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Is vaccinating monkeys against yellow fever the ultimate solution for the Brazilian recurrent epizootics?

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Abstract

Vaccinating monkeys against yellow fever (YF) has been a common practice in the beginning of the 17D vaccine development. Although it may seem strange at first sight, vaccinating monkeys as a public health strategy is, we think, feasible and theoretically could eliminate the infection among non-human primates, interrupting the virus circulation (or significantly reducing it) and therefore reducing the risk of spilling over to the human population. We propose a series of studies that could demonstrate (or not) the efficacy and feasibility of vaccinating non-human primates YF reservoirs living in green areas of urban centres to cut off or curb the virus circulation that recurrently spill over to the human population. Therefore, vaccinating monkeys in relatively small green areas of the urban centres is perhaps the ultimate solution for the Brazilian recurrent YF epizootics.

In 2016, a yellow fever (YF) outbreak occurred in Minas Gerais, Brazil. It was characterised as a sylvan or jungle epizootic [1]. The disease spread itself to other South Eastern States of Brazil causing close to 1300 human cases and 216 confirmed deaths. All of these deaths were in human individuals who had recently visited green areas where there have been reported the deaths of non-human primates. Urban monkeys are, therefore, responsible for triggering human outbreaks of YF in Brazilian cities in 2016.

Until the end of 2017, the State of São Paulo reported 501 deaths of monkeys from YF of which 177 deaths occurred in the Capital alone [2]. These deaths of monkey triggered a huge vaccination campaign of humans living in the neighbourhood of parks and green areas of Sao Paulo city, with an expected number of close to 3 million people to be vaccinated [3]. This rapid response of the health authorities is undisputedly the correct strategy to avoid the resurgence of urban YF. There are, however, complementary strategies that could cut off the virus circulation among non-human primates. Among them, we would like to propose the vaccination of monkeys, the main reservoirs of YF in Brazil [4, 5].

Although it may seem strange at first sight, vaccinating monkeys is, we think, feasible and theoretically could eliminate the infection among non-human primates, interrupting the virus circulation (or significantly reducing it) and therefore reducing the risk of spilling over to the human population [6].

Vaccinating monkeys against YF has been a common practice in the beginning of the 17D vaccine development. In 1928, Theiler and Sellards ([7] see also [8]) demonstrated that serum from immune humans protected monkeys from YF infection. After this first attempt to immunise monkeys, mice substituted the latter as a cheaper and more convenient animal model for the test of further vaccines. Many years later, in 1973, Mason *et al.*, [9] directly challenged monkeys given graded doses of the 17D YF vaccine with the live virus. Forty-three of the 45 monkeys vaccinated with the dilution of $1{:}10^{2.3}$ or greater weanling mouse mean lethal doses of 17D vaccine were resistant to challenge 20 weeks later with virulent strains of YF virus. In 1986, Schlesinger *et al.*, [10] demonstrated that monkeys immunised with the YF virus nonstructural protein NS1 resulted protected against the infection with the wild virus. Four out of five immunised monkeys survived the challenge, whereas all monkeys, which received ovalbumin injections, died. These are just examples that support the strategy of vaccinating monkeys as a safe and efficacious way to protect the animals against the infection.

Before proposing vaccinating monkeys against YF as a routine public health strategy, however, many challenges should be overcome.

The first challenge is to determine how safe and efficacious and at which dose the 17D YF vaccine is for the two currently most important monkey reservoir, namely the genus *Callitrix* and *Alouatta* [11]. Past literature, however, provide important information on YF vaccination in different species of monkeys [12].

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Second, the sheer area of forest in and around the city of Sao Paulo (just to examine an extreme case) possibly has a large (and unknown) number of monkeys living there that should be vaccinated [13]. The city of São Paulo has an estimated 642 km^2 of forested areas [14]. Assuming, just as an exercise, an animal density of 50 animal per km^2 [15], it should be expected 32 100 non-human primates living in the capital. If we assume a basic reproduction number of YF of 2.0 [16], the herd immunity necessary to cut off the virus circulation in the city should be about 16 000 monkeys to be vaccinated. The actual number of animals living in São Paulo, however, is likely to be much lower, and an educated guess of the target number to be vaccinated, restricted to the most affected areas, would be around 2 000 monkeys, a much more feasible figure. Future studies, however, should determine the exact number.

Finally, the logistic involved in vaccinating such a number of animals is, perhaps, the most important limiting factor. The animal must be darted with anaesthetics, collected in a safety net to avoid falling into the ground, vaccinated and cared for until recovering from the anaesthesia and marked to avoid overvaccination [17]. This involves trained staff and some hours of work per monkey vaccinated. These difficulties, however, can be circumvented by additional studies, as described below.

In addition, it has been argued that vaccinating monkeys would eliminate an important sentinel represented by the death of *Alouatta* monkeys as a surveillance evidence of YF virus circulation in certain areas. This, however, involves the ethical thorny issues on exposing or leaving unprotected one species in benefit of our own species. We will not be involved in this discussion here. Noteworthy, however, is the fact that some species like the ones from the genus *Callitrix*, in many circumstances, do not die from the disease, although they may be infectious to the wild mosquitoes.

Systematic vaccination of wild non-human primates would certainly require appropriate regulatory agency approval for use of the vaccine in veterinary context. Therefore, studies will be required to license YF vaccines for veterinary use (see suggestion list below).

In spite of all the above difficulties, we would like to recommend the following steps in future studies:

(1) Laboratory work I: the equivalent a phase I/II clinical trial to determine the safety and efficacy doses of 17D-YF vaccine per species and per size/weight of the animals;
(2) Laboratory work II: starting the development of a possible oral vaccine that could be used in baits, in the same fashion as the oral rabies vaccine used in Europe to control rabies in foxes and in the USA in raccoons (we are well aware that an oral vaccine would be very difficult to work due to the lack of stability of YF virus proteins at low pH). There is, to the best of our knowledge, no YF vaccine that could be successful in an oral formulation;
(3) Laboratory work III: the development of an alternative deployment of the 17D-vaccine that could be used in darts, avoiding the capturing of the animals;
(4) Field work I: determining the actual size of the monkey population by one of the commonly used techniques like the capture–recapture technique [17];
(5) Field work II: the equivalent of a phase III clinical trial in a pilot area to test possible vaccination strategies/logistics;
(6) Theoretical work I: determining the basic reproduction number and the herd immunity threshold in order to design an optimal vaccination strategy to cut off the virus circulation in the wild;
(7) Field work III: the equivalent of a phase IV clinical trial that would involve large number of animals with an optimised strategy, as calculated in step 6;
(8) Theoretical work II: modelling the impact of vaccinating non-human primates against YF on the risk of re-urbanization of the infection;
(9) Theoretical work III: modelling the likelihood that YF virus transmission becomes established in a human–mosquito–human (the risk of the urban cycle, see [18]) before the local non-human primates are significantly affected.

Provided the above studies support the idea of vaccinating monkeys as an effective public health strategy, the issue of costs should also be addressed. The per capita cost of vaccinating human is estimated to be around US$1.5 [3]. Therefore, the total cost of the estimated 3 million people to be vaccinated in the near future in São Paulo is US$4.5 million. In the case of the target vaccination of about 2000 monkeys in the most affected areas, considering the costs of capturing and vaccinating each monkey, there would be a ceiling cost of less than US$200.00 per monkey vaccinated.

The risk of urban YF resurgence, as shown in reference [18], is dependent on the introduction of one or more infected individual into an *Aedes* infested area. This may occur regardless of the involvement of local non-human primates since the infected index case could acquire the infection from visiting areas in which the urban cycle is established. However, this is not the case for Brazil where the urban cycle has been interrupted for at least 70 years now. Therefore, if and when the urban cycle of YF will recur in Brazil will certainly be triggered by individuals who acquire the infection in wild areas where epizootic cycles are already well established.

We are well aware of the apparently difficult hurdles that should be overcome before the vaccination of monkeys against YF becoming a public health strategy. However, not to start the necessary studies to determine how and if vaccination monkeys against YF is a feasible strategy is, in our point of view, unethical if not inconsequential from the public health perspective.

To conclude, it is obvious that it is not feasible to vaccinate monkeys in the Amazon forest, but in smaller green areas of the urban centres, it is perhaps the ultimate solution for the Brazilian recurrent YF epizootics.

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