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COMMENTARY

Yellow fever virus: historical and current issues regarding recent epidemics and vaccination in Brazil

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ABSTRACT

Yellow fever has been recently described in nonurban areas of Brazil despite 80 years of commercial vaccine use. Although the disease does not spread fear in the general population as it did in the past, yellow fever virus continues to cause many cases of severe disease. Persistence of the virus in the host is a new mechanism to be considered in the pathology of the disease. Immunization with a fractional dose of vaccine during emergency situations needs to be evaluated for antibody duration, and new and improved vaccines should be considered.

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Introduction

To discuss Yellow fever (YF), it is necessary to understand the history of yellow fever virus (YFV) during the last 150 years, both worldwide and in Brazil. YFV is a member of the family *Flaviviridae*, an important group of viruses with members that are transmitted by several species of arthropods to animals and men and whose transmission puts them into the arbovirus subgroup. The clinical epidemiology of arboviruses has been studied since the early 1900s and has contributed greatly to US health policy in terms of the dangers of tropical diseases, thus affecting the travel of citizens and the deployment of armed forces.[1] In 1951, the Rockefeller Foundation started significant financial support for a collaborative program in search of new arboviruses that were identified in laboratories in Egypt (Cairo), India (Poona), Trinidad (Port of Spain), Brazil (Belem), South Africa (Johannesburg), Colombia (Cali) and Nigeria (Ibadan).

Historical and updated points

The transmission of diseases was first believed to occur mainly from person to person; in 1878, Patrick Mason suggested a novel route for the transmission of *Wuchereria bancrofti* by insect bites.[2] Later, there were some indications that YF could also be transmitted by insects,[3-5] which led a team headed by Walter Reed,[6,7] a medical doctor who was a colonel in the USA Army, to describe the role of *Stegomyia* (the *Aedes* denomination then) in the transmission of the then unknown infectious agent etiologically associated with the disease. The knowledge of virus transmission changed the history and epidemiology of yellow fever; for instance, William Gorgas improved the working conditions at the end the construction of the Panama Canal by eliminating the mosquito, and the disease was controlled in urban areas, including Havana, New York, London and Rio de Janeiro.[5]

YFV is one of the historical examples of a vaccine that was prepared without truly knowing the exact nature of the infectious agent involved. Smallpox and rabies viruses are the most significant and representative examples of this approach. The initial contents of the vaccines prepared by Jenner (and before him) and Pasteur were completely unknown, but both resulted in tremendous benefits to humanity. The YFV vaccine was not very different. Virology was then a new science included as part of microbiology, and the biological properties of viruses were not sufficiently characterized to fully understand their interaction with the human host. During these uncertain times, the Asibi strain (named after the young man from whom the virus was recovered) was isolated, and soon after, the development of 17DD, a live attenuated strain, was used for the immunization of susceptible human populations around the world.[8]

With the establishment of vector control and vaccines, two important prophylactic measures, the number of cases of yellow fever were strongly diminished all over the world over a few decades. The intriguing fact that new cases continued to arise led to the discovery in Brazil that YFV could also be transmitted by sylvatic arthropods[9] of the genus *Haemagogus* and *Sabethes* in a life cycle naturally maintained with vertebrate hosts (particularly monkeys). The transmission to humans, when it occurred, was conventionally called nonurban yellow fever (or forest, sylvatic and other denominations). It is relevant, however, to mention that the clinical disease in nonurban yellow fever cases is not different from that of cases occurring in urban areas.

The sylvatic cycle of YFV brought a new understanding of the epidemiology of the virus such that it would be impossible to eradicate the virus and its disease, although prevention and control would be feasible with the application of few preventive steps, of which vaccination is a crucial one. The eradica-

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tion of YF in urban areas was once believed to be dependent on the elimination of *Aedes aegypti* in the Americas,[10] but it was soon understood that this was a difficult goal to reach.[1] Vaccination campaigns were strongly promoted, and in Brazil, YFV was successfully controlled in every geographical area of the country, including urban and nonurban areas, where the vaccination procedure was effectively used as the major component to control virus spread.

Millions of people have been vaccinated around the world since the late 1930s, and the YFV vaccine was considered to be one of the safest produced by far. The benefits of the YFV vaccine for humans outweighed any of the possible complications related to its administration. A few years ago, following one of the dozens of prior major vaccination campaigns, there were a few reports of severe adverse reactions, including hepatic failure and death.[11-13] This was a major point that brought the Brazilian Ministry of Health's successful intervention, which had been maintained for decades to control the disease, to a halt. The suggestion of mass vaccination was immediately rejected, which led to a considerable setback in the protection of the majority of the population at risk in the present epidemics.

There are side effects following vaccination with the YFV vaccine. However, these are generally not serious. Vaccines, in general, have very favorable benefit-to-risk ratios, and the YFV vaccine, in particular, delivers the benefit of protection against a serious disease that weighs very positively relative to the risk of YFV vaccination side effects.

Some essential decisions need to be made regarding the YFV vaccine. Academic information has been forwarded, but it has sometimes been ignored or has taken too long to be put into practical use, as considered in the following examples. Until the 1990s, there was an intense search to improve the maintenance of vaccine infectivity for longer periods of transportation and delivery to humans in remote areas, even in the absence of an appropriate cold chain. The high temperatures of the tropics and difficulties in delivering the vaccine in forests and other geographical areas with difficult access continue to defy technical improvements. Everywhere in Brazil, it was common to see flasks with a large number of unused doses discarded at the end of a day's work. By the 1980s, vaccine manufacturers started to deliver vials with a smaller number of doses during nonepidemic times, a simple procedure that avoided wasting thousands of unused doses. The previous rationale for vaccine disposal was the loss of infective potential to immunize, but experiments showed that the vaccine virus was still viable for at least twice the recommended time after opening the vial.[14]

In 1943, there was an initial publication indicating YFV persistence in experimentally infected nonhuman primate hosts.[15] Two decades later, the persistence of YFV neutralizing antibodies was demonstrated in the sera of persons who had received a single dose of 17DD vaccine 17 years prior.[16] Subsequently, three important pieces of information were produced,[17-19] which showed that a single immunization with the YFV vaccine was sufficient to elicit antibodies for a minimum duration of 40 to 50 years. In 2013, the WHO changed and adjusted their recommendations regarding YFV vaccination and requirements for international travel.[20,21] It is possible that the change was more a consequence of facing the actual shortage of vaccine production worldwide than the acceptance of the academic data. The timeline shows that more rapid decisions need to be made with regard to the YFV vaccine.

Contrary to the times of Jenner, Pasteur and Theiler, today, biological information on viruses and YFV is well known. The YF virus is a member of a family in which several other human pathogens are included, such as the arboviruses dengue and Zika viruses and the non-arbovirus hepatitis C (HCV). HCV is able to persist in some infected human hosts, causing a long incubation period of severe diseases, including cirrhosis and liver cancer.[22,23] An array of severe diseases are still being described from the recent epidemic of Zika virus in Brazil; this is probably a consequence of the persistence of the virus in the infected host. As RNA viruses, the members of the *Flaviviridae* family (HCV for instance) do not integrate their nucleic acid in the same way as viruses in the *Retroviridae* family (HIV, HTLV). They are probably maintained in the host for a long period at low levels of replication before an outburst of virus replication leads to late clinical manifestations. It is reasonable to consider that YFV and the 17DD strain also maintain persistence in the host for a long period of time. This would certainly explain the late recovery of YFV from the brain tissue of infected asymptomatic nonhuman primates[15] and the more recent recovery of YF viral RNA from the urine of vaccinees for a period of six months following vaccination.[24] These are both strong and important pieces of information supporting the remarkably long duration of virus and antibody presence and antibodies, most likely because of persistent infection and continuous antibody production. The consequences of YFV persistence have never been clearly studied and deserve some attention in future research.

The current approach to administer one-fifth of the usual dose of the vaccine to immunize persons during emergency epidemic situations due to a vaccine shortage is still not a regular procedure, despite the successful results obtained.[25-28] Two issues are raised. Vaccines are produced and released for general use with a minimum antigen load sufficient to immunize the recipients. If one considers that the present vaccine has a substantial unnecessary load of antigen, it is reasonable to infer that public resources for vaccine production could be saved. Second, the regular YFV vaccine confers lifelong immunity, and the reduced-dose vaccine promotes at least eight years of immunity. Indeed, both vaccines should work equally. It may be more realistically stated that the observation period postvaccination with the reduced-dose vaccine is still under evaluation to determine the actual duration of antibodies. Indeed, we should expect that the fractionated vaccine will also confer lifelong immunization as long as the vaccine maintains a minimum dose of the antigen, as recommended by the WHO.[29]

Recommendations for a human vaccine rely upon strong scientific data; however, so far, this has not been the case. If the vaccine elicits a response with a reduced dose, it would be reasonable to think that it is also lifelong. The eliciting virus is the same. However, this has not

Box 1. Areas of focus for a future YFV vaccine.

- Are there any new vaccines available currently for testing in humans?
- Are the currently available YFV vaccines still capable of inducing lifelong antibodies? Is it necessary to repeat such experiments?
- What number of persons with antibodies is currently enough to confer herd immunity to the general population in all geographical areas of the country?
- Is a second immunization of the YFV vaccine necessary to confer herd immunity? Is a second immunization free from severe complication risk similar to what has been reported previously?
- How should rapid tests for counselling persons who will be at risk and are not sure of their immunological status be prepared, and is this population in need of an additional immunization?
- Are the available reduced-minimum-dose vaccines capable of producing long-lasting antibodies in the same fashion as the regular vaccine?
- Does YFV persist in the host in the same fashion as HCV?
- Is (are) there any disease consequence(s) associated with YFV persistence?
- Is a new approach for vaccine production needed? Who will fund the research for the new vaccine? Is there any manufacturer ready to go ahead with the production of a vaccine that will be mainly directed toward poor populations in the tropics?

been clearly stated to the general population; it has also not been clearly stated that the reduced-dose vaccine is still under study, but it elicits antibodies that persist for at least eight years. Communication is a key factor when attempting to convince people to adhere to mass vaccination campaigns in the current era.[30]

Conclusions

Presently, there is no "new YFV vaccine" for human use. Efforts, however, are underway to achieve this goal. It will take considerable time to obtain an immunogenic YFV vaccine that is as safe as the present one. At this time, it is certainly unacceptable to postpone the prevention of YF with the currently available vaccines. All the existing information refers to a preparation that did not substantially change since the vaccine was developed by Theiler and Smith in 1937.[8] The attached (Box 1) lists some points for discussion regarding possible financial research support for the development of a new immunogenic and safe YFV vaccine for human use that can be produced at low cost.

In the meantime, it is proposed that the YFV vaccine should be promoted for use in the country as a whole and should continue to be part of the National Immunization Plan (NIP) in Brazil, with coverage extended to all children. The development of a future oral transgenic food vaccine for nonhuman primate use should also be considered in view of the role nonhuman primates play in the maintenance of the YFV cycle in the jungle.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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