Malaria, Vaccine and Mosquitos

A small but promising approach to conclude the ever-ongoing search for a really working malaria vaccine

The news of a newly developed vaccine against malaria is met by a chorus of disapproval from the 'anti-vax movement,' particularly from those not in danger of being infected. The commotion is triggered by the mistrust in vaccines after the COVID-19 calamity, mainly because of the genetically engineered mRNA vaccines (1). It is aggravated by the fear that immunization through the air from person to person might be possible and illegally forced since the news by NATURE mentioned the transmission of the antigen by mosquito bites (2). In fact, aerosol vaccination in humans is tested. For example, it is investigated against tuberculosis using an adenovirus as a vector and against influenza as a simultaneous aerosol and intramuscular application among pigs, with the expectation that this will also work in humans (3-5). For the anti-vax movement, the report by NATURE indicates that involuntary aerosol vaccination is on the horizon.

Evolution created malaria as a very smart infection

The public animosity against new vaccinations is a very unfavorable development. It is high time to openly discuss what went wrong with the mRNA vaccines during the COVID-19 years so that mistakes were done can be corrected in the future. In Africa, Malaria tropicana, caused by Plasmodium falciparum, causes high mortality, especially in children. The disease is also of major concern for public health of many other tropical countries, including Southeast Asia, as pointed out in this blog previously (6). To soften the malaria threat is a major challenge to public health.

Control measures directed at the various species of Malaria vectors are only partly successful. Evolution created clever female mosquitos to ensure they succeed sucking blood against the odds of being eliminated by multiple means (7). Likewise, the vector, evolution also favored the pathogenic agents, providing them with a very complex life cycle and enabling them to develop resistance against therapies. During the Vietnam War, Chloroquine resistance made treatment very difficult in Southeast Asia, as Artemisinin resistance does now in Africa (8).

Need to add malaria vaccines into the multifactorial approach to control its spread

Malaria kills, and sometimes very fast. Among a 'multipronged' approach to curb the infection by sensitizing the communities against the threat, intensifying epidemiological monitoring, vector control, and drug therapy, vaccination cannot be excluded (8). COVID-19, despite all the damage it did, should not be allowed to obstruct useful and fascinating developments of vaccines by taking great care to avoid harmful effects. However, for those observing malaria vaccination for many decades, it seems that announcements of a very effective malaria vaccine were too often just around the corner, but so far, it turned out not to be true (9).

Unfortunately, this is still the case for the vaccines available. The two vaccines presently worked with are RTS,S/AS01, and R21. The first preparation attacks the sporozoite, directed towards a

sporozoite surface antigen, in this case, the circumsporozoite protein (CSP). The sporozoite is the part within the plasmodium lifecycle from which the blood stage within the host's liver develops. The protection against the disease is about 56%, at best for one year, and it works better in children than infants (10). The R21 used a higher proportion of the sporozoite antigen than the RTS,S injection, which was tested in children five to seventeen years old, and the vaccine efficiency was about 70% for one year (11). The accomplishments of the two vaccines are insufficient, and a better vaccine efficiency would be an improvement.

Genetically altered sporozoites as antigens

To achieve this, a change in the antigen used by the vaccine could be promising. Instead of relying on a particular protein enabling the sporozoite to function, the active sporozoites could be genetically altered, 'attenuated,' which means to become asymptomatic at certain stages of the parasite's life cycle. By genetic engineering, genes are switched off to interrupt the parasite's further development, such as within the hepatocyte. That could be done at different stages within the liver cell, where merozoites are formed and finally released in the human host's blood. Whole attenuated sporozoites could be developed to stimulate the host's immune system towards several stages of Plasmodium falciparum's life cycle (12).

Learn to know 'PfΔb9Δslarp (GA1)' and PfΔmei2 (GA2)

Radiation-attenuated sporozoites vaccines against falciparum malaria vaccines (PfSPZ) are the most advanced improvements in the field, resulting in high efficiency by stopping the liver stage in the replication of the plasmodium (13). The method served to carry out a double-blind, controlled clinical trial to evaluate the efficacy of immunization with two genetically attenuated parasites, where one gene of the sporozoite form is knocked out. One application acted at intrahepatic development after 24 hours of inoculation, indicated as PfΔb9Δslarp (GA1), while a different engineered preparation, indicated as PfΔmei2 (GA2) acted towards completing the liver stage after 6 days. Healthy adults who hadn't had malaria volunteered to get immunized by bites of infected mosquitos (14).

The trial: Methods and results

The trial was conducted in two medical centers of two universities in the Netherlands during the COVID-19 period, which limited the number of volunteers who could participate in the investigation. In a first attempt, the safety of vaccination with GA2 infected mosquitoes was tested against GA1 by either 15 (GA1) or 50 (GA2) bites of the mosquitoes. The second double-blind stage used a placebo uninfected mosquito and GA1, and GA2 infected mosquitoes with 50 bites for all three groups (14).

From eight out of nine participants of the GA2 group, no blood stage of parasitemia was detected, and only one produced a positive P. falciparum polymerase-chain reaction (qPCR) in the prepatent period. All eight volunteers of the GA1 group had a positive pPCR test and blood-stage parasitemia. So, from the GA2 group, out of nine volunteers, eight were saved from malaria, but only one from eight participants in the GA1 group (14). Three out of twenty-five participants were protected in a previous trial with a venous injection of GA1 (15).

Proinflammatory reactions were observed in the humeral and cellular immune responses to vaccines. The immune reaction increased significantly for GA2 above GA1, as shown for interferon-γ, TNF-α , and Interleukin-2. Participants were protected against malaria by chemoprophylaxis with chloroquine, which actively acts only in the blood stage of the parasite (14).

Conclusion

Using the vector to outwit the Malaria plasmodium appears to be a smart way to rob it of its evolutionary benefits above the host. The elaborate small investigation is considered quite promising, as it was published in the respected New England Journal of Medicine. The number of volunteers was very small. The next step might be to repeat this trial with a much higher number of participants before one step after the other to go on to a field trial and implement it to benefit African populations suffering and losing their children from malaria.

Not only tricky technical problems have to be solved. The trust in innovative medical and public health endeavors must be regained. Those who are against Malaria vaccination might not be those who are threatened by the disease. History holds a very bad example of trying to work against malaria and filariasis with genetically altered mosquitos (16). The project was denounced as a biological warfare experiment in India, had to be stopped, and is said to have caused the failure of the that time prime minister Indira Gandhi to be reelected in 1977.

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