

How Brazil joined the quest for a yellow fever vaccine

Brazil recently announced an agreement between its Bio-Manguinhos vaccine unit and two US companies to research and develop a new yellow fever vaccine. Claudia Jurberg and Julia D'Aloisio talk to Jaime Benchimol about the controversial history of the development of the vaccine that benefits millions of people today.

Q: How did Brazil become the world's biggest producer of yellow fever vaccine?

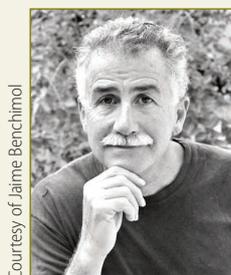
A: The disease was a major health priority in Brazil in the late 19th and early 20th centuries, when the city of Rio de Janeiro along with Havana (Cuba) saw major yellow fever epidemics. Brazil also witnessed the failure of the Rockefeller Foundation's effort to eradicate the disease by funding research and implementing campaigns with local authorities in the Americas and West Africa. This led to a complete reorganization of the campaign. With the discovery (1928–1933) that yellow fever was transmitted by monkeys in forested areas, it became clear that it could not be controlled using traditional methods – methods based on the misconception that the disease had a single urban vector (*Aedes aegypti*) and one animal host (humans). Given these factors, the quest for an effective vaccine became imperative and Brazil was well placed to take up the challenge.

Q: What kind of expertise did Brazil have at the time?

A: Brazil built up tropical diseases expertise and established strong biomedical institutions for the research and development of vaccines in the last quarter of the 19th century. In the 1920s and 1930s, researchers working mainly in Brazil and Nigeria began to view yellow fever as a viral disease with multiple vectors, ecologies and forms of transmission. That led the Rockefeller Foundation to set up a yellow fever laboratory at the Oswaldo Cruz Institute (today's Bio-Manguinhos unit in the Oswaldo Cruz Foundation) in Rio de Janeiro, where important improvements were made to a new vaccine developed in New York with combined North-American and Brazilian expertise.

Q: How was the resulting vaccine tested?

A: In the early 20th century little was done to check the safety of vaccines as they moved from the laboratory to the streets. In 1937, when the new vaccine had just been produced and was being tested in Brazil, Angelo Moreira da Costa Lima, a researcher



Courtesy of Jaime Benchimol

Jaime Benchimol

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at the Oswaldo Cruz Institute, accused the Rockefeller Foundation of using Brazilians as human guinea-pigs. His criticism, however, was hardly reported by the Brazilian media at the time. When we analysed the documents related to the 1930s, it was clear that the doctors had indeed been far too hasty in administering the vaccine, especially in Latin American and African countries, where other yellow fever vaccines developed earlier by British and French experts were used. The history of the large-scale field trials from 1929 to the outbreak of the Second World War in 1945 is marked by many cases of serious health complications and deaths from yellow fever vaccines. These complications included jaundice, which was later recognized as a sign of hepatitis, and encephalitis. Thousands of US soldiers received the vaccine at the beginning of the war resulting in the largest recorded hepatitis epidemic. But to understand more fully how the vaccine was tested and the consequences, more historical research is needed.

Q: How were these vaccinations organized in Brazil?

A: Mass-vaccinations were done as large epidemiological surveys got under way to map the zones where yellow fever was occurring. Rural health workers prepared the ground for the introduction of the vaccine among an otherwise neglected population. This was vital, given a massive rebellion against the smallpox vaccine three decades earlier in Rio de Janeiro. The

yellow fever vaccination teams elicited the support of local elites – mayors, priests, physicians, pharmacists and landowners – in small towns and on country estates in the interior of the country to attract often poorly educated, illiterate people to their vaccination centres. Judging by some documents, many were willing to submit to vaccination but we still don't know whether local elites also received the vaccine, how people reacted when recipients suffered serious health complications and how doctors and other groups reacted when they were informed of these adverse effects.

Q: So people submitted to vaccination without questions?

A: No. Once the mass-vaccinations got under way, lay people from these rural communities were trained and paid to conduct partial autopsies on people with suspected fever who had died and send liver fragments to the Yellow Fever laboratory in Rio de Janeiro. Many people in these communities reacted strongly against the viscerotomies and the prohibition on burial as a desecration of the dead, reflecting the cultural clash between physicians from the coast and devout Catholic communities of the interior.

Q: How was the vaccine made?

A: Starting in 1928, serum was taken from the blood of patients, who were recovering from yellow fever, and injected into researchers working on the disease to protect them. In England and at the Oswaldo Cruz and Butantã

institutes in Brazil, vaccines were made at first (1928–1929) from yellow fever-infected monkey livers and spleens, using chemical methods to reduce its virulence. Two breakthroughs were key: the discovery that membranes of embryonated eggs were susceptible to infection and that white mice inoculated intra-cerebrally with the yellow fever virus developed encephalitis. On the basis of these discoveries by Max Theiler working in London then later at Rockefeller's New York laboratory, scientists were able to modify the virus by changing the conditions under which it was cultured, so that the resultant strain would display fewer adverse effects and confer protection; and to obtain sera richer in antibodies to reduce potential adverse reactions.

Q: So the result was the forerunner of today's vaccine?

A: Yes, one line of research after 1931 yielded the 17D strain, the so-called "friendly" virus, which protected monkeys inoculated with virulent material and no longer caused encephalitis when injected into their brains. In the last months of 1937, 17D was given to about 50 000 people in Brazil. As problems such as low immunity, jaundice and encephalitis emerged, the observations made by North American and Brazilian specialists in their clinical studies are surprisingly sophisticated compared with earlier studies of new vaccines. But, of course, they do not meet today's standards. From 1937 researchers at the Oswaldo Cruz Institute's yellow fever laboratory made important changes to the technique to boost the vaccine yield developed in New York by Theiler, who won the Nobel prize in 1951 for the breakthrough.

Q: How did Brazil respond to the resurgence of yellow fever in the 1970s?

A: In 1958, the 15th Pan-American Conference declared parts of Brazil and other Latin American countries free of the urban yellow fever vector, the *Aedes aegypti* mosquito. In 1967, it reappeared in northern Brazil and soon regained its original ground. Outbreaks of yellow fever led to the reconstruction of hundreds of viscerotomy units. A five-year vaccination programme was implemented in the 1970s in the most at-risk regions. New epidemics in Africa, an increase in yellow fever cases in the Americas and an increase in

Aedes aegypti mosquitoes in urban areas prompted renewed research into the disease and its vaccine. Brazil's health authorities expected a major resurgence of yellow fever infection in urban areas. But in 1982 in the northern city of Roraima, the *Aedes aegypti* mosquito triggered an unexpected crisis: the first modern outbreak of dengue in Brazil which reignited fears that yellow fever could re-emerge in urban areas across the country, as it is transmitted by the same mosquito.

Q: What was the result of renewed research efforts into yellow fever and its vaccine?

A: New technical requirements for the vaccine and new manufacturing protocols were developed between 1980 and 1990 to comply with requirements made by international health agencies and to increase production and distribution capabilities. In 1998, routine vaccination against yellow fever was introduced as part of the Expanded Programme of Immunization. The annual yellow fever vaccine output of Bio-Manguinhos, the unit of the Oswaldo Cruz Foundation that manufactures vaccines, increased from 2.6 million doses in 1996 to 16 million doses in 1999. In 2000, it reached 21 million doses. At the peak of this cycle (1999–2000), two people died due to complications associated with the yellow fever vaccine. The fact that these were quickly detected and fully investigated shows us that much has changed compared to the first years of the vaccine's development.

Q: Your book Yellow fever – an unfinished history was published in 2001. Do you still think this history is unfinished?

A: Yes, for several reasons. Follow-up vaccinations are deemed to be justified in high-risk areas, despite the fact that more sensitive surveillance continues to detect serious adverse effects. Many mysteries surround the interactions between attenuated viruses used to make the vaccine and the human organism. We still don't fully understand why certain individuals respond differently to the vaccine. There are several unfinished lines of investigation, for example, an attempt to develop a vaccine on tissue culture, *in vitro*, that would replace embryonated chicken eggs and another seeking to manipulate the genome of the vaccine virus and "engineer" mutants.

These new live viruses can trigger an immune response against the yellow fever virus and other diseases: raising the prospect of a vaccine that protects us against both yellow fever and dengue. Other promising new strategies are the genetic modification or biological infection of the *Aedes aegypti* mosquito.

Q: How tight are ethical and regulatory controls on such trials today?

A: Today, Brazil adheres to international standards. A new vaccine is adopted after pre-clinical tests that include many phases during which safety and efficacy standards are verified in increasing numbers of people. Our complex centralized bureaucratic system seems to present obstacles to innovation. With regard to past practices, it would be an unforgivable anachronism to expect that social actors behave in accordance with regulatory norms established much later on. It's not my role as a historian to make judgments. My task is to explain the social and technical forces and interests that shaped the regulatory systems and, in this field, much work remains to be done. ■