



Pareelproject

RAPDIF

Better diagnosis and treatment of fever in Africa

A study of young children in Burkina Faso has found that people in Sub-Saharan Africa benefit from a better chain of diagnosis and treatment for infectious diseases that cause fever. Scientists from Amsterdam and Burkina Faso investigated which bacteria cause fever besides the malaria parasite, in a project known as RAPDIF. The project also developed a new malaria test that is many times more sensitive than the tests currently available. It will be launched in five countries in Africa in 2021. RAPDIF coordinator Dr. Henk Schallig received a Parel (or 'Pearl Award') from ZonMw on 24 March.

Infectious disease, fever and antibiotics

Despite WHO measures and guidelines, malaria is still one of the leading causes of fever in children in Sub-Saharan Africa (see also 'Figures' box). There are however many other causes of fever. The RAPDIF study found that treatment of malaria and other conditions that cause fever is not going well. Children who present with fever are often wrongly prescribed malaria medication and antibiotics.

This treatment practice exacerbates antimicrobial resistance and leads to unnecessary illness and death among children. The RAPDIF team discovered that antibiotics were ineffective in no fewer than 50 to 90% of cases in which they were prescribed.

Collaboration between Amsterdam and Burkina Faso

The RAPDIF project focuses on improving the chain of diagnosis and treatment for infectious diseases that cause fever. Research was performed in Burkina Faso, one of the poorest countries in Africa, where malaria is the leading cause of fever among children under the age of five. Indeed, 67% of people who die of malaria are under five. RAPDIF is a collaboration between microbiologists and parasitologists from Amsterdam UMC and researchers from IRSS (Institut de Recherche en Sciences de la Santé), a research institute in Nanoro, Burkina Faso. The research coordinator is Dr. Henk Schallig from the Parasitology Department of Amsterdam UMC (at AMC).

Malaria tests no longer adequate

The malaria tests currently available were launched in Africa about ten years ago, after WHO approval as part of their 'test and treat strategy'. These tests show the presence of the PfHRP2 (Plasmodium falciparum-specific histidine-rich protein 2) protein in patients' blood. P. falciparum is the most common and most dangerous malaria parasite in Africa. However, the PfHRP2 protein remains in the blood long after treatment, so the tests produce false positive results due to the fact that malaria appears to be present in the blood, even though the parasite has been killed. The tests can also give false negative results because the P. falciparum parasite has mutated in some areas, and no longer produces the specific HRP2 protein.





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ZonMw financiert projecten op het gebied van gezondheidsonderzoek en zorginnovatie. Het doel is dat kennis uit deze projecten gebruikt wordt in beleid, praktijk, onderzoek en/of onderwijs. Jaarlijks worden een aantal projecten die een goed voorbeeld zijn, in het zonnetje gezet. Deze Pareelprojecten hebben een innovatief, bruikbaar resultaat dat van grote waarde is voor de wetenschap en/of maatschappij. Daarnaast werken de juiste partijen samen, wat de benutting van de resultaten ten goede komt. Als laatste hebben de resultaten uit Pareelprojecten een wetenschappelijke of maatschappelijk impact. Met het uitreiken van een Parel aan deze projecten wil ZonMw projectleiders en hun teams belonen, en anderen inspireren om het beste uit hun projecten te halen.

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Vooruitgang vraagt om onderzoek en ontwikkeling. ZonMw financiert gezondheidsonderzoek én stimuleert het gebruik van de ontwikkelde kennis – om daarmee de zorg en gezondheid te verbeteren.

ZonMw heeft als hoofddopdrachtgevers het ministerie van VWS en NWO.

Basically, therefore, the current quick malaria tests are often unable to give a clear diagnosis as to whether a child presenting with fever has malaria or another infection. Local health workers therefore have less and less confidence in them. This doubt has led to inconsistent treatment, with prescription of both malaria medication and antibiotics 'to be on the safe side'. Pressure from parents is also a factor. This is quite understandable, as malaria can be fatal.

New specific, sensitive malaria test

The RAPDIF team developed a new malaria test that is both fast-acting and highly sensitive and, like the current tests, can be carried out close to patients' homes. The unique thing about this molecular biological test is that it does not involve any complex DNA extraction. The db-PCR-NALFIA method (Direct-on-Blood PCR Nucleic Acid Lateral Flow Immunoassay) multiplies the DNA of the malaria parasite from the patient's blood sample using PCR (a laboratory method used by molecular biologists). This method has now been refined and miniaturised, so it can be performed using a portable mini-PCR that runs on batteries or solar energy, which the health worker can operate quite easily using a mobile phone, tablet or laptop. The malaria parasite's multiplied DNA is detected using a dipstick test. Local health workers can thus establish within an hour whether a child with a fever is infected by a malaria parasite. Studies have shown that the new malaria test is no less than 100 times more sensitive than the current quick tests. The RAPDIF study has also shown that local health workers in Burkina Faso are happy to act on the results of this reliable test, and it is hoped this will lead to a change in the way treatment is prescribed.

Large-scale study in 5 African countries

The ZonMw-funded RAPDIF project was completed in 2018 but the study will continue with funding from the European & Developing Countries Clinical Trials Partnership (EDCTP). The researchers in Amsterdam and Burkina Faso are currently making preparations for a large-scale study in which local health workers will test the new malaria test on around 5700 children and adults with fever. This study will take place in five countries in Sub-Saharan Africa: Namibia, Sudan, Ethiopia, Kenya and Burkina Faso. The test will also be used by Amref Flying Doctors, who work in remote areas. The researchers will investigate how well the malaria tests work in different circumstances (each country is affected by a different type of malaria) and whether local health workers trust the test and act on the result. The study will also consider its cost-effectiveness. Health economists will investigate whether the costs of the new test might potentially hamper its implementation in the healthcare system. Fieldwork for this large-scale study will commence in 2021 and the results are expected at the end of 2023.

Combating antimicrobial resistance

The RAPDIF team examined over 700 children in Burkina Faso and found that, besides malaria, the E. coli, Salmonella typhi, pneumococcus and streptococcus bacteria are the most common causes of fever. The goal was then to devise a diagnostic test which, like a malaria test, would quickly and easily detect the presence of bacteria in the blood. However, picking up bacterial DNA in the blood requires DNA isolation, a technically difficult process without the facilities of a research institute. The researchers have now developed a laboratory version and have ideas about how the technical issues might be resolved. They do not however have the funding to continue this work. A rapid portable diagnostic test for bacteria would give local health workers in Africa the resources to provide better targeted treatment with the right antibiotics for children with fever. This would not only improve healthcare in Africa, but also help combat antimicrobial resistance.

International impact

The research results will be very useful in the fight against antimicrobial resistance in Africa. If treatment of infectious diseases fails in Africa, this has a knock-on effect in the Netherlands and other parts of the world, due to international travel. Coronavirus is a current example of this. The new malaria test will probably also be highly suitable for use in other parts of the world where malaria is prevalent, such as Southeast Asia and Latin America. The researchers successfully tested an earlier prototype in the border region of Thailand and Myanmar, where there is also a lot of travel back and forth.

Step-by-step diagnostic plan

The RAPDIF study made it clear that the chain of diagnosis and treatment for infectious diseases that cause fever must be improved. The researchers are working on a step-by-step diagnostic plan that uses medical history, clinical symptoms and epidemiology to produce a good diagnosis and treatment. At the moment the researchers in Burkina Faso are working on a way of converting this plan to an electronic decision-making model that is available to all care providers.

Funding: ZonMw and Partnership between Europe & Sub-Saharan Africa

The RAPDIF project receives financial support from ZonMw and WOTRO Science for Global Development. The researchers also received a grant from the European & Developing Countries Clinical Trials Partnership (EDCTP), a partnership between countries in Europe and in Sub-Saharan Africa, and the European Union. EDCTP is subsidising an upcoming large-scale study which will involve the rollout of the new malaria test in five countries in Africa. www.edctp.org

ZonMw Priority Medicines Antimicrobial Resistance programme

Curbing antimicrobial resistance or antibiotics resistance and developing new resources and methods for preventing resistance is a matter of global importance. The ZonMw Priority Medicines Antimicrobial Resistance (AMR) programme, which was completed in 2018, aimed to help control and resolve the issue of antimicrobial resistance. Researchers from various disciplines worked on the problem. The programme funded 28 projects, including the RAPDIF project.