Vaccination against the big three killers: an illusion ?

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For 30 years, the largest investment in life sciences has been in seeking an immunization against the "Big Three": AIDS, tuberculosis and malaria. This choice appears logical as these diseases are among the largest killers among infectious diseases, accounting probably together for >1.750.000 deaths per year [1, 2]. Attempting to develop a vaccine prevention strategy that yielded extraordinary results on smallpox and which was very significant for poliomyelitis, diphtheria, mumps and measles, could have yielded spectacular results. However, this attempt, despite the increasing levels of financial and scientific investment with hundreds of publications every year, has not produced any tangible and applicable results. Despite the annual declarations of new vaccine strategies for these three diseases, real applicable strategies have never followed. This does not seem surprising to us, and we think that we need to change our strategy in the current state of our knowledge.

Malaria is a non-immunizing disease [3]. People who are exposed to malaria can receive several hundred infective bites per year, suffered several malaria episodes with different strains, and the low immunity that has been eventually acquired, disappears very quickly after a several months in a malaria-free country. We are currently experiencing this in France with African students and Comorian migrants. Vaccine development continues but none of the malaria vaccine candidates developed to date have been shown to provide long-lasting benefits at a population level. Even what appeared to some researchers in the recent years as promising results, the RTS,S/AS01 malaria vaccine administered at months 0, 1, and 2 to 5-17

months children confered, when boosted, about 32% protection against severe malaria for a few months [4].We think that when several episodes of a natural disease fail to determine immunity for more than a few months, the chance of finding a vaccine is extremely low.

Likewise for HIV infection, none of the efforts have had any effect despite the spectacular announcements. Twelve late-stage trials worldwide are testing experimental vaccines [5]. After 30 years still there is no preventive HIV vaccine [6]. Current research efforts are mainly addressed to “curative” vaccine in HIV infected people, with aim to reach ”functional” cure. Anyway, HIV infection is not an immunizing disease. The only forms of real resistance known to retroviruses are either natural resistance, such as in gorillas for HIV [7], or, for a number of animals, the internalization and neutralization of the retrovirus that protects against subsequent viral infections. This is called endogenization, which is a phenomenon perfectly observed in Koalas [8].

Finally, with regard to tuberculosis, BCG is a theoretically ideal vaccine, a live vaccine, a variant of tuberculosis agent. A mild disease is inoculated, that gives a perfectly effective immune response that can be tested and provides robust immunity. It is effective in protecting infants and children against severe miliary and meningeal TB, although its protection is variably lost in adluts [9]. Nevertheless, there are currently several million new tuberculosis cases per year, including 1.2 million deaths, which indicates that more than a century of vaccination policy by the BCG has not really cleaned the situation. More than 20 novel TB vaccine

candidates are now in clinical trials [9, 10]. We'll see what will be the future of this renewed research effort.

What has changed the prevalence of these diseases is, for malaria, long-lasting insecticide-treated bednets, and for the three diseases, the treatment of carriers in order to significantly reduce the reservoir. The fight against the big three killers is still ongoing, but strategies based on mechanical and therapeutic prevention coupled with shortened treatments are more likely in the next 20 years to help further reduce the prevalence of the three major killers, rather than the hypothetical discovery of a miracle vaccine that would contradict the natural observation of the cycle of these three diseases.

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