DIAGNOSTICS

Point-of-care tools for malaria care

Determining glucose-6-phosphate dehydrogenase (G6PD) deficiency to guide patient treatment for *Plasmodium vivax*

The challenge of radical cure

Malaria is an infectious disease caused by the *Plasmodium* parasite that causes disease for millions of people worldwide each year. Malaria is targeted for global elimination—the reduction of transmission until new cases no longer occur.

Up to 2.85 billion people may be at risk of infection with *Plasmodium (P.) vivax*, a form of malaria found in Asia, Latin America, and the horn of Africa. *P. vivax* is the most difficult type of malaria to treat because a form of the parasite known as the hypnozoite can lie dormant in the liver and cause illness weeks or months after the first infection. *P. vivax* is also hard to eliminate because during these relapses the patient becomes infectious, perpetuating the transmission cycle of *P. vivax* in the community.

All hypnozoites in the body must be killed to completely cure a patient with *P. vivax* and stop the spread of disease. This is known as “radical cure.” Currently, radical cure for *P. vivax* can be achieved only through treatment with 8-aminoquinoline–based drugs such as primaquine and *Kozenis* (tafenoquine). However, patients deficient in glucose-6-phosphate dehydrogenase (G6PD), an enzyme that helps protect red blood cells from oxidative damage, are at risk of hemolytic anemia when treated with these drugs.

New G6PD deficiency detection tools are needed

Due to the risk of hemolytic anemia, patients with severe G6PD deficiency should not receive the standard course of primaquine or tafenoquine for radical cure of *P. vivax*. Furthermore, because females can carry the gene that causes G6PD deficiency on one or both X chromosomes (known as heterozygosity), these females can have varying levels of G6PD activity (deficient or intermediate), which may put them at risk of adverse reactions to 8-aminoquinolines.

A common hereditary condition known as G6PD deficiency poses a threat to efforts to eliminate *P. vivax* malaria. G6PD testing is essential for patient safety and to accelerate elimination efforts.

Patients with G6PD deficiency are at risk of adverse reactions to radical cure for *P. vivax* malaria, and must be tested at the point of care before being given 8-aminoquinolines. PATH/H. Chivoan

It is estimated that 400 million people worldwide are G6PD-deficient, and the condition is common in areas where malaria is endemic. However, simple and rapid tests for G6PD deficiency are not widely available at the point of care (POC), and the tests that are available are not able to detect heterozygous females with intermediate G6PD activity who may be at risk of hemolytic anemia. A POC diagnostic for G6PD deficiency is needed to enable wide-scale radical cure treatment of patients with *P. vivax* malaria and accelerate elimination of the disease.

Our approach

PATH and our partners are advancing new diagnostic tests for G6PD deficiency that may help guide appropriate clinical care of patients and support *P. vivax* elimination efforts. PATH performed comprehensive analyses of the G6PD diagnostic landscape, conducted prospective comparative studies of G6PD assays, and applied the data to develop target product profiles for tests to support malaria case management.

PATH also developed a unique specimen repository containing samples of blood across a range of G6PD activity, including deficient and intermediate samples; the repository allows PATH and its partners to draw upon reliable sources of G6PD-deficient

samples to use in the development and evaluation of new diagnostic tests. The specimen repository is available to all manufacturers developing G6PD diagnostic tests to support malaria treatment.

PATH is part of multiple product development partnerships that aim to ensure the availability of G6PD testing options that best meet the needs of healthcare providers managing malaria cases. These new test options are designed to support use of 8-aminoquinolines such as primaquine (the standard treatment for *P. vivax*). We are closely collaborating with GSK to ensure a point-of-care quantitative test for G6PD deficiency is available in malaria-endemic countries to support use of the new single-dose 8-aminoquinoline drug tafenoquine (*Kozenis*), developed by GSK and Medicines for Malaria Venture. PATH is also looking at use cases beyond malaria programs, as new rapid tests for G6PD may have significant use in newborn screening and other clinical care settings.

A portfolio of G6PD tools

PATH works with multiple diagnostic test developers to develop and evaluate G6PD diagnostic tests with different characteristics to suit the needs of test users. We are advancing quantitative tests that are able to identify all G6PD-deficient patients potentially at risk of clinically significant hemolysis, including heterozygous females with low to intermediate G6PD deficiency. These tests include biosensor devices capable of measuring both a patient's G6PD activity and hemoglobin levels. Qualitative tests with a simple control line readout are also in development, providing a low-cost option for use at the community level to guide administration of primaquine.

These new G6PD diagnostic tests became available in the first malaria endemic countries in 2017. The STANDARD™ G6PD test has received provisional approval through the Expert Review Panel for Diagnostics (ERPD) for procurement with Global Fund and other procurer's support through July 2021. PATH has also been working with global and in-country partners to increase access to the new POC G6PD diagnostic tests. As new tests come to market, PATH supports and guides manufacturers to facilitate test registration, manufacture, and sale in countries where they are needed most.

Community of Practice

PATH is the convener of the G6PD Operations Research Community of Practice (GORCoP), a collaboration of researchers, organizations, and clinicians committed to advancing the introduction and scale-up of G6PD diagnostics in support of safe access to radical cure. The community of practice aims to achieve the maximum impact on health outcomes by harnessing best practices and lessons learned from multiple stakeholders and benefiting from the expertise of participants in areas such as diagnostics introduction, operations research, implementation science, quality assurance, and training. The community of practice's activities include quarterly webinars and resource sharing through a digital repository.

PATH is advancing biosensor devices that provide a reading of G6PD activity and hemoglobin levels. PATH/SD Biosensor

Contact

To learn more about G6PD diagnostics, visit www.path.org/programs/diagnostics/ or contact Gonzalo Domingo, scientific director malaria diagnostics at PATH, at dxinfo@path.org.

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