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Comment Vaccinating against mosquitoes – anticipating the unexpected --Manuscript Draft--

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Comment

Vaccinating against mosquitoes – anticipating the unexpected

Mosquitoes bite. Within a few minutes, the hungry female probes the skin, inserts her pointed proboscis into the dermis seeking a capillary, and then sucks up 0.001 to 0.01 ml of blood. Generally, this process leaves an irritating, pink swelling which we try desperately not to scratch. But sometimes the satiated mosquitoes leave behind more than a passing itch. In fact, mosquitoes act as vectors of a remarkable number of viruses and some other parasites, which they transmit in their saliva while they feed on blood. Among these mosquito-borne agents are pathogens causing some of the most medically devastating infectious diseases – malaria, lymphatic filariasis, dengue, yellow fever, Zika, Chikungunya, Japanese encephalitis, West Nile fever. While some have long been with us, in the last few decades epidemics caused by viruses such as West Nile, Chikungunya, and Zika took us by surprise, overwhelming health systems.

Covid-19 reminds the world how quickly a virus can cause havoc. Our vulnerability is compounded by the lack of off the shelf treatments like antibiotics. Hopefully, increased handwashing, and controlled coughing and sneezing, will reduce the future incidence of directly transmitted viruses like coronaviruses, influenza, and noroviruses. But vector-borne pathogens will be unaffected by improved personal hygiene as their indirect transmission relies on infected arthropods (eg. mosquito, sandfly, tick) or aquatic snails. According to WHO (<https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases>), vector-borne pathogens account for at least 17% of all infectious diseases. Each year they cause more than 700,000 deaths.

Dependency on a vector could be the Achilles heel of vector-borne infections. This is the view of Manning and colleagues¹ who report in *The Lancet* the first step towards creating a vaccine against mosquitoes. Although blood-feeding vectors are known to induce an immune response when they feed, attempts to harness this knowledge have resulted in only two marketed vaccines – both for control of the cattle tick – but derived from midgut rather than salivary antigens.² One reason it has proved so difficult to develop an anti-vector vaccine is the arms race between vector and vertebrate host: responses of

the host (nociceptive, inflammatory, and immune) to prevent the bloodletting are countered by bioactive molecules (mostly proteins and peptides) synthesised in vector salivary glands and secreted into the host as the vector attaches and feeds.^{3,4}

For the clinical trial, a vaccine was prepared comprising 4 peptides of 32 to 44 amino acids. The peptide sequences are predicted T cell epitopes of proteins from *Anopheles gambiae* salivary glands, conserved across *Anopheles*, *Aedes*, and *Culex* mosquitoes. Inoculation of this peptide vaccine (with or without adjuvant) into 33 healthy adults had no untoward systemic effects even when 10 hungry *Aedes aegypti* mosquitoes were fed on participants. This basic result is encouraging given the potential for severe allergic responses. It may be argued the challenge was 'soft' – *Anopheles*-induced immunity challenged with *Aedes* saliva antigens. The outcome could have been different with *Anopheles gambiae* mosquitoes though the vaccine was based on conserved antigens.

Although more needs to be done on safety testing, the next big challenge is demonstrating a mosquito peptide vaccine provides protection against mosquito-borne pathogens. This is a big ask, but not implausible. Extensive research on developing anti-sandfly vector vaccines to control leishmania provides some design clues.^{5,6}

Leishmania parasites, inoculated into the skin when an infected sand fly bites, infect macrophages and form skin lesions (cutaneous forms) or migrate to the spleen, liver, and bone marrow (visceral forms). Pre-clinical studies showed that rhesus macaques immunised with a sandfly salivary protein (PdSP15) were protected against cutaneous leishmaniasis when exposed to sandflies infected with the parasite.⁷ Protection correlated with accelerated *Leishmania*-specific CD4⁺IFN- γ ⁺ lymphocyte production. A similar effect was observed when mice immunised against a tick salivary protein survived an otherwise lethal challenge with ticks infected with tick-borne encephalitis virus.⁸ Immune responses to the vector create an environment in the skin hostile to feeding-injected pathogens, promoting a protective anti-pathogen response.⁶

The great attraction of anti-vector vaccines is the prospect of one vaccine protecting against all the different pathogens – known and unknown – transmitted by one vector (or even related vectors). This compares favourably with conventional anti-pathogen approaches, e.g. yellow fever vaccine protects against yellow fever virus transmitted by *A. aegypti* but not against chikungunya, dengue, Zika or as yet unrecognised pathogenic viruses transmitted by the same mosquito species. Relying on an anti-vector

vaccine is risky and a combined anti-pathogen + anti-vector vaccine approach is considered safer. However, as a first line of defence, an effective mosquito peptide vaccine could save lives and buy time to develop a targeted vaccine.⁹

I declare no competing interests.

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