The challenge of asymptomatic malaria infections

Evolving from presumptive treatment to identifying asymptomatic, submicroscopic disease on the road to malaria elimination. William Brieger reports

After the world's first attempt at eradicating the complicated disease malaria mainly through a single tool, a period of control set in where the aim was to reduce mortality through prompt and presumptive treatment of fevers with anti-malarials, particularly in young children. During this period in the 1980s and 1990s, it was recognised that parasite-based diagnostic capabilities in the form of microscopy were limited, so in malaria-endemic areas, it was worth providing inexpensive medicines like chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) to febrile children in order to save lives. When the fevers did not resolve, other illnesses explored.

The difficulty arose in identifying cases that did not offer clinical clues that they might be malaria. Today countries approaching malaria elimination face challenges, such as seen in Zanzibar where, 'outdoor transmission, a large asymptomatic parasite reservoir and imported infections, require novel tools and reoriented strategies to prevent a rebound effect and achieve elimination'. Here we examine the challenge of asymptomatic malaria infections.

Background

By 1998, when the Roll Back Malaria partnership formed, there had been enough research done so that the malaria community had a better arsenal of interventions including insecticide-treated bed nets, artemisinin-based combination therapy (ACT) and intermittent preventive treatment with SP during pregnancy. The Abuja Declaration of 2000 set a target of 80% coverage of these interventions by the year 2010.

While ACTs overcame the challenges of parasite resistance that had developed for the single drugs, CQ and SP, it cost several times more than those medicines. The need for easy-to-use, inexpensive, point-of-care diagnostics was recognised so that not only would ACTs be targeted only to parasitologically confirmed malaria cases, but also in the process, overuse and misuse would not contribute to parasite resistance of these new drugs. Unfortunately, the development and dissemination of antigen-based rapid diagnostic tests (RDTs), lagged behind the availability of ACTs, meaning that health workers unfortunately continued their business as usual with presumptive treatment using ACTs.

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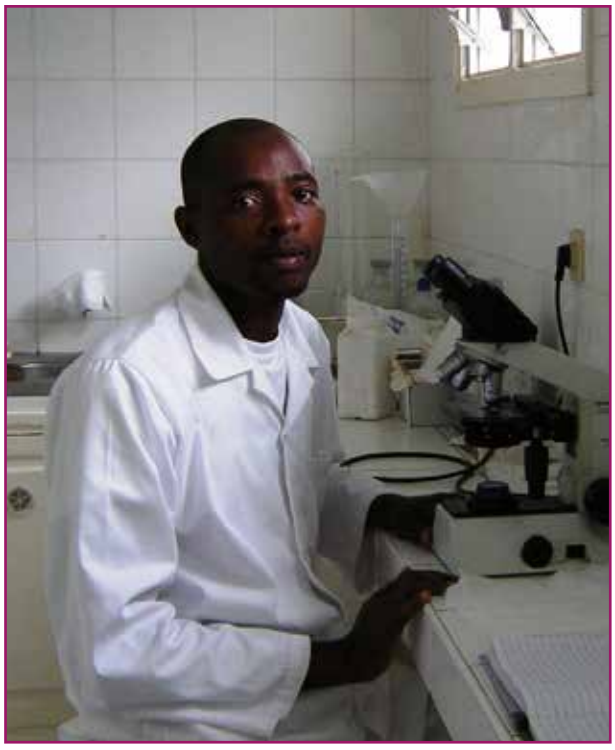
Microscopy in Angola

The benefits of RDTs were generally two-fold. First, they could be used by front-line, auxiliary and community-based health workers. Secondly, they tended to identify more cases than microscopy. The big challenge was convincing health workers to use them and trust the results, because the era of presumptive treatment had given these staff a false sense of confidence in their own clinical diagnostic abilities.

Although reaching the 2010 coverage targets has remained illusive for most endemic countries, there has been enough progress for major reductions in incidence (despite a recent upsurge). As the proportion of actual malaria cases among febrile illness patients declines, concern has risen that transmission might continue among people with subclinical or asymptomatic malaria. Here we explore the extent of this problem and new directions in parasitological testing needed to ensure continued progress toward elimination in each endemic country.

Understanding risk of asymptomatic malaria

Risk can relate to geographical, epidemiological, and socio-demographic factors as well as history of malaria interventions. Kenya has stratified the country by higher and lower malaria transmission areas. Even the higher areas are comparatively low compared to its higher



Microsopy in Mozambique

transmission neighbors. Studying the prevalence of asymptomatic malaria in some of these higher transmission areas in the west of the country was seen as a way to better identify people at risk and learn about intervention effectiveness. An examination of apparently healthy children (no symptoms) revealed a Plasmodium falciparum malaria prevalence 36.0% (27.5%, 44.5%) by RDT and 22.3% (16.0%, 28.6%) by thick film microscopy. Living in a household with electricity was protective but the adjusted odds ratio of prevalence comparing households with and without indoor residual spray showed only borderline benefit. Unfortunately, in Zanzibar, asymptomatic malaria infection was not associated 'with use of any vector control'.[1]

A major challenge in detecting cases through routine health care systems is care seeking patterns of care seeking for fever. The 2018 World Malaria Report acknowledges that there are major equity challenges in care seeking wherein families with higher incomes, better education and living in urban areas are more likely to seek help for their febrile children that rural, poor and less educated families who would be more at risk. Care-seeking without the signs of fever is more challenging. A dual strategy of enabling better service utilisation as well as outreach to detect cases will be necessary to detect asymptomatic cases.[3]

In Burkina Faso, the prevalence of asymptomatic malaria infection in children under 5 years of age was estimated at 38.2% in 24 of its 70 health districts. Those at most risk for asymptomatic malaria infection included the following:

- older children (48–59 vs < 6 months: OR: 6.79 [5.62, 8.22])
- children from very poor households (Richest vs poorest: OR: 0.85 [0.74–0.96])
- households located more than 5 km from a health facility (< 5 km vs ≥ 5 km: OR: 1.14 [1.04–1.25])
- localities with inadequate number of nurses (< 3 vs ≥ 3: 0.72 [0.62, 0.82]
- rural areas (OR: 1.67 [1.39–2.01])

Nine districts reported significantly higher risks (Batié, Boromo, Dano, Diébougou, Gaoua, Ouahigouya, Ouargaye, Sapouy and Toma. The researchers concluded that, 'Such national spatial analysis should help to prioritize areas for increased malaria control activities.'

A study in Ghana found that, 'children and pregnant women had higher prevalence of submicroscopic gametocytes (39.5% and 29.7%, respectively) compared to adults (17.4%).'

An additional concern is emerging in terms of sharing of malaria parasite species between humans and primates, especially as urbanisation and deforestation push these two populations into closer contact. For example, Mapua and colleagues working in Central Africa Republic, 'found the human malaria parasite P. ovale wallikeri in both asymptomatic humans and western lowland gorillas in Dzanga Sangha Protected Areas. Molecular analysis revealed that the genotype of the P. ovale wallikeri DNA found in a gorilla was genetically identical to that of a human isolate within the mt cytb and mt cox 1 genes, indicating potential human–ape transmission.' They noted similar sharing of parasites in the region between humans and chimpanzees.

Responding to asymptomatic cases

WHO's Framework for Malaria Elimination recognises the important role of case detection and subsequent treatment as well as broader community level preventive responses around detected cases. In the context of elimination WHO notes that case detection 'requires use of a diagnostic test to identify asymptomatic malaria infections'. WHO stresses that a case is a case, regardless of whether it is symptomatic or asymptomatic, as long as the diagnostic process confirms presence of malaria infection.

It is important to monitor Plasmodium parasitemia in areas where malaria transmission has declined and efforts to achieve malaria elimination are under way, such as Zambia, where 3,863 household members were tested. Only 2.6% were positive by either microscopy, RDT, or PCR. Of these, 48 (47%) had subpatent parasitemia, and 85% of those with subpatent parasitemia were asymptomatic. 'Compared with individuals without parasitemia, individuals with subpatent parasitemia were significantly more likely to be aged 5–25 years.' The authors suggested that their findings pointed to the need for active or reactive case detection to identify asymptomatic individuals and thus better target individuals with subpatent parasitemia with appropriate malaria interventions.

WHO explains that active case detection (ACD) takes place in areas of limited or under-utilisation of health-care services.[4] It may start with initial screening for symptoms, followed by appropriate parasitological

laboratory confirmation. In low-transmission settings or as part of a focus investigation, 'ACD may consist of testing of a defined population group without prior symptom screening (population-wide or mass testing) in order to identify asymptomatic infections.' Elimination cannot be achieved until even asymptomatic infections have stopped. The challenge is the expense of community-wide screening.

Reactive Case Detection (RCD), according to WHO, takes place in settings low transmission intensity where the few 'occurring malaria cases are highly aggregated'.[4] When a case is identified, usually through identification of an actual infected patient at a local clinic, the community where the patient comes from is visited and a 'net is cast around the index case' where household members and neighbors within a selected radius are tested. In this process asymptomatic cases are also identified.

Our existing diagnostic tools may be inadequate. McCreesh and colleagues reported on subpatent malaria in Namibia that, 'fever history and standard RDTs are not useful to address this burden. Achievement of malaria elimination may require active case detection using more sensitive point-of-care diagnostics or presumptive treatment and targeted to high-risk groups.' This includes loop-mediated isothermal amplification (LAMP) using dried blood spots, which they tested. Likewise from experience in a Zambian study, Kobayashi and co-researchers suggest, 'more sensitive diagnostic tests or focal drug administration may be necessary to target individuals with subpatent parasitemia to achieve malaria elimination'.

Responses to detecting asymptomatic cases start at the individual level with prompt treatment of those found through RCD to be infected. Then focused preventive interventions such as distribution of insecticide treated bednets can be provided to those in the cluster or village. Follow-up would be needed for such 'hot spots.'

On a broader basis we have Seasonal Malaria Chemoprevention (SMC) as practiced in Sahelian countries where during the peak transmission (rainy) season intermittent preventive treatment is given to children monthly by community health workers and volunteers. Of course, many of these children would be asymptomatic carriers and SMC could benefit the reduction of parasites in circulation. At present SMC focuses on pre-school aged children, but Thera and co-researchers stress the importance of reaching school aged children who are also often asymptomatic carriers.

Another intervention being tested for mass drug administration (MDA) use providing the community with ivermectin, a drug that has been highly effective in controlling filarial diseases and also found to kill mosquitoes who take a blood meal from a person who has recently taken it. This strategy is still being tested, but again MDA means all community members, especially those with asymptomatic infection, would be reached.

A major question requires further research. To what extent do asymptomatic, submicroscopic and subpatent parasitemia contribute to continued malaria transmission? Another question is how can we address malaria infection in other primates? We know that scientists recommend targeting of malaria elimination interventions based on mapping of these infections.[5] We therefore need to study the actual transmission potential of this phenomenon.

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