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Editorial

Evolution of the Diagnostic of Mosquito-Borne Diseases, the Examples of Malaria and Dengue

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Editorial

The Mosquito-Borne Diseases (MBDs) represent a serious threat to human health especially in tropical areas. The burden of MBDs depends on several factors including the availability of effective control tools. In this regard, the current epidemiology of malaria is very instructive. The use of Artemisinin-based Combination Therapies (ACT) and Long Lasting Insecticides Net (LLIN) has led to a significant decrease of malaria morbidity and mortality in endemic areas reducing therefore the burden of the disease in Sub-Saharan Africa [1]. On the other hand, despite the considerable efforts that are being made, the control of some MBDs such as dengue remains problematic. Indeed, dengue disease is expanding its geographical distribution and the numbers of cases are increasing every year [2]. In addition, there is a significant risk of dengue emergence in temperate countries. This emergence has become a reality for some others MBDs like chikungunya which is causing regular outbreaks [3,4]. Chikungunya disease is now not occurring only in forest and rural areas of Africa. This disease is spreading with a considerable burden in urban areas.

The use of vaccines is the most appropriate way to address this situation. However, vaccines against MBDs are very rare. The only one available are against yellow fever and Japanese encephalitis. In addition, with the exception of malaria, there are very few effective drugs against pathogens transmitted by mosquitoes. Currently, the most valuable strategy to fight MBDs lies on vector control despite the emergence of mosquito's resistance to insecticides [5]. However, the implementation of an adequate vector control strategy requires a good knowledge of the level of disease transmission. This involves the use of good indicators to diagnose the disease and assess its prevalence within population. This challenge is considerable and even more important that the markers used should be adapted to the epidemiological context of the disease. The diagnostic methods can range from a rudimentary technique to sophisticated tools. A brief analysis of some diseases diagnostic methods can help to understand their evolution, current relevancy and future challenges.

For many years, the thick smear has been used as the main technique for malaria diagnostic and it still remains the gold standard for the detection of the parasites in human blood. This microscopic method can be used to diagnose the disease as well as to indicate the intensity of the infection by calculating the parasite density. In addition it helps to evaluate the level of malaria prevalence within a well-defined population. However, this method requires a well-trained staff and a good quality of thick smears to avoid a false positive diagnosis. Furthermore, the diagnosis of low level of parasitemia by thick smear is often challenging representing therefore a weakness for the current malaria pre-elimination strategies.

In order to overcome this situation the diagnosis of malaria is evolving toward a systematic use of Rapid Diagnostic Test (RDT). The RDT is based on the quick detection of the parasite proteins such as *Plasmodium* Histidine-Rich Protein 2 (HRP2), lactate dehydrogenise (pLDH), and aldolase. This immunochromatographic test, can also detect very low level of infection [6]. The advent of this method has allowed significant improvement of malaria diagnosis due to its simplicity of use that does not require specific skills or special instrument. The recommendation to use RDT systematically in cases of malaria suspicion has improved the diagnostic of non malarial fever.

The advantage of this method is not limited only to malaria diagnosis. The use of RDT based on the detection of dengue virus Non-Structural glycoprotein-1 (NS1) is now widespread in dengue diagnosis [7]. This method helped to enhance the capacities of diagnosing dengue disease and is now complementary to the serological assay based on the detection of IgM and IgG anti dengue virus. The serological-based dengue diagnosis is not specific enough to discriminate against others flaviviruses or to differentiate new dengue infection to an older one. Moreover, it is now possible to combine the detection of both NS1 antigen and IgM/IgG anti dengue virus in a single RDT [8].

However, despite the significant contribution of the use of RDT, these diagnostic tools are limited regarding their capabilities to quantify the magnitude of the infection. Therefore the use of RDT cannot help to grasp the severity of the infection such as what can be done with thick smear [9] or the measure of the circulating level of dengue NS1 [10]. Also, according to the principle of the RDT it is not possible to distinguish treatment failure to re-infections. This constitutes a serious shortcoming to their relevancy as pathogen resistance can be a cause of treatment failure.

The use of molecular biology in MBDs could represent a valuable alternative to address these deficits. The molecular tools have the potential to: i) detect the pathogen at a very low level and in a specific manner and ii) to quantify the amount of pathogen presents in a sample. These two conditions make that molecular biology can be use to effectively monitor MBDs. Their main weakness lies in the difficulty to be use routinely as their costs represent a substantial investment

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and may not be available in most endemic areas. However, there is a growing number point of care in rural areas where these molecular tools are available for routine diagnostic [11].

We have several tools to diagnose the MBDs infections. However, much remains to be done in view of the current situation. Indeed, despite all the resources available, it is still difficult to diagnose easily, rapidly and accurately some diseases. Chikungunya is expanding and still now, ELISA and molecular biology are used to diagnose this infection. The development of RDT could improve this disease management. On the other hand, existing markers should evolve according to the epidemiological situation of the disease. For example, despite that it is possible to detect low level of malaria parasite by the RDT and molecular biology; new markers are needed to assess the level of population protection or individuals who are at risk. New complementary tools should be developed on this direction. For example, *Plasmodium* antigens that can be use to evaluate accurately the level of anti malarial immunity and the disease transmission in areas of very low transmission should be identified This may be useful in areas dealing with malaria pre-elimination strategies as at this stage the level of parasites circulation could be very low. To this end, it would be helpful to identify easily individuals carrying *Plasmodium* gametocytes. The detection of the gametocytes in the blood is mainly done by thick smear technique which is very tedious and with a low level of sensitivity. Supplementary efforts should be made to develop rapid and specific test for detecting these gametocyte carriers who are maintaining malaria transmission. The same case is valuable for dengue disease. We are lacking reliable marker for the severe form of dengue disease. The identification of marker that can help to establish an early diagnostic of the severe form of the disease would be a valuable step in the clinical management of dengue patients.

In addition, the co-occurrence of MBDs is frequent in tropical areas and sometime the symptoms are identical and insufficient for clinical differentiation. The development of diagnostic devices that could detect in a single sample and at the same time a broad range of MBDs must be encouraged. The development of this type of devices can help to diagnose and monitor quickly MBDs [12].

MBDs are dynamic with a changing epidemiology over the time, some new pathogens or strains can emerge, we should be aware and prepared to develop markers for these potentially spreading pathogens. New paths should be explored to add supplementary tools to the arsenal of diseases markers. The study of the interactions between the vertebrate, the vector and the pathogens can help to find new possibilities to improve the current tools and to develop new ones. The study of human antibody response against mosquito salivary proteins is in this perspective. It has helped to identify individuals at risk of disease transmission [13].

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