciparum* infection: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19:91–101. doi:10.1016/S1473-3099(18)30596-6.

12. World malaria report 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/365169, accessed 20 October 2023).

13. Confronting *Plasmodium vivax* malaria. Geneva: World Health Organization; 2015 (https://iris.who.int/handle/10665/181163, accessed 20 October 2023).

14. Kho S, Qotrunnada L, Leonardo L, Andries B, Wardani PAI, Fricot A, et al. Evaluation of splenic accumulation and colocalization of immature reticulocytes and *Plasmodium vivax* in asymptomatic malaria: a prospective human splenectomy study. PLoS Med. 2021;18(5):e1003632. doi:10.1371/journal.pmed.1003632.

15. Kho S, Qotrunnada L, Leonardo L, Andries B, Wardani PAI, Fricot A, et al. Hidden biomass of intact malaria parasites in the human spleen. N Engl J Med. 2021;384:2067–9. doi:10.1056/NEJMc2023884.

16. Brito MAM, Baro B, Raiol TC, Ayllon-Hermida A, Safe IP, Deroost K, et al. Morphological and transcriptional changes in human bone marrow during natural *Plasmodium vivax* malaria infections. J Infect Dis. 2022;225(7):1274–83. doi:10.1093/infdis/jiaa177.

17. Rapid diagnostic tests [website]. In: Global Malaria Programme. Geneva: World Health Organization (https://www.who.int/teams/global-malaria-programme/case-management/diagnosis/rapid-diagnostic-tests, accessed 20 October 2023).

18. Cunningham J, Jones S, Gatton ML, Barnwell JW, Cheng Q, Chiodini PL, et al. A review of the WHO malaria rapid diagnostic test product testing programme (2008–2018): performance, procurement and policy. Malar J. 2019;18:387. doi:10.1186/s12936-019-3028-z.

19. Cheng Q, Cunningham J, Gatton ML. Systematic review of sub-microscopic *P. vivax* infections: prevalence and determining factors. PLoS Negl Trop Dis. 2015;9(1):e3413. doi:10.1371/journal.pntd.0003413.

20. Anstey NM, Douglas NM, Poespoprodjo JR, Price RN. *Plasmodium vivax*: clinical spectrum, risk factors and pathogenesis. Adv Parasitol. 2012;80:151–201. doi:10.1016/B978-0-12-397900-1.00003-7.

21. Agarwal R, Choi L, Johnson S, Takwoingi Y. Rapid diagnostic tests for *Plasmodium vivax* malaria in endemic countries. Cochrane Database Syst Rev. 2020;11:CD013218. doi:10.1002/14651858.CD013218.pub2.

22. Gualdron-Lopez M, Flannery EL, Kangwanrangsan N, Chuenchob V, Fernandez-Orth D, Segui-Barber J, et al. Characterization of *Plasmodium vivax* proteins in plasma-derived exosomes from malaria-infected liver-chimeric humanized mice. Front Microbiol. 2018;9:1271. doi:10.3389/fmicb.2018.01271.

23. Howes RE, Gregg A, Harbers M, Lover A, Puspitasari AM, Noviyanti R, et al. Developing a serological rapid test for an unmet diagnostic niche: the *Plasmodium vivax* hypnozoite. Am J Trop Med Hyg. 2020;103(Suppl 5):761.

24. Longley RJ, White MT, Takashima E, Brewster J, Morita M, Harbers M, et al. Development and validation of serological markers for detecting recent *Plasmodium vivax* infection. Nat Med. 2020;26:741–9. doi:10.1038/s41591-020-0841-4.

25. Noviyanti R, Utami RA, Nekkab N, Ekawati LL, Trianty L, Fadila N, et al. Identifying future *Plasmodium vivax* relapses with serological markers of exposure in a returning Indonesian soldier cohort. Am J Trop Med Hyg. 2021;105(Suppl 5):0886.

26. Ding XC, Ade MP, Baird JK, Cheng Q, Cunningham J, Dhorda M, et al. Defining the next generation of *Plasmodium vivax* diagnostic tests for control and elimination: target product profiles. PLoS Negl Trop Dis. 2017;11(4):e0005516. doi:10.1371/journal.pntd.0005516.

# Annex 1. Definition of health system infrastructure levels

Table A1 outlines the definition of health system infrastructure levels, as described in Ghani et al. *(1)* and the Maputo Declaration *(2)*.

**Table A1. Definition of health infrastructure levels**

| Characteristics | Level 0 | Level 1 | Level 2 | Levels 3 and 4 |
|---|---|---|---|---|
| **Description** | In the community or home | Lowest level of health care system with a laboratory | First level of referral health care and laboratories | Second and higher levels of referral health care and laboratories |
| **Examples of locations** | In homes, health fairs, health posts, clinics with no laboratory, pharmacies | Health centres (Africa), rural health centres (Asia and Latin America) | Hospitals (Africa), urban health clinics (Asia and Latin America), clinical laboratories in the developed world | Hospitals (Latin America and Asia), national clinical/ reference laboratories (Africa), surveillance laboratories, research laboratories |
| **Electricity** | Not reliably available | Not reliably available | Available, expected to have refrigeration | Available |
| **Clean water** | Not reliably available | Not reliably available | Available | Available |
| **Physical and laboratory infrastructure and laboratory equipment** | No laboratory | Not all facilities have laboratories. If present, minimally equipped (e.g. microscope, centrifuge) or moderately equipped (see level 2 description laboratories) | Moderately equipped laboratories (e.g. additional equipment for basic chemistry and manual immunoassays) | Well equipped laboratories (e.g. automated and advanced equipment) |
| **Personnel** | Community health care workers, nurses, family members, pharmacists, traditional medicine practitioners | Nurses, sometimes physicians, laboratorians with a range of training | Nurses, physicians, moderately and well trained laboratorians | Nurses, physicians, well trained laboratorians |

## References


1. Ghani AC, Burgess DH, Reynolds A, Rousseau C. Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. Nature. 2015;528:S50–2. doi:10.1038/nature16038.

2. The Maputo Declaration on strengthening of laboratory systems. Brazzaville: World Health Organization Regional Office for Africa; 2008 (https://www.who.int/publications/m/item/the-maputo-declaration-on-strengthening-of-laboratory-systems, accessed 6 June 2022).

# Annex 2. WHO development process for preferred product characteristics and management of conflicts of interest

For this PPC on diagnostic tests for detecting risk of *P. vivax* relapse, in alignment with a WHO standard procedure for developing preferred product characteristics (*1*), a review of the available literature was conducted to inform key questions and issues to be discussed during the technical consultation with experts. Initial landscaping exercises and summary documents by the Bill & Melinda Gates Foundation were part of the background documents that helped to inform the discussion of the WHO scientific development committee. The development process of the WHO PPC was independent to activities conducted by other institutions, but the background information available helped to provide context to the existing status of the field.

A scientific development group/committee was constituted, including leading scientists and relevant experts, regulators, and in-country end-user representatives. For the scientific development committee, standard WHO declarations of interest procedures are followed (see Assessment and management of conflicts of interest below).

Following the development of the draft PPC document by the Global Malaria Programme and the scientific development committee, the PPC was posted for public consultation in August 2023. Feedback received during the public consultation period were reviewed and, where appropriate, addressed in a revised version of the PPC.

## Assessment and management of conflicts of interest

Declarations of any competing interests were received from 16 experts. WHO processes were used to assess declared interests and to manage any conflicts of interest. Six experts declared potential competing interests. Four members – Chris Drakeley, Ivo Mueller, Michael White, and Rosalind Howes – declared significant interests related to receiving research grants (Professor Drakeley, Professor Mueller, Dr White, and Dr Howes) and being listed as inventors for patents (Professor Mueller, Dr White) on *P. vivax* serological tests. After review and due diligence by the WHO Secretariat, it was concluded that these persons would only participate to provide scientific information to the committee and would be excluded from decision-making, and one member (Dr Howes) would participate as a rapporteur. All remaining 12 members were not considered by WHO to have declared any interest that may be perceived as a potential conflict with regards to the objectives of the meeting.

## References

1. WHO target product profiles, preferred product characteristics, and target regimen profiles: Standard procedure. Second edition. Geneva: World Health Organization; 2024 (upcoming).

For further information please contact:

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

9789240089846