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The essential role of infection-detection technologies for malaria elimination and eradication

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Recent emphasis on malaria elimination and eradication (E&E) goals is changing the way that experts evaluate malaria diagnostic tools and tactics. As prevalence declines, the focus of malaria management is pivoting toward low-density, subclinical infections and geographically and demographically concentrated reservoirs. These and other changes present challenges and opportunities for innovations in malaria diagnostics aimed at meeting the needs of malaria elimination programs. Developing such technologies requires a review of the operational approaches to detecting malaria infections in areas of declining prevalence. Here we review recent research on epidemiology and biology related to malaria elimination and operational factors that influence E&E strategies. We further propose use-scenarios and a target product profile framework to define and prioritize the required attributes of infection-detection technologies.

Malaria diagnostic priorities

Malaria control efforts have yielded substantial progress toward reducing the burden of malaria. In the past decade, cases of malaria fell by an estimated 274 million and malaria-related deaths were reduced by 1.1 million compared with the previous decade [1]. However, the emergence of multiple forms of resistance, the cost of sustained control efforts, and the long history of malaria resurgence [2] following near elimination have fueled recent policies, guidance [3], and funding dedicated to achieving E&E goals. According to the latest World Health Organization (WHO) World Malaria Report: 'Of 97 countries with ongoing transmission in 2013, 11 are classified as being in the pre-elimination phase of malaria control, and 7 as being in the elimination phase. A further 7 countries are classified as being in the prevention of reintroduction phase.' [1]

The WHO currently recommends malaria diagnosis either by microscopy or rapid diagnostic test (RDT) in patients with suspected malaria prior to treatment [1]. Microscopy is a highly versatile tool that can be used for species differentiation, parasite quantification, and identification of parasite life stage. However, microscopy requires expensive capital equipment and a high skill level to achieve acceptable sensitivity. Malaria RDTs are easier to use and can detect specific *Plasmodium* parasite antigens using one or more of three target antigens: histidine-rich protein 2 (HRP2), lactate dehydrogenase (LDH), and aldolase. HRP2 is expressed only by *Plasmodium falciparum* and is the most widely used target antigen for malaria RDTs. LDH and aldolase are expressed across all *Plasmodium* species but tend to yield lower diagnostic accuracy in commercially available RDTs [4].

As national malaria control programs contemplate their options for shifting tactics and tools to support malaria elimination [5], it is imperative that the malaria community reassesses diagnostic priorities in reduced prevalence settings. The epidemiology of malaria changes considerably as regions transition from the control to the pre-elimination phase [6]. Infections tend to become focused in defined geographic areas, are often imported from higher-transmission regions, and become increasingly dependent on behavioral risks associated with certain subpopulations. During malaria elimination, a comparatively larger proportion of ongoing transmission is attributed to low-density and subclinical infections in these subpopulations, and these infections cannot be readily detected by currently available RDTs or microscopy [7,8].

Accordingly, passive case detection (PCD) (see Glossary) strategies that dominate the focus of control programs need to be augmented by active infection detection (ID) tactics and more accurate diagnostic tools in an elimination context. To support and catalyze the rapid development, commercialization, and implementation of the most temporal- and cost-effective ID technologies for malaria E&E, we review the essential role of ID technologies and propose a use-scenario-oriented approach to development of target product profiles (TPPs).

Elimination and eradication goals

The WHO has established a clear distinction between the programmatic goals of malaria control, elimination, and eradication [9]. Although the goal of malaria control is to reduce morbidity and mortality, the goal of malaria

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Keywords: malaria; elimination; asymptomatic; low density; active surveillance.

1471-4922/
 http://dx.doi.org/10.1016/j.pt.2014.03.003

Glossary

Active infection detection (active ID): the detection of malaria (clinical and subclinical) infections at community and household levels in population groups that are considered to be high risk.
Border testing: a proactive ID tactic aimed at preventing cross-border transmission at checkpoints. Border testing may be preceded by fever screening followed by testing of all patients with a recent history of malaria symptoms.
Community testing: a reactive ID tactic to identify and treat infected persons within a defined proximity to a community-based index case.
Controlled reproductive number (R_c): a quantitative description of whether and to what extent (in the presence of local interventions such as long-lasting insecticidal nets, indoor residual spraying, and detect-and-treat tactics) a single index case is likely to result in onward transmission. High R_c indicates a highly endemic area where control measures have not resulted in preventing significant onward transmission and where a single index case represents a risk of an outbreak. $R_c < 1$ indicates sustained onward transmission is unlikely.
Elimination: the reduction to zero of the incidence of infection by human malaria parasites in a defined geographical area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required.
Eradication: a premeditated plan for global reduction to zero of all plasmodia parasites that are human pathogens.
Focused testing and treatment (FTAT): a focused testing for infection followed by treating all infected persons in a localized area such as a neighborhood or village irrespective of whether they have clinical symptoms. FTAT may be conducted broadly over non-contiguous areas on high-risk populations and hotspots.
Index case: a malaria case identified by parasitological confirmation via passive case detection.
Hotpops: demographically clustered populations of malaria incidence. In an elimination context, hotpops are often associated with travel history and occupation.
Hotspots: also referred to as foci, hotspots are large or small geographically clustered populations that are identified as having comparatively higher levels of transmission. Hotspots occur at every level of transmission and therefore are fractal in nature.
Limit of detection (alternatively, detection limit): the lowest quantity of an analyte that can be distinguished from the absence of that analyte (typically within a stated confidence limit, generally 1%).
Mass testing and treatment (MTAT): mass testing for infection followed by treating all infected persons in a targeted contiguous area or population, irrespective of whether they are symptomatic. MTAT aims to reduce the size of the infectious reservoir in the targeted area.
Network testing: a reactive ID tactic to identify (and subsequently treat) all infected persons traveling with a mobile index case.
Passive case detection (PCD): the detection of malaria cases among patients who go to a health post for treatment on their own initiative, usually for febrile disease.
Proactive infection detection (proactive ID): investigation tactics focused on populations defined by high-risk geography (hotspot) or high risk demography (hotpop). Proactive ID may be preceded by fever screening of all patients with a recent history of malaria symptoms or by testing the target population without prior screening.
Reactive infection detection (reactive ID): the detection of malaria infections in community or occupation-based population groups in close proximity to an index case. Reactive ID involves testing (and subsequently treating) co-workers, household members, and neighbors of an index case. Reactive ID may be preceded by fever screening of all patients with a recent history of malaria symptoms or by testing the target population without prior screening.
Screening: an active ID practice used to select a subpopulation for testing based on each individual's recent history of malaria symptoms.
Time-location testing: a proactive ID tactic aimed at testing (and subsequently treating) a hotpop using prior knowledge of their occupation-specific location. This might include visits to mines, fishing docks, and forest camps, as well as mobile military units.
Transmission risk: the qualitative description of an individual's or population's ability to spread *Plasmodium*.
Use-scenario: the outcome-oriented categorization of the interaction between a user, the setting, and a diagnostic tool.

*Adapted from the Malaria Elimination Group at the University of California San Francisco.

elimination is to reduce malaria transmission to zero in a given geographic region. Sustained elimination in all regions over an extended period of time is a prerequisite for malaria eradication, defined as the permanent reduction to zero of the worldwide incidence [1]. These E&E goals and definitions have been debated [10], and alternative operational definitions have been proposed focusing on varying regional endemicity [10] and on the elimination of *Plasmodium* parasites from the human population [11]. Independent of the specific definition applied, however, in order to achieve elimination in areas of high endemicity, the PCD focus that dominates control programs must be augmented by increased emphasis on active detection to support driving malaria incidence, transmission, and the parasite population to zero [12]. Especially in areas with a controlled reproductive number (R_c) [13] that is significantly greater than one, detection and complete cure of all infections representing a transmission risk are paramount if elimination is to be achieved.

The dynamic epidemiology of elimination

Malaria has often been described as heterogeneous to address wide variations in phenotype, vector–host reactions, and spatial distribution of disease [14]. Despite this variability, some general themes about the epidemiology of low-prevalence malaria can be inferred: (i) there is an increased contribution to transmission from subclinical individuals and from infections that are undetectable by microscopy and RDTs; (ii) defined parasite reservoirs, a bellwether of elimination, represent both opportunities and challenges to new tools and tactics aimed at achieving E&E goals; and (iii) species re-proportioning and higher-fitness phenotypes affect the selection of ID tools and tactics and their success toward achieving elimination goals.

Clinical presentation

Although patients with subclinical infections do not present with malaria symptoms, and thus are typically missed by PCD methods, they still contribute to the cycle of transmission in a population [15]. The relative contribution of subclinical infections has considerable implications for the design and use of elimination diagnostics. Although subclinical cases correlate with lower-density infections and lower rates of infecting mosquitoes [16,17], subclinical individuals remain infective for longer than treated patients [18], and the prevalence of symptomless, untreated individuals can be four to five times higher than the prevalence of individuals with symptomatic infections [19]. Detection techniques relying on clinical presentation are unsuitable for identifying and treating subclinical infections.

Submicroscopic carriage

The frequency and relevance of submicroscopic carriage was recently reviewed by Okell *et al.* [17]. Submicroscopic parasite densities were found to be common in adults, in settings of low endemicity, and in chronic infections. The authors concluded that microscopy detects only about 54% of all polymerase chain reaction (PCR)-detectable malaria infections, and there is significant variation in this percentage between studies. Low-transmission settings have proportionately greater submicroscopic carriage rates, yet there are relatively few studies that evaluate the transmission risk associated with parasite density. Two published studies [18,20] and one unpublished study [17] found that human-to-mosquito transmission rates are four