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Opinion Article

Have the malaria eradication measures been behind the COVID-19 pandemic?

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The world is now facing a pandemic from the novel Coronavirus (COVID-19), medical experts are puzzled and searching for some explanation. This is a crucial time for Translational research, which is an overarching exploration strategy that overcomes arbitrary, conventional obstacles dividing medical specialties and isolate basic science from clinical practices (1).

It is the responsibility of all of us working in the medical field to observe, think, and ask to inspire those who are more specialized in dealing with this disaster.

The story started on 31 December 2019, the World Health Organization (WHO) was alerted to the emergence of cases of pneumonia of unknown etiology detected in Wuhan city, China. Within days, Chinese health authorities identified 44 more cases.

A novel coronavirus was subsequently isolated from patients (2).

On 12 January 2020, the World Health Organization (WHO) temporarily named this new virus as the 2019 novel coronavirus (2019- nCoV).

On 30 January 2020, WHO announced the 2019- nCoV epidemic a public health emergency of international concern. On 11 February 2020, the WHO formally named the disease triggered by 2019- nCoV as coronavirus disease 2019 (COVID- 19) (3).

Coronaviruses are enveloped, positive single-stranded large RNA viruses that infect humans, but also a wide range of animals. Four subfamilies, namely alpha-, beta-, gamma- and delta coronaviruses exist (4).

The situation is terrifying and foggy, but there are some observations that need to be explored and several questions to be answered.

Looking at a world map showing the prevalence of COVID-19, we can find that Countries, where malaria and mosquitoes are endemic, have the lowest rates of COVID-19.

Are mosquitoes capable of changing the human immune response? Once mosquitos ingest blood they start a brief yet close bidirectional interaction with several different implications (5).

Host blood may contain pathogenic species, protozoa, nematodes, and viruses that can infect the fly from the bloodmeal (6, 7).

In addition to its obvious nutritional value, the host blood carries with it a variety of factors that may remain actively engaged in the midgut after ingestion. For example, if mammalian TGF- β is introduced in the bloodmeal, it triggers mosquito-endogenous

pathways modulated by an analogous TGF- β (5).

The feeding mosquito brings a mixture of salivary proteins like enzymes and inhibitory proteins into the host, many of which are antigenic (8).

The degree of host reaction to mosquito bite depends on the length and severity of exposure to biting mosquitoes and the host's immune profile, such as its prior history of allergy or exposure. The production of this reaction is more dependent on exposure than on age. Thus, a child highly exposed to mosquito bites may be at a more advanced stage of a reaction than an adult who receives a small number of bites annually (5).

Mosquito saliva modulates the immune response of the host (both innate and adaptive) (9).

Human immune responses to mosquito saliva are major and complex: mosquito saliva affects the levels of many populations of immune cells, in different tissues, many times after blood feeding. Mosquito saliva also affects the levels of serum cytokine, these effects last up to 7 days after the bite (10).

As proof of concept, vaccination with sand flies salivary antigens to stop infection with leishmania has shown promising results in animal models (11). In this context, Manning and colleagues reported that a similar approach using salivary proteins from important vector mosquitoes, such as Aedes aegypti, could prevent multiple mosquito-borne viral infections (9).

There are hundreds of known arthropod-borne viruses (arboviruses), about 30 of which are believed to cause human disease (12).

Most mosquito-borne viruses are RNA viruses (same as coronaviruses), with single or double-stranded RNA (13). Which role do hundreds (not known to cause human diseases) of mosquito-borne viruses play? Is it possible to make human immune against them or against other viruses (i.e., cross-immunity)?

Chang and colleagues reported that "although coronaviruses usually infect the upper or lower respiratory tract, viral shedding in plasma or serum is common. Therefore, there is still a theoretical risk of transmission of coronaviruses through the transfusion of labile blood products. The authors also reported that limited data have shown that viral RNA could be detected in plasma or serum from COVID-19 patients.

In the first 41 patients in the city of Wuhan, viremia was found in 6/41 (15%) patients" (14).

Can mosquitoes transmit coronaviruses when they get to the blood and result in stimulation of immunity against these viruses?

In line with this idea, about 10 years ago, a group of Japanese researchers has developed a mosquito that spreads vaccine instead of disease (15).

Why in China, and why at that time? For decades, China's food habits have not changed, so it is hard to see them as the only cause of the COVID-19 epidemic. The question arises as to why the COVID-19 epidemic appeared in late 2019?

If we trace the health measures that China has followed during the past ten years, we will find among them the malaria eradication program (16).

China was aiming to eliminate malaria by the year 2020 (17).

Is it possible that this program succeeded in eliminating the mosquitoes

that were spreading immunity among the Chinese? A Middle East country (i.e. Iran) that follows a similar successful eradication program for malaria (18), faced the same fate as China regarding the COVID-19 epidemic. This also refers to Europe and the USA, which have long been recognized as areas free of malaria because of successful eradication campaigns (19).

Moreover, the Americans' excessive fear of the Zika virus caused them to take strict measures to get rid of mosquitoes and prevent their bites (20).
Just before the outbreak of the COVID-19 was considered a global pandemic, Velavan and colleagues reported that dense communities are at particular risk and the most vulnerable region certainly in Africa, due to dense traffic between China and Africa. The authors also reported that WHO has identified 13 top-priority African countries which either maintain direct links to China or a high volume of travel to China (4).
But what happened was the reverse, the countries of Europe and the USA were the most affected and at the time of writing this article, the African countries still have a reasonable situation. Is it conceivable to depend on the endemicity of mosquitoes in these African nations and its ability to strengthen the immunity of Africans? The situation is also still favorable in some other regions of the world known to be endemic for malaria, such as India(21), Yemen(22), and Mexico(23).
As a part of Africa, Egypt has a low prevalence of COVID-19 and this was true even in the winter. One of the noteworthy remarks is that about a decade ago, the mosquito known as Aedes Aegypti was re-emerging in Egypt again (24).
An Egyptian study published in 2018, reported that the finding of both larvae and adults is strong evidence of the re-establishment of this mosquito (i.e. Aedes Aegypti) vector species particularly in Southern Egypt (25).

With the exclusion of countries where malaria never existed or disappeared without specific measures (26), we will find that countries that take strict measures to eradicate malaria or arboviruses are most affected by COVID-19. This makes me think that the issue is more focused on the intermediate host (i.e. mosquitoes).
In order to understand the current situation, we have to go back a little and remind ourselves of the unprecedented outbreak of the Ebola virus from 2013-2016 in West Africa (where the blame also occurred on the bats) (27), we will find that it happened after the West African countries succeeded in taking steps towards eliminating malaria (28).
In my opinion, the intermediate hosts (mosquitoes and others) are double-edged weapons, that induce certain diseases and defend against others and the opposite occurs in their absence.
All the above observations and questions need to be reevaluated by the investigators in the fields of tropical medicine, public health, parasitology, and microbiology, to show us if the COVID-19 pandemic was the result of an environmental imbalance because if it were, restoration would become imperative to save humanity from this disaster.

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