Immunodiagonsis of Malaria

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Abstract

Malaria remains one of the world's most important public health threats, and prompt, precise diagnosis is still an essential component of malaria control and elimination strategies, even in the postelimination phase. There are many kinds of diagnostic tools used for malaria diagnosis, including microscopy, rapid diagnostic tests, and nucleic acid amplification testing. There are advantages and disadvantages among these methods in practice. In this chapter, we introduce different techniques for the immunodiagnosis of malaria based on malarial antigens and antibodies and provide recommendations for the future research and development of novel technologies for malaria diagnosis and transmission risk evaluation in China after malaria elimination.

Keywords

Malaria · Antigen · Antibody · Immunodiagonsis

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7.1 Introduction

With the advancement of the global malaria control process, an increasing number of countries have entered the preelimination stage or the malaria elimination stage (WHO 2021a). However, the trends have been partially stalled by COVID-19, and a significant increase in malaria cases and deaths were reported in 2020 in the World Malaria Report 2021 (WHO 2021b), where the estimated number of cases in 87 endemic countries in the world reached 241 million, and the estimated number of deaths reached 627,000. This was attributed to the disruption of medical services for malaria due to the COVID-19 pandemic. Therefore, there is still a long way to go to achieve the global eradication of malaria.

Prompt, precise diagnosis is an essential component of malaria control and elimination strategies, and parasitological testing is the only way for accurate malaria diagnosis in febrile patients (WHO 2011). It is also critical to the reliability of surveillance data and the understanding of malaria transmission. There are several methods to detect the presence of malaria parasites in the blood. The gold standard method is microscopy, although rapid diagnostic tests (RDTs) have rapidly become a primary diagnostic test in many endemic areas. Furthermore, many kinds of novel serological and molecular methods have been developed and assessed to overcome the limitations of microscopy and RDTs.

In this chapter, immunoassays for malarial antigen or antibody detection are discussed.

7.2 Immunoassays for Antigen Detection

7.2.1 Rapid Diagnostic Tests

Immunochromatographic-based diagnostic tests are already the most common diagnostic methods for malaria that detect antigens, and they are also known as rapid diagnostic tests (RDTs), which are extensively used worldwide (Wilson 2012). These methods are lateral flow assays usually in the format of cassettes, dipsticks, or cards, consisting of capture antibodies against *Plasmodium*-specific antigens immobilized on nitrocellulose membranes and bound to gold particles or other visually detectable markers (labeled antibodies) in the mobile phase. Antigens of the parasite are detected when the blood of a person suspected of having malaria is dropped in a membrane strip, where the liquid sample flows across. As a result, the immobilized complexes "capture antibody–antigen–labeled antibody" will be formed and can be visualized with colored lines when the blood is infected with *Plasmodium* (Gimenez et al. 2021).

RDTs are cost-effective and simple to operate, the results are displayed in less than 30 min and are easy to interpret, and little infrastructure and no electrical equipment are required (Mukkala et al. 2018). They are important alternatives for malaria diagnosis in areas where microscopy or other approaches are used to detect malaria parasites in the blood. Meanwhile, they are the most commonly used method

for malaria diagnosis in resource-limited endemic settings. Not only are they increasingly used in malaria screening and epidemic investigations, but they are also useful tool for malaria self-diagnosis. It was reported that 3.1 billion malaria RDTs were sold globally in 2010–2020, with nearly 81% of these sales going to sub-Saharan African countries (WHO 2021b). Correspondingly, 2.2 billion RDTs were distributed by national malaria programmes, with approximately 88% in sub-Saharan Africa (WHO 2021b).

However, various factors, such as *Plasmodium* species, level of parasitemia, storage conditions, interpretation of the results, and the variability of the parasite antigen tested, may impact the performance of RDTs. First, RDTs are only suitable for the diagnosis of *P. falciparum*- and *P. vivax*-specific infections thus far. Currently, commercial RDTs available on the market are mostly able to detect *P. falciparum*-specific histidine-rich protein 2 (HRP2), *P. vivax*-specific lactate dehydrogenase, *Plasmodium* panspecific lactate dehydrogenase (pLDH), or *Plasmodium* spp. aldolase. However, their sensitivity to detect nonfalciparum spp. is low overall (Yerlikaya et al. 2018), and even for the detection of *P. vivax*, the sensitivity of the most frequently used RDTs was 75–87% compared to microscopy (Abba et al. 2014). Moreover, no RDTs can specifically detect *P. ovale*, *P. malariae*, or *P. knowlesi,* even with high sensitivity. Second, the performance of RDTs is also limited to low parasitemia, and they usually have the capability of detecting >100 parasites/μl. It is worth noting that the presence of a low number of parasites is relevant, especially for pregnant women and children under the age of 5 years, who are the most vulnerable populations. Third, humidity and extreme temperatures tend to easily affect RDT performance, and persistence of antigens in the patient's blood circulation after treatment may lead to false positives (Yan et al. 2013). Fourth, interpretation of results can be confusing when testing for combinations of antigens, especially when control and *Plasmodium* panspecific lines are displayed together. Fifth, the emergence and spread of *Pf*HRP2/3-deleted strains in countries where malaria is endemic results in the increasing occurrence of false negativity in symptomatic patients who are infected with variants of *P. falciparum* that do not express HRP2 (Cheng et al. 2014). It was reported that *Pf*LDH-based RDTs could be used for *P. falciparum* detection in *Pf*HRP2-deleted samples at high density but vary greatly at lower densities (Gatton et al. 2020).

Therefore, quality-assured RDTs can be important for case diagnosis and case management, and users such as clinicians and laboratory personnel must be familiar with the RDTs used in their facilities and their associated performance characteristics, while the causes of fever in nonmalarial patients should be followed up and properly managed appropriately. Consequently, the minimum procurement criteria were recommended by the WHO Malaria Policy Advisory Committee, and independent global quality assessment programmes for malaria RDT lots have been carried out by the WHO in collaboration with other Malaria programmes, such as the Foundation for Innovative New Diagnostics (FIND), and coordinated the WHO Malaria RDT Product Testing Programme (Cunningham et al. 2019). In detail, any RDT should be fast and independent of the device, available to those who need it, and require minimal training. Furthermore, their sensitivity and specificity were

recommended to reach at least a 75% "panel detection score" at 200 parasites/μL, with a false positive rate of less than 10% and an invalid rate of <5%, for the detection of *P. falciparum* and, if applicable for *P. vivax*, in all transmission settings (https://www.who.int/teams/global-malaria-programme/case-management/diagnosis/rapid-diagnostic-tests). To date, eight rounds of WHO product testing of malaria RDTs have been completed since 2008, and the summary results of malaria RDT performance have been published (Malaria Rapid Diagnostic Test Performance Summary results of WHO product testing of malaria RDTs: rounds 1–8 (2008–2018)) (Cunningham et al. 2019).

Given the significantly lower sensitivities for nonfalciparum species mainly due to the lower parasitemia and the importance for the detection of low levels of parasitemia, malaria RDTs used for malaria diagnosis should be confirmed by other laboratory tests (e.g., blood film examination and nucleic acid amplification test). Moreover, high-sensitivity RDTs for *P. falciparum,* such as Alere Malaria Ag *P. f* (Alere) and NxTek Eliminate Malaria *P. f* (Abbott), have been developed and tested for their ability to detect malaria infection in asymptomatic individuals or individuals with very low parasitemia, and this might be a good strategy to better detect malaria parasites in the future, especially in the low-transmission setting or malaria-eliminated areas. In addition, there are also real-world implications for the discovery of new malaria RDT candidate antigens. One is Plasmodium glutamate dehydrogenase (pGDH), which has come to the attention of researchers; it is specific to *Plasmodium*, but the similarity among different species is so high that it is difficult to identify different *Plasmodium* spp. (Ahmad et al. 2019; Krishna et al. 2015). The other is GAPDH, which includes unique regions that make it possible to raise antibodies against pan-*Plasmodium* specificity and to detect *P. falciparum* or rodent malaria parasites specifically, but other species-specific detection for GAPDH has not been reported (Krause et al. 2017). Therefore, more work is needed in the future to determine whether pGDH-based or GAPDH-based RDTs can be used to detect malaria parasites.

7.2.2 Other Laboratory Assays for the Detection of Malaria Parasite Antigens

The development of assays used in the laboratory for malaria antigen testing has greatly benefited from the significant advances in the development of stable hybridomas as sources of monoclonal antibodies and improvements in immunoassay platforms throughout the decades (Plucinski et al. 2021). For example, a colorimetric sandwich ELISA has the capacity to detect HRP2 at levels of <100 pg/ml, with assay wells showing the intensity of color proportional to the amount of antigen in the sample (Jang et al. 2018). Other multiplexed detection systems for malaria diagnosis using different panels of *Pf*HRP2 and panmalarial antigen targets to differentiate species in malaria infection have been developed, such as the Luminex xMAP bead-based assay (Martianez-Vendrell et al. 2020) and the Quansys Q-Plex Human Malaria assay (Jang et al. 2019). For instance, the former assay can screen

P. falciparum with simultaneous analysis of glutamate-rich protein (GLURP) antigens R0 and R2, merozoite surface protein 3 (MSP3), MSP1 hybrid, and apical merozoite antigen 1 (AMA1) in blood from a person suspected of having malaria infection, according to the fluorescence intensity signals for different antigen targets for samples (Rogier et al. 2017). Furthermore, these assays are usually sensitive to detect malaria parasite antigens at low concentrations, plus their operator independence and reliability; thus, they have routine clinical application for malaria diagnosis. In addition, some promising laboratory tests of nontraditional immunoassays and aptamer-based antigen detection systems with good sensitivity and specificity have been developed (Frith et al. 2018; Mu et al. 2017; Hemben et al. 2017; Paul et al. 2017).

7.3 Immunoassays for Antibody Detection

Although serologic testing is generally not recommended for the routine diagnosis of malaria, it is still used for some cases, such as febrile patients traveling to malaria-endemic areas with repeatedly negative blood smears and cases of suspected topical splenomegaly syndrome. Moreover, it is also used to screen blood donors and evaluate donors with suspected cases of transfusion-transmitted malaria. Additionally, it is used for detecting malarial antibodies in seroepidemiological studies for monitoring malaria control and elimination under specific and predictable requirements. Thus, the ideal test should be high throughput, easy to operate, easy to interpret, and quick to display the results. Most of the tests available are either immunofluorescence assays or enzyme immunoassays and can be performed on serum or plasma.

7.3.1 Complement Fixation Test

The complement fixation test (CFT) is a classical laboratory testing and one of the earliest methods for malarial antibody detection, which is more sensitive than microscopy of peripheral blood smears for detecting current infections (Thomson 1918). The test is based on the capacity of complement, a group of heat-labile proteins present in the plasma, to bind to antigen–antibody complexes. When the complexes are present on the surface of red blood cells, complement causes their lysis, which can be measured photospectronically. In practice, heating the serum first leads to the destruction of complement, and then the serum is mixed with the appropriate pathogenic antigen and incubated. Next, exogenous complement is added into the mixture when the antigen–antibody complexes are formed. This complement then binds to the complexes and is "fixed," no longer able to cause lysis of the added indicator red blood cells. The test measures certain types of antibodies (mainly IgG antibodies) that occur only during the acute phase of pathogenic infection and has been widely used as an alternative for malaria diagnosis. However, this method is less sensitive and more complex, as well as labor

intensive; thus, it has been increasingly replaced by modern immunoassays such as enzyme-linked immunosorbent assay (ELISA) (Wilson et al. 1975; Drakeley and Cook 2009).

7.3.2 Indirect Hemagglutination Assay

Indirect hemagglutination assays (IHAs) have been developed and optimized continuously and used for detecting malarial antibodies. This method initially used tanned formolized sheep red blood cells sensitized with an antigen prepared from erythrocytic *Plasmodium* released from the red blood cells (Bray 1966). For instance, it was reported that soluble antigens prepared from *P. falciparum* and *P. vivax* could attach to aldehyde-fixed type "O" erythrocytes and detect antibodies in more than 91% of infections with homologous *Plasmodium* species and 72–76% of infections caused by heterologous species using the IHA (Mathews et al. 1975). Sera are tested by serial dilution but are difficult to standardize, resulting in limitations of cross-comparison of data from different research groups.

7.3.3 Immunofluorescence Antibody Test

The Immunofluorescence Antibody Test (IFAT) was extensively used for malaria seroepidemiology (Drakeley and Cook 2009). First, the whole parasitized red blood cells with the antigen of interest were fixed on a microscope slide, and then the sera sample was incubated on the slide. Finally, the resulting fluorescence according to the binding of a secondary antibody coupled with a fluorescent compound and the bound antibodies in the serum was examined using a specialized microscope. Compared with other methods, it is easier to prepare whole malarial parasite antigens, and these antigens are more stable than extracts of soluble antigens (Ambroise-Thomas 1976). However, this method is also difficult to standardize, and the fluorescence is subjectively determined by visual examination. Moreover, the sensitivity is limited due to the antigens used not being from the target malarial parasites, although *P. falciparum* culture became available as a stable source of antigen. In addition, it is also labor intensive for slide preparation, and the derived antibody responses are not specific since all parasitized red blood cells are used (Drakeley and Cook 2009).

7.3.4 Enzyme-Linked Immunosorbent Assay

The principle of Enzyme-Linked Immunosorbent Assay (ELISA) is similar to that of IFA, but the antigens of ELISA are coated on the microtiter plate instead of the glass slide of IFA, and the antigens are often single recombinant proteins. The bound antibodies are detected with a secondary antibody linked with an enzyme, and color change or fluorescence is quantified by a spectrophotometer if the bound enzyme is

present in the well. Furthermore, it is relatively cheap and easy to perform and generates objective results. Additionally, it is also a high-throughput, standardizable test that can be compared from different laboratories with robust results (Drakeley and Cook 2009; Esposito et al. 1990).

7.3.5 Protein Microarray

Protein microarray is similar to ELISA, but recombinant proteins are bound to a microarray slide in nanogram quantities and screen thousands of antigens simultaneously and have a greater dynamic detection range than ELISA; thus, it is much more suitable for antigen discovery and broad assessments of the immune response to malaria. However, it is not available for field investigation due to many factors, such as equipment requirements and signal variation between slides (Drakeley and Cook 2009; Doolan et al. 2009; Gray et al. 2007).

7.3.6 Cytometric Bead Array

Flow cytometric bead-based Cytometric Bead Array (CBA) can measure the response to multiple antigens in biological and environmental samples simultaneously. There are several advantages: it allows the assessment of multiple analytes in a single sample, collects data with minimal sample size, is reproducible, and can be compared with results from previous experiments and results from other assays, as well as evaluate multiple samples faster. There were different cytokine/chemokine kits, two flow cytometry-based (eBioscience® FlowCytomix™ and BD™ Cytometric Bead Array Human Enhanced Sensitivity) and four Luminex®-based (Invitrogen™ Human Cytokine 25-Plex Panel, Invitrogen™ Human Cytokine Magnetic 30-Plex Panel, Bio-Rad® Bio-Plex Pro™ Human Cytokine Plex Assay, and Millipore™ MILLIPLEX® MAP Plex Kit) kits used to quantify and compare cytokine and chemokine responses in culture supernatants from *P. falciparum* stimulations (Moncunill et al. 2013). Moreover, the protein levels of the cytokines IL-2, IL-6, IL-10, IL-17, IFN-γ, and TNF in the serum, frontal cortex, and hippocampus of controls and *P. berghei*-infected mice treated or not treated with artesunate were determined using a CBA kit (Miranda et al. 2013).

7.3.7 Engineered Yeast Agglutination Assay

A new agglutination assay named the Engineered Yeast Agglutination Assay (Cruz et al. 2022) was developed using modified *Saccharomyces cerevisiae* cells as antigen-displaying bead-like particles to capture malaria antibodies. The epidermal growth factor-1-like domain (EGF1) of *P. falciparum* merozoite surface protein-1 (*Pf*MSP-119) was displayed on the yeast surface and shown to bind antimalarial antibodies. After mixing with a second yeast strain showing the Z domain of Protein

A from *Staphylococcus aureus* and settling in a round-bottomed well, the yeast produced a visually distinctive agglutination test result. This method is relatively inexpensive and may have the potential for regions seeking malaria surveillance information to guide their elimination programmes.

7.4 Challenges and Perspectives

China officially achieved the elimination of malaria (Zhou 2021), but malaria remains one of the world's most important public health threats, and China also faces numerous challenges in the prevention of malaria re-establishment of transmission (Yin et al. 2022b). For instance, a large number of imported malaria cases continue to be reported per year, including border malaria cases, especially at the China–Myanmar border. Moreover, there are potentially unknown infections, including asymptomatic infections and *P. falciparum* with HRP2/3 gene deletions, which are easily missed. Currently, malaria microscopy and RDTs are still the main methods for malaria diagnosis in the first line, but microscopy competency is difficult to maintain, and there is a shortage of sensitive species-specific RDTs except for *P. falciparum* and *P. vivax* in China (Yin et al. 2022a). Moreover, there are no suitable kits for malaria seroepidemiology for the evaluation of malaria transmission after malaria elimination. Therefore, it is still critical to strengthen the detection capacity to meet the timely detection of these sources of infection in the postelimination phase, which will contribute to the prevention of malaria re-establishment in areas with malaria transmission environments.

First, the research and development of improved diagnostic tools, including antigen detection and antibody detection for malaria diagnosis, need to be accelerated, and they can detect asymptomatic infections of very low parasite densities. Moreover, they should be cost-effective, easy to operate and interpret, and thereby suitable for mass screening and surveillance. Additionally, it is recommended to integrate malaria testing into diagnostics for other febrile diseases in health systems after malaria elimination.

Second, more antigen targets should be identified for rapid malaria diagnosis, especially for species-specific identification, not only for *P. falciparum* and *P. vivax* or pan-Plasmodium. Furthermore, it is best for the new targets to solve the challenge in *P. falciparum* with HRP2/3 gene deletions simultaneously.

Third, serologic methods are valuable tools for the measurement of transmission, especially in the postelimination phase. To date, there are many different serologic methods for the detection of malarial antibodies, but the results from different methods cannot be compared. Therefore, method standardization, including antigen standardization, is an important area for further research.

Fourth, noninvasive testing in samples such as saliva or other bodily fluids rather than currently the most commonly used blood deserves further exploration.

In conclusion, although traditional techniques, such as microscopy and RDTs, are still being used in the field, the exploration and field implementation of advanced technologies, including immunoassays for malaria diagnosis, are still needed in the

postelimination phase in China. Not only for the detection of the presence of malaria parasites in the blood of the suspected individuals but also to evaluate the transmission risk through seroepidemiology. It will continue to maintain and strengthen the surveillance and response of imported malaria and contribute to the prevention of malaria re-establishment of transmission.

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