New rapid tests promising for accurate detection of malaria?

Evaluation of malaria diagnostics in Ndala, Tanzania

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Imagine you're in your bed, longing for a good night sleep after a busy day. Suddenly, you hear the most irritating sound, bzzz, bzzz, bzzz. A mosquito wants to keep you awake! After some failed attempts to hunt it down, you give up and accept the irritating itch that may ensue from any bites. In a few minutes, you fall asleep. In some parts of the world, people have more to worry about than just an itch. The mosquito bite can infect them with a serious disease: malaria. To conduct a research project for my medical studies, I traveled to Ndala, a small village in Tanzania, where I performed an evaluation of the diagnostic tests of malaria.

Malaria is one of the most common infectious diseases that is widespread in tropical and subtropical regions. It infects 300 to 500 million people every year and causes one to three million deaths annually, mostly among young children in Sub-Saharan Africa. Malaria in humans is caused by four different species of the Plasmodium protozoa: P. falciparum (which is the most virulent species), P. vivax, P. ovale and P. malariae.

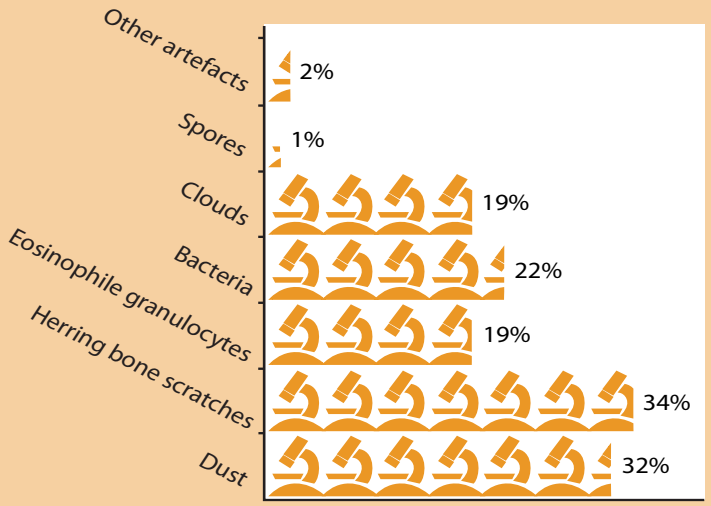
Clinical manifestations

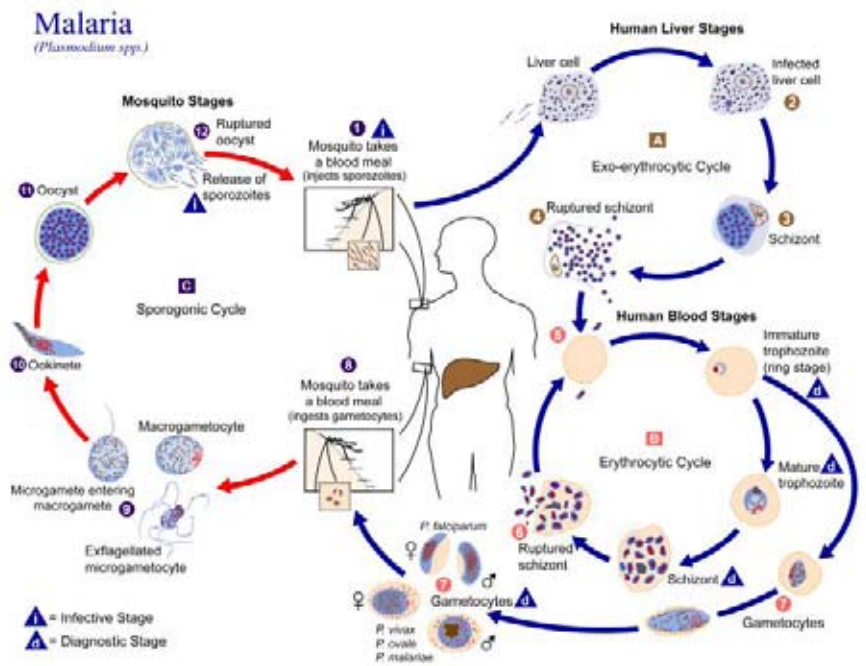
The main manifestations of malaria are fever, chills and anaemia. Parasite replication may produce a regular fever pattern: every two days with P. vivax or P. ovale and every three days with P. malariae. The fever pattern of P. falciparum is often irregular and this species may also produce encephalitis, pneumonia, enteritis and nephritis.

Transmission

Malaria is transmitted between humans by the female Anopheles mosquito. A mosquito infects a person by taking a blood meal. First, sporozoites enter the bloodstream of the human, and migrate to the liver. They infect hepatocytes, where they mature into schizonts, which rupture and release merozoites. The merozoites invade the erythrocytes where

Different kids of artefacts in thick smear





the parasites undergo asexual multiplication. The merozoites form a ring stage, called trophozoites. These mature in schizonts, which rupture releasing many merozoities into the blood stream, causing the clinical manifestations of malaria.

Diagnostics

The diagnosis of malaria is most commonly made by microscopic examination of Giemsa stained thick and thin blood films. Thick smears identify the parasite, thin smears can verify this result and are used for species determination. In recent years, a variety of rapid diagnostic tests (RDTs) have been developed. The RDT works through the Immunochromatographic Strip method and signifies the presence of specific antigens produced by malaria parasites, by a colour change on an absorbing nitrocellulose strip, quite simular to how pregnancy tests work. Molecular techniques such as polymerase chain reaction (PCR) and quantitative nucleic acid sequence bases amplification (QT-NASBA) are very sensitive, but are not widely used in resource-limited settings.

Microscopy vs RDT in young children

Microscopy has always been considered as the 'golden-standard' for malaria diagnosis. This method is cheap, but labor intensive and time-consuming. The reliability of the diagnosis depends on the quality of the blood films and the level of education and expertise of the lab technician. In a rural tropical hospital these factors make diagnosing malaria a big challenge.

In Ndala, the microscopic slides are re-used and the Giemsa stain is not replaced often enough, resulting in artefacts (see box). Secondly, microscopes working on sunlight provide a dark and unclear image. Furthermore, there is not enough time to examine the required amount of microscopic fields, because there are so many patients. This makes microscopy a method with many disadvantages.

Previous studies of malaria microscopy have documented that the frequency of false-positive and false-negative results is very high

and increases at lower parasite densities.
RDTs are a good alternative, particularly in situations where health services are deficient or absent. RDTs are fast, accurate and easy to use. The RDT used in this research is the Binax NOW® ICT malaria test. In this research project we have investigated the quality and accuracy of microscopy in comparison to the RDT Binax NOW ICT in diagnosing malaria in children under five years of age.
ies and an easy tool in control/prevention programs of the disease.

Methods

329 children under five years of age who were suspected for malaria were enrolled. A thick smear was used to determine malaria infection and parasitaemia by the local lab technician. These results were compared with the outcome of the RDT and the thin smears made and examined by the researchers. The quality of all thick smears was investigated by evaluating each microscopic slide for factors such as the level of lysation of the red blood cells and artefacts.

Results

Sensitivity of the thick smear microscopy was 71%, specificity was 77%, which is very low for a diagnostic test. A good lysation of the thick smear contributes to a higher sensitivity. A thick smear with a bad lysation has a sensitivity of 63%, and this increases to 78% with a correct lysed slide. Various artefacts in the microscopic slides were found. Dust and (herringbone) scratches were the most common artefacts (105 and 113 respectively). You can imagine that the parasites in the microscopic slide can be missed with great amounts of scratches or dust covering the erythrocytes. The RDT achieved a high specificity of 98.8% for all Plasmodium species and high sensitivity for P. falciparum infections 96.3%.

Conclusion

The accuracy of the local microscopy is low in comparison to the achieved results with the RDT and thin smear. In Tanzania, a child under five years of age has an a priori chance of 70% for malaria. Because of this high a priori chance, a diagnostic malaria test needs to be very sensitive and specific; otherwise the additional value of a test to detect a malaria infection is limited. Also, more accurate diagnostics will contribute to less false negative test results, which results in better treatment. The quality of the use of microscopic diagnosis for malaria can be problematic in resource-limited settings. RDTs are more suited to health workers in situations where health services are deficient or absent. The costs and availability of RDTs are probably the major drawbacks of extended use in developing countries. We recommend further research on use and implementation of the RDT under field conditions.

Experiencing the malaria burden of disease in the children in Ndala, I became more aware of the importance of developing accurate diagnostics. In the Netherlands, we try to achieve the highest possible quality of medical care for our patients. Besides providing basic healthcare in developing countries, I think we also have to focus on the quality of this medical care. If the costs and availability of RDTs are the major drawbacks to implement this method in Tanzania, there must be a way for the production companies, governments and NGO's to do something about it.

About the author

Leonora Louter is 24 years old and a sixth year medical student in Rotterdam

Further reading

- http://www.who.int/topics/malaria
- Samuel Schillcutt et al, Cost-effectiveness of malaria diagnostic methods in sub Saharan Africa in an era of combination therapy, Bulletin of the WHO 2008;86:101-110