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EDITORIAL

CHANGING TRENDS IN THE DIAGNOSIS OF MALARIA AND TYPHOID FEVER

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Malaria

In tropical Africa, fever is commonly associated with malaria that was known variously as Roman fever, marsh fever(Rocco 2003), and whose name was derived from the Italian 'Mal=bad, Aria=air.'(Prakash *et al.* 2013). Malaria is caused by five species of the plasmodium parasite: *P. falciparum, P. vivax, P.ovale, P. malariae and P. knowlesi* all of which are transmitted by the female anopheles mosquito, which is the vector of the parasite.

Over 2.4 billion people are at risk of *P. falciparum* infection, which results in about 300 to 500 million clinical episodes and 1million deaths annually (Bousema & Drakeley 2011). While about 2.9 billion persons are at risk for *P. vivax* infection with up to 300 million clinical episodes per year(Bousema & Drakeley 2011). A vast proportion of malaria morbidity occurs in sub-Saharan Africa, (SSA). However, there is substantial evidence that the intensity of malaria transmission in Africa is declining (Snow et al. 2012, Graz et al. 2011), and rapid malaria parasitemia tests are well distributed in endemic countries and easy to use (Graz et al. 2011).

Certain recent developments, however, are worth considering when assessing malaria burden and control. First, the discovery of *Plasmodium falciparum* with deleted histidine-rich repeat region of the histidine-rich-protein 2 and the evidence that parasites not detected by HRP2 lateral flow immunoassay(LFI) cause latent infection(Koita et al. 2012), is of extreme importance in endemic countries such as Sierra Leone, where HRP2 LFIs are predominantly used. LFIs have made malaria testing ubiquitous in sub-Saharan Africa, including in very remote areas. However, false negatives resulting from deleted hrp2 in certain *P.falciparum* may result in lower prevalence reports. The alternative dipstick to HRP2 LFIs is the Plasmodium lactate dehydrogenase (pLDH)-based LFI. However, in Sierra Leone, the use of pLDH LFIs is less common, and a similar trend exists in the other parts of Sub-Saharan Africa. LFIs were intended to be used primarily in resource-limited locations where expert microscopists are unavailable. So the use of LFIs is not routinely duplicated with smear results in many developing countries. This could be a setback for resource-poor settings.

The use of point of care, multiplex molecular detection methods have been highlighted as a means of salvaging diagnosis in resource-poor countries, but cost remains a major limitation. Notwithstanding, PCR is emerging as most sensitive malaria diagnostic apart from rapid antigen tests. Antigens and DNA may persist in blood after parasite clearance through treatment. A plausible alternative has sought sexual stages of malaria parasites representing a small fraction of parasites during infection(Tao et al. 2014), but which can also be detected in body fluids such as saliva. Prior evidence indicates that saliva is an excellent non-invasive candidate for rapid malaria testing (Fung et al. 2012), but this aspect of malaria diagnostics is still under development including rapid tests based on nano trap technology.

There has been a renewed global commitment for malaria elimination and both symptomatic and asymptomatic malaria infections are critical for the elimination of malaria. Novel diagnosis of subclinical malaria targeting sexual stages of the parasite are emerging, but the best candidate for such diagnostics are

those that could be adaptable to the resource-poor settings in Africa. One such candidate is the nano trap, saliva-based, malaria rapid test that is under development by Johns Hopkins(http://www.jhsph.edu/news/news-releases/2015/johns-hopkins-bloomberg-school-of-public-health-researchers-receive-grant-to-evaluate-malaria-detection-test.html).

Typhoid Fever

In the case of typhoid fever, there seems to be an over-diagnosis. The gold standard for the diagnosis of typhoid is by blood culture, which has a sensitivity of 40-60%*(*Parry *et al.* 1999), but low-cost tests, mainly the widal test, are more adaptable to resource-poverty and are commonly used in resource-poor settings such as Sierra Leone. Widal tests have been in use for over 110 years, but the results are very controversial(Olopoenia & King 2000, Nga et al. 2012), and the test suffers from low specificity in endemic countries probably as a result of an increase in population antibody levels (Clegg et al. 1994).

A positive Widal test does not always denote the presence of typhoid fever. Apart from increased population antibody levels, there exist up to 40 cross-reacting antigens between Salmonella enterica serotype Typhi and other Enterobacteriaceae(Parry *et al.* 1999). Cross-reacting antigens could also be from malaria, brucellosis, dengue fever, chronic liver disease or endocarditis(Colle *et al*. 1996).

Blood culture which is the gold standard is time-consuming and may delay treatment apart from its inherently low sensitivity. Several typhoid dipsticks have been reported, but side-by-side independent assessments in endemic countries do not always yield the expected outcome.

Polymerase chain reaction is currently a better option for diagnosing typhoid fever with same day result, but cost remains a big issue in countries that could be most in need.

While suitable alternatives based on economic conditions of countries are sought, the cut-off value for the widal test requires evaluation and standardization. Having a wrong diagnosis at the point of care could lead to wrong clinical outcomes.

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