

Sero-diagnosis for rational elimination of malaria

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Malaria is a widespread disease in tropical and subtropical areas. In 2015, 212 million of new cases and 429,000 deaths were reported by World Health Organization (WHO) (1). Five species cause human malaria; two are of most importance: the deadly *Plasmodium falciparum*, and the wide spread and relapsing *Plasmodium vivax*. One arm for malaria elimination is the opportune detection of new cases and accomplishing an effective anti-malaria treatment, to continuously reduce parasite load. Malaria diagnosis has been mainly based on the microscopy examination of thick and thin blood smears from symptomatic patients. It is an individual based method and materials are inexpensive and available in many primary health facilities. Although, its performance depends on the epidemiological situation, and the accessibility to certain laboratory infrastructure and qualified microscopists.

In hyper-endemic regions, the populations at risk suffer several infective bites per day and blood infections along their lives. After many years, those populations develop an antibody response that renders subclinical or asymptomatic malaria and low parasitemias become common. Nonetheless, microscopy of blood smears and rapid diagnostic tests (RDTs), the most common methods for diagnosis would detect only a fraction of infected individuals. According to WHO, at least 35 new countries will interrupt malaria transmission in 2030. Being optimistic, in the becoming years the number of cases in those countries will gradually decrease. Malaria is an ancient and complex parasitic disease and to advance to the elimination will require the most modern and appropriate diagnostics tools, and a region-based strategy to detect these slippery parasites. For the elimination phase, WHO has suggested to use all available methods and strategies to increase the sensitivity for diagnosing the malaria burden (2). There is sufficient research exposing the high sensitivity of the molecular methods (PCR). Also, there are some efforts to integrate the serology to the malaria diagnosis strategy.

An ELISA to detect anti-malaria antibodies was proposed in 1975, it showed that a high proportion of patients with acute malaria had antibodies responses (serology+) against a crude extract of *Plasmodium* blood stages (3). The same work show that a small proportion of symptomatic individuals and microscopy negative were serology+. Using a similar approach, in southern Mexico more than 90% of symptomatic individuals with microscopy+ and less than 10% of those with microscopy-, were serology+ by ELISA (4). Terms such as serodiagnosis, immunodiagnosis or serologic diagnosis have been embraced in different publications, proposing its applicability, based on the idea that the rate of seroconversion correlates with transmission intensity. In communities from southern Mexico, where malaria transmission had been interrupted, about 5-10% of the people were serology+ but had low antibody titers which suggest the presence of residual antibodies. In most endemic areas, there is a fraction of individuals treated or not, whose parasitemia can persist due to multiple relapse episodes, chronic infections, drug resistance, etc.

In areas of low transmission, the risk for acquiring an infectious mosquito bite is low, approximately <1-2 per year. That is expected to gradually decrease while progressing to malaria elimination. Considering that there is not enough evidence to rule out the use of serodiagnosis, some findings from a hypo-endemic region supporting this method will now be highlighted. In these regions, malaria elimination might be viable in the short and medium terms.

We found in southern Mexico that in most *P. vivax* infected patients the antibody titers against a native blood stage antigen declined in the first few

months (2-4 months) after administration of an effective anti-malarial scheme (5). In the lack of relapse episodes, a high proportion of the individuals turned seronegative (seroreverted) overtime. If such patients had a new blood infection, the antibody titers increased again, and declined after malaria treatment was administered and so on. Not only in children the antibody responses decreased rapidly, there were a proportion of adults above 20 years of age with a similar antibody response-pattern. A large proportion of those individuals might have not been exposed before. From an immunological perspective, the persistence of malaria antibodies in high titers must be due to the presence of parasites or antigens stimulating antibody production. This agrees with our results, patients with persistent antibodies at middle-high titers without symptoms, turned symptomatic and their parasitemia was detected by microscopy or by PCR. Other patients continued asymptomatic and microscopy - for months, but eventually were PCR+. In one patient five blood samples were obtained within 10 months, and the antibody titers remained high at all time points, but only one of these samples was PCR+. The previous case and results from others, suggest that only a fraction of asymptomatic and seropositive individuals will be PCR+ at a certain time-point.

Interpreting the antibody titers is challenging, since infected or recently cured individuals might present a wide-range of antibody titers; grouped into weak, intermediate and strong antibody responses. Nonetheless, patient with high antibody titers are more likely to have a recent parasite exposure. In our study, the use of anti-relapse therapy in *P. vivax* patients guaranteed that more than 90% of cured individuals would serorevert. In contrast, if hypnozoites are not target by a radical treatment, it is highly probable to experience new blood infections due to relapse episodes followed by re-stimulation of specific antibody responses.

Others had reported that specific anti-malaria antibodies can persist for years after parasite exposure, using mostly recombinant or peptide proteins as antigens (6). Those studies might have some drawbacks as the participants were populations living in endemic areas. These individuals were at risk to acquire a new blood infection at any time, some of them might carry a long lasting chronic and asymptomatic infection that might cured spontaneously after a long time.

It is wide known that seropositive populations might represent parasite reservoirs and an obstacle for malaria elimination. Recently, to identify the hidden parasite burden, both PCR and serology have been implemented, and in some cases the information of the detailed malaria report aided to detect populations eligible for antimalarial treatment. However, to date this strategy has been used only at a research level. Although there are some advances more research is needed to identify informative antigens. There are a vast number of potential antigens to explore their effect in inducing short or long-lasting antibodies. Also, to determine if the antibody persistence "at middle-high titers" corresponds to parasite persistence, groups of seropositive individuals with no confirmed malaria (given by the detail malaria record compiled at local level) must be treated with the adequate antimalarial scheme and follow the dynamics of their antibody response. It might be anticipated that anti-malarial treatment will cause the reduction of antibody titers in infected individuals, but the magnitude is not known.

Whether or not patients had long lasting antibodies in the absence of an active infection (PCR-) should be investigated using an integrative approach. A complex disease deserves a complex diagnosis strategy e.g. multiple

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methods, appropriate antigens, screening system, combine data, deep interpretation and test hypothesis, update the report system, etc.

It is finish with a question to ponder. Considering current knowledge, is it indispensable to deliver results from only blood smear or/and RDT to record a malaria case?

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