NIMR | National Institute for Medical Research, Tanzania

POLICY BRIEF

Country wide assessment of presence of deletions of protein responsible for malaria diagnosis in the rapid diagnostic tests in selected regions in Tanzania

Key messages

- Current interventions to control and eliminate malaria include early diagnosis and prompt treatment using effective medicines. Malaria rapid diagnostic tests (mRDTs) are recommended and widely used in resource poor settings in all endemic countries including Tanzania.
- Although early detection of malaria halts disease progression and severe conditions or deaths, there are reports of parasites which cannot be detected by mRDTs due to changes which prevent production of the protein contained in the tests used.
- Until 2021, there were no reports of presence or absence of parasites which cannot be detected by mRDTs, but a nation-wide survey reported very low prevalence (<1%) of potentially undetectable parasites.
- These results suggest that Tanzania does not need to change its diagnostic guidelines but intensive surveillance is urgently needed to monitor and prevent future occurrence of undetectable parasites in the country.

EXECUTIVE SUMMARY

Reports from other countries have showed presence of parasites which cannot be detected by the widely used malaria rapid diagnostic test (mRDT). The problem is caused by changes in

parasites which make them fail to produce the protein detected by the tests. Studies have reported results due to these parasites and showed that they have now emerged from selected regions of Africa and Asia [1-3]. This policy brief presents evidence of the problem of undetectable malaria parasites in Tanzania and recommendations of how to deal with it.

BACKGROUND

Malaria is an acute febrile life-threatening disease caused by *Plasmodium* parasites, which are spread to people through the bites of infected female Anopheles mosquitoes. However, without prompt diagnosis and effective treatment, a case of uncomplicated malaria can progress to a severe form of the disease, which is often fatal without treatment. The World Health Organization (WHO) recommends prompt diagnosis for anyone with suspected malaria. Malaria diagnosis should be based on clinical history and parasitological confirmation of malaria parasites using rapid diagnostic tests and microscopy. Diagnostic testing enables health providers to distinguish malarial from other causes of febrile illnesses, facilitating appropriate treatment.

Although microscopic examination of stained blood smears remains the gold standard for malaria diagnosis, its benefit is limited by the absence of adequate skilled personnel and infrastructural and logistic resources, particularly in resource-poor areas [4]. To overcome this problem, WHO recommended use of malaria rapid diagnostic tests (mRDTs), a less expensive and easily accessible test, as one of the alternative testing systems for malaria diagnosis prior to the prescription of anti-malarial drugs. Most of the malaria mRDTs exploit the presence of a protein known as “histidine-rich protein 2” (HRP2) for the detection of malaria parasites [5].

This protein is produced by the parasites and accumulates to high levels in the bloodstream

of patients and serves as a diagnostic and prognostic marker for falciparum malaria. In the absence of microscopy, mRDTs utilizing HRP2 detection are recommended for the diagnosis of falciparum malaria, particularly in endemic regions. However, parasites have been reported to change their genetic materials which make them unable to produce HRP2. Such parasites have now been observed in multiple African countries although there are no reports in other countries such as Tanzania. This poses a serious threat to the use of these protein markers to reliably detect parasite infections in suspected malaria patients [6-9].

In countries where the problem of undetectable parasites has been confirmed, WHO recommends switching to a non-HRP2 mRDT when ≥5% of the patients tested with the mRDTs return false negative results [10,11]. mRDTs employing different proteins are widely used for malaria diagnosis in areas with limited capacity for microscopy. For various settings with limited information that malaria parasites have changed their genetic-make up so that they no longer produce the HRP2 proteins, immediate surveys are needed to provide evidence of absence or presence of the problem. This is critical to prevent public health concerns of misdiagnosis as the parasite become undetectable by mRDTs. Due to a lack of information, a study was undertaken in Tanzania in 2021 to provide evidence of the performance of mRDTs in the country. This document presents the findings of the 2021 nation-wide survey and recommendations for future tracking of parasites which cannot be detected by mRDTs containing HRP2.

Context and importance of the problem

Recent evidence has shown that Plasmodium falciparum has been reported to modify/change their genetic make-up which make them unable to produce protein responsible for detecting

malaria infections using hrp2/3 based mRDTs.

Globally, emergence of malaria parasites undetectable by mRDTs was first reported in Peruvian Amazon region of South America in 2009 [12]. Recent evidence showed that such parasites have been reported in other countries in Asia, Africa and South America, but data from some countries including Tanzania have been lacking or scanty [2,10]. Thus, WHO recommended that all countries without reports of parasites unable to produce HRP2 or neighbouring countries where the problem has been reported should undertake an urgent survey to confirm presence/absence of the problem.

Through the project on molecular surveillance of malaria in Tanzania (MSMT), the team from NIMR conducted a survey in 2021 to determine the prevalence of parasite which cannot be detected by mRDTs. The survey covered 10 regions with different burden of the disease and recruited patients aged six months and above. The survey was conducted according to the WHO guidelines. The survey reported that there were no parasites with changes that fully made mRDTs fail to detect and confirm a malaria infection. However, there was evidence of changed parasites and these can compromise the performance of mRDTs in the future.

POLICY RECOMMENDATIONS

1. Since the study conducted by the MSMT project from NIMR showed no evidence of undetectable parasites by mRDTs, there is no need to change the current guidelines for diagnosis of malaria in Tanzania.
2. Due to presence of some parasites with changes of genetic materials, intensified surveillance is urgently needed to track and detect the extent and spread of parasites that are unable to produce HRP2. The surveys should include

both symptomatic and asymptomatic individuals to ensure any parasite with the changes is timely and fully captured.

3. By conducting this surveillance, we will avoid risks of missing the true malaria positive patients who will be missed by the HRP2 based mRDTs and hence reduce malaria complications and deaths.
4. Since the costs of introducing non HRP based mRDTs is huge (around 0.7 USD per test kit); the sustainability for the proposed tests might not work in the routine testing particularly to the public health facilities unless the government is willing to subsidize the cost of the test.

Implementation considerations

Conduct countrywide assessment to both symptomatic and asymptomatic patients throughout the year using HRP and non HRP based mRDTs to detect discordant results between the two test kits in malaria positive patients in selected regions within Mainland Tanzania.

Competing interest

The author declares that there are no competing interests.

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Glossary

mRDT	Rapid malaria diagnostic test
WHO	World Health Organization