Yellow fever vaccine in Brazil: fighting a tropical scourge, modernising the nation

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Introduction

In the wake of the Pasteurian revolution, vaccines and serums were developed for yellow fever in many countries. Yellow fever was one of the key public health challenges in Brazil for at least a century, from the 1850s to the 1950s. During this period, the most notable developments were the Domingos Freire vaccine in the last quarter of the nineteenth century, the vaccine and serum created by Hideyo Noguchi in the 1920s and – beginning in 1928 – a succession of experiments that culminated in large-scale production of the vaccine from 1937 onwards in a Rockefeller Foundation laboratory at the Oswaldo Cruz Institute in Rio de Janeiro (a laboratory which was later taken over by the Institute). In the last quarter of the twentieth century it became a cornerstone for major transformations in vaccine production capacity and regarding the use of vaccines to fight other diseases in Brazil.

I see these vaccines as complex sociotechnical constructs involving many different phenomena: the interactions of microorganisms, culture media and other physico-chemical and biological components that produce substances with alleged or proven immunisation effectiveness; unique dynamics in the understanding of the aetiology, pathogenesis and transmission of yellow fever; established traditions for fighting the disease in which vaccines play different roles; and different levels of institutionalisation in scientific research, public health, and the production and use of immunological products. Freire and Noguchi's vaccines and the vaccine produced by the Rockefeller Foundation/Oswaldo

Cruz Institute were fraught with controversies that galvanised not only specialists but also various other social actors whose interests were helped or hindered by the route these products took from the laboratory to the public domain. The first two vaccines dwindled from a position of considerable social standing to mere inventions that died out with their respective creators. The 1937 vaccine, after much dispute, became a relatively stable part of the public health machinery, though it is now being overtaken by new developments.

Focusing on the successive yellow fever vaccines, while also alluding to other immunological products, I seek to show how they have influenced the construction of the Brazilian nation state in three distinct periods: the patriarchal oligarchic state (1822–1930), the national developmentalist state (1930–80), and the state which has since then oscillated between liberal dependency and national interventionism.¹

Yellow fever: from miasma to microbes

Although the New World had seen yellow fever outbreaks ever since its colonisation by Europeans, it was only in the nineteenth century that it became the scourge of the continent, turning two cities, Havana and Rio de Janeiro, into ‘infectious volcanoes’.² Public hygienists blamed the environment, citing both the nature of the ‘torrid latitudes’, considered unhealthy for European settlers, and the artificial environment created by urban society. Epidemics developed as regularly as seasonal fruit, always during the hot, rainy periods. Yellow fever seemed perfectly adapted to coastal lowlands, especially the port cities, which were filled with rotting matter. Various interventions were proposed, focusing on the different environmental components seen as the culprits of the disease, depending on the local topography.

In the second half of the nineteenth century, the second Industrial Revolution – of steam trains and ships – made England a world power and led to other consequences in the Americas: the abolition of the slave trade, the consolidation of nation states, the advance of agro-export economies, the growth of port cities and increased migration to these ports. This in turn aggravated the sanitation problems in these cities, where yellow fever was a serious threat precisely because it struck immigrants the hardest. At a time when virulent epidemics were the norm, a new social actor emerged: the microbe.

In December 1879, Domingos José Freire of the Rio de Janeiro School of Medicine announced his discovery of *Cryptococcus xanthogenicus*, and it was not long before he had developed a vaccine for yellow fever. João Batista de Lacerda, the long-serving director of the National Museum of Rio de Janeiro, claimed that *Fungus febris flavae* was the true agent of the disease. Meanwhile, in Mexico, Manoel Carmona y Valle developed another vaccine with *Peronospora luteum*. Juan Carlos Finlay identified *Micrococcus tetragenus* while he was using mosquitoes infected by yellow fever sufferers as live immunising agents. In the 1890s, bacilli were also considered possible causative agents of the disease, and curative serums were developed.³

The impact of Freire's vaccine was partly due to the proliferation of microbe hunters, medical and scientific associations and periodicals, colonial and commercial interests, in addition to Freire's zeal in fostering social alliances at a time when science was helping to transform Brazil's political and social structures.

Freire's vaccine

In 1883, the Central Board for Public Health authorised Freire to inoculate people with an attenuated form of *Criptococcus xantogenicus*. At first, the yellow fever vaccine was administered at the Instituto Vacínico, which was responsible for smallpox vaccination, but soon it was taken out to the *cortiços* (slums) and other working-class areas. In the late nineteenth century, Rio de Janeiro was the capital of an imperial slavocracy governed by Emperor Pedro II, and its economy depended on exports of agricultural commodities. Soon, a committee set up by the Imperial Academy of Medicine endorsed the opinion of Jules Rochard of the Academy of Science in Paris: vaccinations should be suspended since the immunity they conferred was still dubious. Nevertheless, vaccination continued, surrounded by controversies that involved an intricate web of personalities and institutions in Brazil and abroad. Britons J. H. Sutton and J. B. Harrison, Frenchmen Félix Le Dantec, Hyacinthe Vincent, Paul Gibier and Victor Cornil, Romanian Victor Babès, and American George Sternberg are a few of the experts involved in verifying the work conducted by Freire and other bacteriologists. All of them favoured their own microbes and ruled out those of the others.

In 1886, Freire presented his ideas at leading French scientific institutions in Paris with the assistance of Claude Rebougeon, a veterinary surgeon hired by the Brazilian government to introduce the animal smallpox vaccine to Brazil, and Paul Gibier from the Museum of Natural History in Paris.⁴ When Freire returned to Brazil in June 1887, he was acclaimed by delegations from different educational and health institutions and by republican and slavery abolitionist groups. Weeks later, he travelled to Washington to take part in the Ninth International Medical Congress, which drew attention to his vaccine among countries affected by yellow fever.⁵

In 1890, George Sternberg, President of the American Public Health Association, published damning conclusions about Freire's vaccine and other discoveries made in Central and South America.⁶ His conclusions were endorsed by the Pasteur Institute.⁷ This did not prevent the expansion of Freire's vaccine in Brazil, however, which was undergoing a transition from monarchic rule to republicanism, a period marked by political power struggles, rapid economic and demographic changes, and unprecedented devastation caused by yellow fever and other epidemics in Brazilian cities.

Initially, only the poor were given the vaccine, but soon other sectors of society began requesting inoculation, since there was growing scepticism about the drugs used to treat yellow fever patients and the plans to improve sanitation in Rio de Janeiro. After Freire's republican friends seized power in 1889, the Domingos Freire Institute was created, with functions similar to those conferred on the Bacteriology Institute of São Paulo, a state-run health department set up in 1891. These were the first institutional results of the impact of microbiology on Brazil's public health system.⁸

Carried by the abundant influx of migrants to Brazil after the abolition of slavery in May 1888, yellow fever spread to numerous inland towns, strengthening the assumption that it was caused by a microorganism that could travel by train or ship via people or objects. According to a source published in 1898, 13,000 people had been vaccinated by that point in the capital city and the states of Rio de Janeiro, Minas Gerais and São Paulo, and the vaccine had been used as far afield as the British and Spanish Caribbean and other European colonies.⁹

New contributions to yellow fever research by the Italian bacteriologist Giuseppe Sanarelli heightened the competition to discover the real

germ and the right cure. Sanarelli was invited to run the Institute for Experimental Hygiene, inaugurated in March 1896 in Montevideo, Uruguay. At a well-attended conference held at the Institute in June 1897, he announced the discovery of *Bacillus icteroides*. Months later, he started field tests with a curative serum in São Paulo.¹⁰ The Rio press begged the Brazilian government to determine whether the true agent of yellow fever had been discovered. Improving sanitation in the Brazilian capital was considered urgent, mostly in order to combat yellow fever, but the uncertainty surrounding the aetiology and prevention of the disease hampered the progress of the social forces interested in cleaning up the city.

Freire's vaccine and microbe fell into disuse after his death on 21 August 1899. The National Academy of Medicine¹¹ passed a motion to pay homage to him as a 'great servant of humanity', and in the very same session a new member of the academy was appointed: Oswaldo Gonçalves Cruz. Aged just 27 and recently returned from the Pasteur Institute in Paris, he had been put in charge by the federal government of a new laboratory on the Manguinhos farm on the outskirts of Rio de Janeiro, with the goal of manufacturing a serum and vaccine for bubonic plague. Under the leadership of Gonçalves Cruz, a change in the approach to yellow fever was about to propel a new generation of bacteriologists to the front line of public health in Brazil.

Sea change in the approach to yellow fever

Two events lie behind this change in approach: Cuban scientist Carlos Finlay's theory, proposed in 1880–81, that yellow fever was mosquito borne and transmitted by *Culex fasciatus*, a theory conclusively confirmed twenty years later by the US army Yellow Fever Commission headed by Walter Reed.¹² The Americans only conceded defeat to Finlay after occupying Cuba in 1898 and having to face their patent inability to deal with the disease there. Equally important was the presence on the island of Herbert Edward Durham and Walter Myers of the newly founded Liverpool School of Tropical Diseases. In June 1900, soon after Ronald Ross and the Italian team headed by Giovanni Grassi demonstrated that both bird and human malaria were transmitted by *Culex* and *Anopheles* mosquitoes, Durham and Myers travelled via Cuba to the Amazon region to investigate yellow

fever.¹³ Their hypothesis was that the disease was also transmitted by mosquitoes.

In August, soon after they left Cuba, American physician Jesse William Lazear, a colleague of Reed's on the Yellow Fever Commission, began experiments with mosquitoes supplied by Finlay, while his fellow researchers James Carrol and Aristides Agramonte continued work on what were by then high priority studies of the alleged yellow fever bacillus. In September, Lazear died after he was bitten by mosquitoes infected by yellow fever. Walter Reed hurriedly wrote a preliminary note and began a series of better controlled experiments to prove that the mosquito was the host of the yellow fever 'parasite', that the disease was not transmitted by air, and that fomites were not contagious.

In 1901, the Reed Commission presented its results, William Gorgas inaugurated a mosquito campaign in Havana, and entomologist Frederick Vincent Theobald of the British Museum included the *Culex* species associated with yellow fever in the new genus *Stegomyia*, as *S. fasciata*. The Reed Commission's findings were verified elsewhere; Rio de Janeiro was visited by researchers from Hamburg's Institute for Maritime and Tropical Diseases and, for longer stays, by members of the Pasteur Institute in Paris.¹⁴ The yellow fever campaigns organised by Oswaldo Cruz in Rio de Janeiro (1903–7) and Belém (1909), by Gorgas in Havana and Panama, and by the British and French in parts of West Africa were all based on the idea that the unknown yellow fever agent had only two hosts: humans and a single mosquito species, rechristened *Aedes aegypti* in the 1920s.

The Reed commission left unsolved the hypothesis that the yellow fever agent was a 'filterable virus', and analogies drawn between malaria and yellow fever prompted many researchers to believe it was protozoan. In 1905, Schaudinn and Hoffmann announced the discovery of the syphilis agent, *Spirochaeta pallida* (*Treponema pallidum*). *Spirochaetae* were then seen by some researchers as protozoa. Shortly before this discovery, Schaudinn¹⁵ formulated the hypothesis that a *Spirochaetae* small enough to pass through the finest bacteria filters was the cause of yellow fever. Three years later, Arthur Marston Stimson of the US Public Health Service found *Spirochaeta interrogans* in a victim of the disease. This theory gained much ground during the First World War, when Japanese bacteriologist Ryokichi Inada and his collaborators

named *S. icterohaemorrhagiae* the agent of Weil's disease, or haemorrhagic jaundice, known today as leptospirosis. In 1918, in Guayaquil, Ecuador, Hideyo Noguchi, a bacteriologist with the Rockefeller Institute, described a spirochete as the agent of yellow fever. He established a new genus, *Leptospira*, which encompassed both Inada's agent and this *Leptospira icteroides*, with which he developed a vaccine and a serum for yellow fever.¹⁶

The Rockefeller Foundation had decided, since 1914, to eradicate yellow fever using the key theory: they would destroy the breeding grounds for *Stegomyia fasciata*, but only in a few endemic centres along the coast, from which the disease was presumed to spread to inland settlements.¹⁷ The campaign began in Guayaquil in November 1918, and by 1922 the Rockefeller Foundation's International Health Board considered the east coast of South America virtually free of the disease. This left Brazil as the main endemic area in the hemisphere. The Foundation's sensitive negotiations with President Artur Bernardes (who was elected in 1922) regarding yellow fever intervention in Brazil were fuelled by an epidemic in the north-eastern part of the country. People there turned to the serum and vaccine produced in Noguchi's laboratory.¹⁸

On 1 May 1923, the Brazilian government authorised the National Department of Public Health to accept the cooperation of the International Health Board, despite heated patriotic objections to its intention to take over a field where Brazilian health experts had proven expertise.¹⁹ In November 1923, members of the Rockefeller Foundation's anti-yellow fever campaign team set sail from New York, accompanied by Noguchi, who would stay in Salvador, Bahia, until February 1924. Noguchi's intention was to demonstrate his discoveries to Brazilians so as to neutralise criticism voiced by well-known Cuban yellow fever specialists. In a letter to Frederick F. Russell, director general of the International Health Board, Henry Rose Carter assessed Noguchi's time in Brazil as an 'outright success'.²⁰ As one of the masterminds of the project to eradicate yellow fever worldwide, Carter had taken part in the mission headed by Gorgas in 1916 to map out key centres on the American continent. In the same letter, he wrote that: 'Noguchi showed consummate tact – and tact founded on good feeling – when he had the Brazilians find their own *Leptospirae*.'²¹ Russell endorsed this appraisal in a letter to Noguchi: 'Your success will help our yellow

fever campaign in Brazil more than anything else that could have happened.²²

New developments in the approach to yellow fever

In 1920, Juan Guiteras Gener, a collaborator of Finlay, succeeded Gorgas as the head of a Rockefeller Foundation commission entrusted with ascertaining whether the measures adopted against yellow fever in the Americas would be viable in West Africa. Studies in the region on *Leptospira icteroides* and attempts to identify authentic clinical cases of yellow fever met with failure. Doctors at the time firmly believed that black people were resistant to yellow fever. The stories that Guiteras heard in Africa and his own statistical inferences prompted him to draw a correlation between the low number of whites and the limited range of the disease, which he thought was dying out on the African continent. Since yellow fever had supposedly originated in the Americas, and since it was almost under control there, Guiteras assumed that it would also die out on the other side of the Atlantic.²³

In the early 1920s, Carter began investigating the origins of yellow fever, research which was published in book form posthumously.²⁴ Backed by an arsenal of historical documentation, Carter endorsed the theory defended by Brazilian Emilio Goeldi, former director of the Pará Museum of Natural History and Ethnography, according to which *Stegomyia fasciata*, and therefore yellow fever, were African in origin.²⁵

In 1925, a second Rockefeller Foundation commission, headed by Henry Beeuwkes, was sent to Lagos, Nigeria. For two years they examined many cases of yellow fever, but failed to isolate Noguchi's micro-organism or to establish a clear epidemiological profile of the disease. This fuelled suspicions that African yellow fever was different from its American counterpart.²⁶

In Africa, the colonial authorities often requested Noguchi's serum and vaccine. In 1926, his work began to be questioned by laboratories versed in the techniques of immunology. Two groups, one headed by Max Theiler and Andrew Watson Sellards and the other by Wilhelm Schüffner and Achmad Mochtar, noted that the reactions of *L. icteroides* and *L. icterohemorrhagiae* were identical.²⁷ This entailed a complex research programme. If *L. icteroides* did not cause yellow fever, that meant that cases of leptospirosis were being misdiagnosed, as

Rockefeller staff in the Americas were using Noguchi's theory to confirm what were frequently unclear diagnoses. At the same time, some specialists believed infectious jaundice to be the yellow fever of temperate zones, and in the opinion of Sellards,²⁸ the idea that the cycle of the yellow fever agent was confined to man and mosquito required serious scrutiny.

In May 1927, Beeuwkes had purchased some rhesus and crown monkeys from India and marmoset monkeys (saguís) from Brazil. He then set off for Lagos with Adrian Stokes, who had taken part in the first commission sent to Africa in 1920 and who was one of the first researchers in Europe to verify Inada's discoveries. In Kpeve, near Accra, they drew blood samples from patients with mild infections, one of whom was a 28-year-old African male named Asibi. Days later, monkeys and guinea pigs were inoculated with blood from groups of human cases, as it was hard to tell if any one individual had the disease. Some monkeys died, with changes suggestive of yellow fever. In a report dated 14 July 1927, the search narrowed: a rhesus monkey (*Macaca mulata*) inoculated with material from Asibi showed promising signs of the disease. However, there were still many unresolved issues on both sides of the equation. There were few reliable tools for diagnosing human yellow fever, especially mild cases, and very little was known about incubation of the virus in monkeys, whose normal and pathological histology was poorly understood. Furthermore, how could the few strains obtained be preserved? A whole new set of problems was raised by these microorganisms, invisible to the most powerful microscopes and only detectable in the lesions produced as they moved relentlessly from one organism to another.

The Americans and Britons collaborating with them needed a clear-cut human case affected by the virus. Human experimentation did indeed take place, but it was involuntary and dramatic: after accidentally becoming infected, Stokes died on 19 September 1927, an incident that promptly accelerated the pace of work. The following year, a preliminary note and then a more comprehensive article were published by Stokes (credited posthumously), Bauer and Hudson,²⁹ showing that the infection was transmitted from monkey to monkey and from monkey to man by blood injection or by *Aedes aegypti* bite. Bauer also reported on the transmission of yellow fever by three other mosquito species.³⁰

In November 1927, Noguchi disembarked in Accra. His observations took him in a totally different direction, which, if proven, would corroborate the idea that American and African yellow fever were in fact distinct but related diseases, like *Leptospira icteroides* and *icterohaemorrhagiae*. He was preparing to return to New York when he was hospitalised with yellow fever and died on 21 May 1928. William Alexander Young, director of the British hospital in Accra, did all he could to preserve evidence of Noguchi's work. Eight days later, however, he too died of yellow fever.³¹

Viral aetiology and a change of strategy

In that same ill-fated month of May 1927, Rio de Janeiro experienced the outbreak of an epidemic³² demolishing any hopes that it would be an easy task to eradicate yellow fever. The newly discovered evidence from West Africa inspired a flurry of experimental studies and intense exchanges of information among Europe, the Americas and Africa. In the 1920s, yet another characteristic of the virus, which was already linked to sixty-four other diseases, was identified: it depends on living cells to reproduce.³³ New biochemical techniques for manipulating viruses were being developed in the field of virology, which was then emerging from its Pasteurian cocoon.

Diagnosing yellow fever meant interpreting often misleading clinical signs or relying on observations of lesions after death. A new diagnostic technique came into widespread use after 1930, thanks to Max Theiler's discovery that when white mice received intracerebral inoculation, they died of encephalitis and suffered lesions to their central nervous system. In this culture medium new breeds of virus were obtained, with properties not observed in human or animal hosts. The retrospective diagnostic routine performed by hospital pathologists was replaced by a technique that could be used by non-specialised personnel in regions where dissecting corpses was a grievous sin. It involved the viscerotome, an instrument with a handle and blade that could be used to remove a fragment of liver from people who had died of suspect fevers. Viscerotomy posts were set up around Brazil, and systematic research began on the distribution of yellow fever immunity using mice, which revealed the problem to be much broader than imagined.³⁴

In 1930, Frederick Lowe Soper was put in charge of totally reorganising Brazil's yellow fever service, taking advantage of new techniques for visualising the disease and also of the revolution of 1930, which brought Getúlio Vargas to power³⁵ and led to a political environment that was more favourable to the vertical control of both vectors and humans. In order to eradicate *Aedes aegypti* completely, all buildings were numbered and inspected and urban areas were divided up so that one inspector could cover each area in one week. Inspection staff was now part of the service's strictly hierarchical structure for supervising both the population and the work of yellow fever service personnel.³⁶

Soper and his Brazilian collaborators³⁷ verified that in Latin American forests the virus was also transmitted by vectors other than *Aedes aegypti* and that it had other vertebrate hosts besides people. In those vast, sparsely inhabited regions, yellow fever attacked mostly adults who ventured into the jungle.³⁸ After it was noted that mosquitoes were abundant in the crowns of trees,³⁹ new collection methodologies made it possible to identify other species associated with the transmission of yellow fever – especially of the genus *Haemagogus* – and other arboviruses.⁴⁰ Protection tests, also used on wild animals, helped to identify the virus's vertebrate hosts, such as howler monkeys (genus *Alouata*).

Serological research on the African continent also led to a more precise definition of yellow fever's endemic zone. In addition to *Aedes aegypti*, at least sixteen species proved capable of transmitting the yellow fever virus there. The enzootic cycle in African tropical forests, from monkey to monkey, is sustained mainly by *Aedes africanus*.⁴¹

In the Americas, the last urban epidemic was reported in 1942, in Sena Madureira, Acre, until urban yellow fever reappeared in 2008 in San Lorenzo, Paraguay.⁴² However, the extensive presence of sylvatic (jungle) yellow fever – from Panama to Argentina and from Peru to Brazil – showed that it could adapt to a wide variety of ecologies.

By 1940, the Yellow Fever Service, now run solely by Brazilians, had succeeded in eliminating *Aedes aegypti* over wide stretches of Brazil. After DDT was introduced in 1947, the eradication programme was accelerated. The Pan American Health Organization (PAHO) approved a yellow fever eradication plan for the whole continent in October 1947, the year Soper became head of its executive agency, the Pan American Sanitary Bureau (PASB). Eleven years later, on 2 October 1958, the Fifteenth Pan American Sanitary Conference declared Brazil, the Canal

Zone, and nine additional countries (Belize, Bolivia, Ecuador, French Guiana, Nicaragua, Panama, Paraguay, Peru and Uruguay) free of the urban vector.⁴³

Progress towards a new vaccine

Sylvatic yellow fever made vaccine development imperative.⁴⁴ In 1928, Max Theiler and Andrew Sellards showed that an injection with serum and virus produced active immunity in monkeys, but serum vaccination was deemed risky after human testing in Rio de Janeiro and Bahia. In 1928–29, Edward Hindle in England and Henrique Aragão and Lemos Monteiro at the Oswaldo Cruz and Butantã Institutes in Brazil made a vaccine from monkey livers and spleens using chemical methods to attenuate the pathogen's virulence. Aragão's vaccine was administered to some 25,000 people in the Brazilian capital.

An alternative to using tissue from live animals materialised in 1931, when it was observed that several membranes of embryonated eggs were susceptible to infection by different viruses. As mentioned, encephalitis developed in white mice inoculated intracerebrally. The virus 'fixed' in this fashion behaved differently from the virus that provoked lesions in organs like the liver. After several passages through mouse brains, the 'neurotropic' virus lost its ability to cause visceral lesions in monkeys, although it still attacked the central nervous system. In 1931, immunisation experiments were conducted at the Rockefeller Institute for Medical Research in New York using the neurotropic virus combined with human immune serum. This vaccine was used to control infections in laboratories. The New York researchers had two goals: modifying the virus by changing the conditions under which it was cultured, so that the resultant strain would display fewer adverse effects and greater immunising power; and obtaining sera richer in antibodies – so-called hyperimmune sera – to better protect people from the risk of the vaccine itself.

In 1936, Lloyd, Theiler and Ricci successfully cultured a virus derived from Asibi, the African patient mentioned earlier, in embryonic mouse tissue. His blood had been injected into a rhesus monkey on 30 June 1927, and over the subsequent six-and-a-half years, the virus had passed through mosquitoes and other monkeys. The letters following the experiment numbers indicated the culture media being tested.

One route yielded 17D, from the same origin but modified through successive cultures in different media, until arriving at in vitro passage through embryonic chick tissue from which the central nervous system had been removed. Using subculture 214, many parallel series were begun, some in embryonated eggs. In 1937, the process yielded what Brazilians called the 'friendly' virus, which protected rhesus monkeys in subsequent inoculations with virulent material and no longer caused encephalitis when injected into their brains (although it still did so in mice).

In March 1937, a laboratory to produce the vaccine opened on the campus of the Oswaldo Cruz Institute. By the end of that year, in municipalities of Minas Gerais experiencing sylvatic yellow fever, 38,077 people were vaccinated. Another 49,000 received coverage during a single week in January 1938. The vaccine was used in Colombia, where production began in January 1939.⁴⁵ In 1938, in the south and southeast of Brazil, a wide-ranging sylvatic epidemic prompted the immunisation of 1,059,328 people, primarily in rural settlements.⁴⁶

The vaccine had to be kept at a low temperature, all the more complicated at a time when refrigerators were still rare. To ensure it had survived the trip, each vaccination unit used mice. The first dose from each vial was used for intracerebral inoculation of a group of mice, while the last dose was used on a second group, both of which were observed for twenty-one days. Ending up with an inactive virus or one with a low titre were not the only risks: the yellow fever virus killed mice after the third day.⁴⁷

The move from laboratory to large-scale vaccination was not seamless.⁴⁸ At the Oswaldo Cruz Institute laboratory, Hugh Smith and Henrique de Azevedo Penna made important changes to the technique developed in New York to boost vaccine yield. The virus was cultured in live chick embryos, in fertile eggs. On the fifth day, the embryos were extracted, minced and mixed with normal human serum, and filtered. In 1939, certain vaccine batches achieved an immunisation rate of only 20 per cent.⁴⁹ The vaccine's decreased antigenic strength was blamed on the many transfers of the virus. The maximum number of subcultures was then set at 255 and the minimum at 210.⁵⁰ Vaccination resumed but a new problem cropped up: catarrhal jaundice. A study among those vaccinated in Espírito Santo, Brazil, in 1939–40 identified 1,000 cases and twenty-two deaths.⁵¹ The technique was modified, eliminating the

human serum suspected of transmitting another virus, later identified as hepatitis B. In November 1940, vaccination resumed again with a new 17D strain, but the next year a third serious problem surfaced: cases of encephalitis among the immunised due to a mutation of the 'friendly' virus itself.⁵² The seed lot system was then introduced, later adopted worldwide in the manufacture of other vaccines.⁵³

The problems at the laboratory in Rio de Janeiro seemed to be under control, but not at the New York laboratory, which was still using human serum. It had to move quickly to large-scale production, and the change in technique would require a number of tests. Output was around 56,000 doses in January 1941 and nearly eight million by December, shortly after the USA entered the Second World War. Fearing a biological attack from Japan, in January 1942 the US government decided to vaccinate its entire army.⁵⁴ That March, over 28,000 cases of jaundice were detected among newly vaccinated soldiers in California, resulting in sixty-two deaths.⁵⁵ Later research with veterans showed that about 330,000 had been infected with hepatitis, the largest hepatitis epidemic recorded in the annals of public health.⁵⁶

The clinical studies performed in Brazil by USA and native specialists after immunisation with the vaccine manufactured on a large scale after 1937 were surprisingly sophisticated compared to those conducted previously for yellow fever vaccines (and maybe vaccines in general),⁵⁷ but historians have not yet fully investigated the reactions prompted by such widespread vaccination at this time. Angelo Moreira da Costa Lima, a researcher at the Oswaldo Cruz Institute, accused the Rockefeller Foundation of using Brazilians as human guinea pigs;⁵⁸ however, response to his criticism was limited. As part of a well-oiled vertical structure, vaccination teams mobilised the support of mayors, priests, physicians, pharmacists and large landowners in inland towns and farms before setting out to vaccinate local people, who were mostly rural workers subject to long-standing systems of oligarchic domination.⁵⁹ It seems that they were willing to receive the yellow fever vaccine, although it would be wise to procure more substantial evidence about consent procedures. Were local leaders and doctors also willing to be vaccinated? How did they behave when they heard about vaccination hazards? We should not forget that in 1904 there was a violent uprising against smallpox vaccination in the Brazilian capital.⁶⁰ Yellow fever vaccination, however, benefited from rural sanitation work

conducted in the 1930s to 1940s on behalf of vulnerable people. Yet there were often violent reactions to the viscerotomies conducted in inland parts of the country by physicians and laypersons, demonstrating a culture clash between the mentality and knowledge of coastal doctors and the outlook of rural Catholics, for whom death rites were extremely important.

In the 1950s, the Oswaldo Cruz Institute laboratory was meeting the yellow fever vaccine needs of South America and, less regularly, those of Africa, Europe and Asia. Although *Aedes aegypti* was eliminated from various parts of the continent, South America continued to be swept by outbreaks of sylvatic yellow fever. In 1967, *Aedes aegypti* re-emerged in northern Brazil (Pará) and gradually regained its initial territory. A network of viscerotomy posts was re-established in 1979 and a five-year vaccination cycle was implemented in regions exposed to sylvatic yellow fever⁶¹ aimed at people drawn to the Amazon and west-central Brazil thanks to huge settlement, mining and public works projects. The seriousness of the threat was underscored when American actor Jason Robards caught yellow fever while filming *Fitzcarraldo* with director Werner Herzog in the Amazon rainforest.⁶² Warning that the disease could re-urbanise, a number of specialists argued that a continental response to the resurgence of *Aedes aegypti* was needed.

The reinfestation of Brazilian cities produced not the feared urban yellow fever but Brazil's first dengue outbreak, which occurred in the northern state of Roraima in 1982. Dengue fever had emerged as an imminent danger with the Cuban epidemics of 1977 and 1981. It became a chronic problem in many Brazilian cities and has been an important research field for entomologists and public health workers since. (As I put the final touches on this chapter, Chikungunya and Zika viruses, transmitted by the same mosquito, emerge as new threat in Brazil.)

Waves of yellow fever in endemic areas in the Afro-American belt and fear of an epidemic in, thus far, unaffected areas of the Far East led to an international symposium in Belém, Brazil, in April 1980, to review aspects of the disease in the light of virology, molecular biology and genetics.⁶³ The Rio de Janeiro laboratory produced 80 per cent of the world's output of the yellow fever vaccine. The following sections examine its relationship to other vaccines in the context of

transformations in global health, Brazilian society, and in the institution that is still Brazil's main vaccine producer.

The Oswaldo Cruz Foundation and immunisation programmes

The laboratory established by the city of Rio de Janeiro in 1900 to manufacture bubonic plague serum and vaccine became the Oswaldo Cruz Institute (IOC) in 1908, primarily in recognition of the successful campaign against yellow fever that Cruz had led in the city, then capital of Brazil. Work at the Institute expanded on three fronts: biological products manufacture, research and teaching. Research carried out into human, animal, and to a lesser extent plant diseases fostered relationships with clients and research communities, reinforcing the Institute's social network. The expansion of frontiers also had geopolitical implications, as it did for the institutes operating in European colonies.

Hired by railway companies, hydroelectric power plants, agricultural and livestock raising enterprises, and extractive industries, Oswaldo Cruz Institute researchers journeyed through the Brazilian hinterlands to study and combat diseases such as malaria. They encountered pathologies about which little or nothing was known, along with biological material that greatly broadened the horizons of tropical medicine in Brazil. The 1909 discovery of Chagas disease – the next human trypanosomiasis to be identified after sleeping sickness – turned protozoology and entomology into central research areas at the Institute. Between the two world wars, it manufactured over thirty products; these largely obviated the need to import immunotherapeutics.⁶⁴

In 1970, during the harshest period of the military regime that took power in 1964, the Oswaldo Cruz Institute was reorganised as the Oswaldo Cruz Foundation (Fiocruz).⁶⁵ At this time, modern fermentation methods developed after the Second World War had still not been implemented at the Foundation. With the exception of yellow fever and smallpox vaccines, which were essential for public health, its other products were of dubious quality and did not address the preventable diseases on the agenda of international health organisations.

In the 1960s and 1970s, there were some important synergies between yellow fever and smallpox vaccines. Sixty-four laboratories worldwide, including the foundation named after Oswaldo Cruz, were certified to manufacture the millions of doses required every year for

the global campaign, launched in 1967 and ended ten years later. Henrique de Azevedo Penna, who was responsible for the yellow fever vaccine at the Institute, put one of his assistants in charge of modernising the smallpox vaccine, which until then had been produced using live calves, a technique employed since the nineteenth century. Thomas Milton Rivers had made smallpox vaccines in embryonated eggs in the USA, though he failed to obtain good levels of immunity. Penna began culturing the smallpox virus in one membrane of embryonated eggs, without making the mistake of subjecting the virus to more than five passages.⁶⁶ Both processes coexisted until the end of the smallpox campaign, which was eradicated from Brazil in 1971.

The campaign boosted confidence in the potential of immunisation programmes to eliminate transmittable diseases. In 1968, while student and workers' movements shook major cities in Brazil and elsewhere, the PAHO held a seminar in Montevideo to discuss why vaccination programmes were obtaining such limited results in the Americas. The problems highlighted included poor planning and decision-making and badly inactivated, preserved and distributed vaccines produced using outdated processes.⁶⁷

In September 1973, Brazil launched its National Immunisation Programme, aimed at controlling measles, tuberculosis, diphtheria, tetanus, pertussis (whooping cough) and polio.⁶⁸ In May 1974, the Expanded Programme on Immunization (EPI) was approved by the World Health Assembly, with the aim of reducing morbidity and mortality rates related to these six diseases, and stimulating national and regional self-sufficiency in vaccine production and quality control. Of great importance to the programmes launched at this time was the PAHO's Revolving Fund, created in 1977. Through the joint procurement of vaccination supplies, which meant larger volumes and therefore improved bargaining power with suppliers, the fund effectively enabled drastic price reductions and improved quality.⁶⁹ The percentage of vaccination coverage for the selected diseases rose considerably and the programme began to target the eradication of polio, measles and neonatal tetanus.⁷⁰

In the 1970s, there was a growing gap in Brazil between public health, which came under the aegis of the Ministry of Health, and individual health care, which was within the jurisdiction of the welfare system. Health became big business, a trend that went hand in hand with the

underfunding of public services.⁷¹ Indicators pointed to a decline in the living standard of those who did not share the benefits of economic growth. The gross domestic product was growing at over 10 per cent a year.⁷² Economic policy prioritised durable consumer goods, energy, and transport and communication industries, combining foreign borrowing, tax breaks for major national and foreign investors, wage squeezes, and political and trade union repression. There was a marked concentration of wealth, the public sector and state companies expanded, family and subsistence farming declined, and export-oriented agribusiness flourished. Huge numbers of rural workers migrated to the poverty-stricken outskirts of big cities or to the major worksites and colonisation projects designed to expand land occupation in the Amazon and central-west region.

The Geisel administration (1974–79) launched the Second National Development Plan containing measures designed to strengthen the nation's scientific resources and bring more technology to Brazil, rather than just foreign capital. But by the late 1970s, the signs of economic decline, which would shortly worsen, were already discernible. Foreign debt was growing out of control, inflation started spiralling and industrial growth declined. At the beginning of 1974, a serious meningitis epidemic erupted involving both type C and type A of the *Neisseria meningitidis* bacteria. The Ministry of Health decided to vaccinate everyone in Brazil, something that not even the smallpox campaign had achieved. The vaccine Brazil needed was produced by the Mérieux Institute in France. In March 1975, air shuttle service between the Mérieux factory in Marcy-l'Étoile and Brazil began. In São Paulo, 700 teams vaccinated ten million people in just five days. 'Hundreds of volunteers ... with these new needleless syringes ... vaccinate, so to speak, *à tour de bras* ... men, women and children ... The efficacy of the organisation set up by the Brazilians is outstanding!' Charles Mérieux declared.⁷³

A new lease of life for the Oswaldo Cruz Foundation

On 5 August 1975, while the campaign against meningitis was underway, President Geisel announced the revival of the Oswaldo Cruz Foundation. The primary objective was to modernise vaccine production through technology transfer. Fiocruz vaccines were produced by a

few researchers in laboratories in different buildings of the former Oswaldo Cruz Institute. The only ones delivered on an industrial scale were for smallpox and yellow fever. The yellow fever laboratory formed the core of a new production centre, and Vinícius da Fonseca, the new president of Fiocruz (1975–79), took advantage of the meningitis outbreak to obtain resources, allies and up-to-date technologies.

Brazil's massive orders of the meningitis vaccine helped to convince Charles Mérieux to donate what was required for Brazil to become self-sufficient in a fermentation technique that could be used for other bacterial vaccines. This project was related to global processes that had a major impact on the strategies and organisations of public institutions and businesses in the chemical, pharmaceuticals and biotechnology industry, and on disease prevention policies adopted by states and international health agencies.⁷⁴

In Chapter 6 of this book, Blume analyses how the public and private vaccine production industries in Europe and the USA changed in the 1970s in response to multiple factors: the advent of new biotechnologies; the imposition of intellectual property rights; increased technical difficulties and economic costs incurred in production; increasingly strict surveillance and standardisation of the use of vaccines; and the risk of side effects and related financial consequences. Many companies decided to leave the vaccine market, while others joined via mergers and other market concentration processes.

Under pressure from the French state to scale up its operations, the Pasteur Institute in Paris – the original model for the Oswaldo Cruz Foundation – created the Institut Pasteur Production in 1973.⁷⁵ Three years later, a partnership was cemented with Sanofi, a pharmaceuticals subsidiary of Elf-Aquitaine, a French state-owned petrochemicals company. The negotiations divided Institut Pasteur Production into two: one area for vaccines (Pasteur Vaccins) and another for diagnosis reagents (Diagnostics Pasteur).⁷⁶ In 1985, Pasteur Vaccins merged with the Mérieux Institute, which had sold part of its shares to Rhône-Poulenc, one of the largest chemical and pharmaceutical companies in France.⁷⁷

Mérieux saw investment in Fiocruz as part of a plan to expand activities on animal and human vaccines around Latin America with his partner, Rhône-Poulenc. In 1975, a contract for the donation of equipment and technical services was signed between the Mérieux and

Oswaldo Cruz foundations, with a view to creating a pilot plant for bivalent meningococcal vaccines at Fiocruz. The plant was opened in June 1976, one month after the restructuring of Fiocruz, with the creation of Bio-Manguinhos to produce vaccines and other biological products, and Far-Manguinhos for chemotherapeutics. Akira Homma, a Brazilian veterinarian working at Bayer in Germany, was hired as director of Bio-Manguinhos. In 1977, still within the ambit of the French-Brazilian cooperation agreement, a Centre for Medical Virology was set up at the Oswaldo Cruz Institute (since 1970 one of Fiocruz's key units).

General João Batista Figueiredo (1979–84) became Brazil's last military president in a period marked by severe economic crisis and the crumbling of the authoritarian regime. With recessive economic policies and rising oil prices, the 1980s came to be known as the 'lost decade' for Brazil. This did not prevent the physical restructuring and intellectual repopulation of Fiocruz. The newly established areas of immunology, biochemistry and molecular biology enhanced its expertise in vaccine and drug innovation.

New alliances took shape between the Brazilian Ministry of Mines and Energy and Japan, which had an interest in Brazil's mineral resources; though no less important was the fact that Akira Homma, director of Bio-Manguinhos, was of Japanese descent. He would later run the Ministry of Health's National Programme for Self-Sufficiency in Immunological Products. Between 1980 and 1984, the Japanese government invested around five million dollars in Fiocruz, supplied equipment, and trained technical staff from Bio-Manguinhos, who subsequently set up the measles vaccine laboratory.⁷⁸ The transfer of technology for the Sabin polio vaccine was also covered by the agreement with Japan. This effort helped to control the disease in Brazil. Almost 92,000 vaccination stations were set up for the programme, mostly in schools, and 320,000 workers were involved, most of whom were volunteers. On 12 December 1994, Brazil received a certificate from the WHO attesting to the elimination of wild poliovirus (the last case on the continent was in 1991 in Peru).

For the large-scale immunisation programmes to work, epidemiological surveillance and vaccine quality control had to be improved. In 1981, the National Institute for Quality Control in Health (INCQS), the largest entity of its kind in Latin America, was inaugurated at

Fiocruz.⁷⁹ When it failed samples of DPT produced by Syntex, the US multinational stopped production of immunological products in Brazil in reprisal. The closure of other laboratories exacerbated the shortage of vaccines and serums in the country.⁸⁰ Stricter quality control, the vaccine sector's lack of funding even in developed countries, the formation of monopsonies like the PAHO's Revolving Fund, Unicef's public tenders, and centralised procurement by the Brazilian government discouraged investment by big international laboratories in the local production of vaccines. An added factor were the huge claims filed against vaccine laboratories in wealthy countries by victims of adverse vaccine events. In this context, Brazil launched its Programme for National Self-Sufficiency in Immunological Products, aimed at modernising the country's public laboratories.⁸¹

In Chapter 7, Blume studies the Dutch and Swedish response to similar circumstances, which was to privatise their public laboratories. Meanwhile, Carrillo's analysis of the Mexican case shows it to have much in common with Brazil. In Mexico, the state had produced and regulated the use of immunological products since the late nineteenth century. In 1977–78, all of the Mexican public institutes and laboratories that produced vaccines and reagents were merged into a single government entity, the Dirección General de Producción de Biológicos y Reactivos, which became the country's sole producer of such products. With this move, Carrillo says, Mexico became self-sufficient in the field, and by the end of the 1980s was exporting biological products to several Central and South American countries. It lost this self-sufficiency, however, after the government decided to privatise the industry, resulting in the creation in 1999 of Laboratorios de Biológicos y Reactivos de México (Biomex), albeit maintaining a majority shareholding. I now examine how these broader processes interfered with the production and distribution of the yellow fever vaccine in Brazil.

Changes in the vaccine and in yellow fever control tactics

At the international symposium in Belém in 1980, one of the problems discussed was the lack of thermal stability in the yellow fever vaccine, which made distribution dependent on a chain of often impracticable low temperature conditions. Obsolete equipment also hampered larger-scale production. The vaccine consisted of a virus attenuated in chick

embryo juice, and medical literature showed that eggs provoke allergic reactions. Moreover, it had been found that yellow fever vaccines manufactured in Brazil and other countries were contaminated with viruses of the avian leukosis group.⁸² The approval of a programme to modernise yellow fever vaccines⁸³ coincided with Bio-Manguinhos' cooperation agreement with the Japanese. The yellow fever laboratory received more sophisticated equipment, facilities, and protocols, boosting its production capacity four-fold. A stabiliser was developed for the vaccine based on the measles vaccine technology.⁸⁴ Replacement of embryonated eggs with *in vitro* cell culture was attempted,⁸⁵ but the inoculant consumption was very high and the cost prohibitive: a seed lot, which could feed production in embryonated eggs for ten years, would be exhausted in cell culture in less than one year.⁸⁶

Bio-Manguinhos' most important partner in this innovative endeavour was Canada's International Development Research Centre. Both institutions took part in the modernisation of Nigeria's production laboratory at the height of an epidemic crisis. Fears about the potential urbanisation of yellow fever were rekindled by a new wave of sylvatic yellow fever in Brazil. The number of reported cases rose from three in 1997 to eighty-five in 2000, though we know this is but the tip of the iceberg, with actual mortality rates about 50 per cent higher than reported cases. In the long-standing competition between strategies to combat the urban vector versus vaccination, the second method won out this time. In 1994, the yellow fever vaccine was adopted by Brazil's National Immunisation Programme. Four years later, routine vaccination of children became part of the Expanded Immunisation Programme. Vaccination grew over 600 per cent, soaring from 2,587,788 doses in 1996 to 16,125,871 in 1999.⁸⁷

On 16 October 1999, a 5-year-old girl from Goiânia, Brazil, died days after receiving a dose administered along with the MMR vaccine. Four months later, on 27 February 2000, a 22-year-old woman died in Americana eleven days after being vaccinated with the yellow fever antigen alone. An international committee of experts analysed the two incidents. Passive surveillance of adverse events, introduced in 1998, had recorded 244 incidents, most not serious, out of 34,693,189 doses administered through to March 2000.⁸⁸ Two more deaths were identified during retrospective searches. According to Ricardo Galler of the Oswaldo Cruz Foundation, if a selection mechanism had favoured

replication of a mutant virus in the vaccine suspension, there would be no way to account for its lethal effect in only two individuals. It was the result of processes triggered after inoculation and linked to the vaccinal virus's interaction with as yet unknown organic peculiarities in the individuals.⁸⁹ The expert committee ruled that universal vaccination was no longer advisable but that the risk–benefit equation justified continued vaccination in risk areas, as long as a new protocol was designed for the surveillance of adverse events.⁹⁰

On 23 February 2001, sylvatic yellow fever was confirmed near Belo Horizonte, the capital of Minas Gerais, leaving fifteen dead. Some three million doses of the vaccine were administered in the Belo Horizonte region. On 18 March, another death was linked to the vaccine. Other subsamples of the 17D strain had similar tragic consequences. Up to the present, news of adverse vaccination effects continues to emerge, alongside alarming reports of sylvatic yellow fever close to Latin American cities. Deaths by the disease occurring in early 2008 in San Lorenzo, Paraguay, show that urban yellow fever remains a potential threat.

Post-vaccination accidents have also lent urgency to attempts to clarify the mechanisms of viral virulence and the immune response of the invaded organism.⁹¹ It is known that both the viscerotropism of the wild virus and the neurotropism of the attenuated virus are connected to the intrinsic or genetic properties of both the virus and the vertebrate host. There appear to be some differences between the South American and African types, although their precise nature is unclear. Furthermore, we now have evidence that human immunological response to the disease can be modified by prior exposure to other flaviviruses such as dengue. This cross-protection is actually one of the explanations for the surprising fact that yellow fever has not yet invaded the cities of the Americas.

Bio-Manguinhos is still the world's largest producer of the yellow fever vaccine, but critical changes are about to happen in production techniques based on different approaches still under development. One is infectious clone technology that makes it possible to manipulate the genome of the vaccine virus and engineer mutants capable of expressing heterologous antigens in humans, thereby triggering an immune reaction against more than one disease.⁹² Adverse events associated with the live virus explain the current preference for vaccines made of inactivated virus. A vaccine developed by Monath's team, based on

chemical methods, is now undergoing clinical trial,⁹³ while the vaccine developed at the Oswaldo Cruz Foundation using the Vero cell method and inactivation through high hydrostatic pressure is still in the pre-clinical phase.⁹⁴

In January 2011, Bio-Manguinhos, the Fraunhofer Center for Molecular Biotechnology, and the US company iBio Inc. began another innovative process. The gene that encodes the main protein of the yellow fever virus, which is responsible for inducing an organism's immune response, is being introduced into leaf cells from *Nicotiana benthamina*, a tobacco species. As the plant develops, its leaves produce large amounts of the antigen that can be used in the vaccine. If this biofactory is successful, vaccine production will no longer require special embryonated eggs. These are, however, questions of great complexity that should be dealt with in a separate article.

Conclusion

Domingos Freire's vaccine came at a time when the production of scientific facts was still associated more with individuals than institutions. It was an important catalyst for the reception of Pasteurian medicine in Brazil. At the time, the vaccine was of great symbolic significance, bolstering the dual movements of slavery abolition and republicanism with the power of science. Although the vaccine was presented as a potential redeemer of the nation from the 'slavery' of yellow fever, it never supplanted the sanitisation projects in urban areas, least of all in Rio de Janeiro, then the capital city, where a major urban renewal project was implemented, paralleling Oswaldo Cruz's campaign against yellow fever (1903–7).

At the end of the period of monarchy (1808–89) and in the early republican years known as the First Republic (1889–1930), the Brazilian state was patriarchal, oligarchic, and mercantile, fostered by a society dominated by large-scale export agriculture and mercantile groups. The ruling classes were marked by a patrimonial bureaucracy which, while paying lip service to the ideas of scientific progress, actually demonstrated conservative attitudes and a dependency on the economic and cultural domination of the major world powers. Throughout this period, Britain, France, Germany, and the USA vied for supremacy over Brazil, with the USA finally prevailing in the interwar years. Vaccines and

serums helped propel the institutionalisation of microbiology and tropical medicine in south-eastern Brazil, where the country's economic and political power was concentrated. This process was due not least to the efforts of actors and groups who managed to counteract state inertia. Of all the biomedical institutions created at the turn of the twentieth century, it was the one named after Oswaldo Cruz in Rio de Janeiro that took the lead. The yellow fever campaign was crucial for the Institute's capacity to overcome resistance from the oligarchs and trade groups that controlled the state and gain the support of the public and key opinion-forming groups in the country.

Hideyo Noguchi's vaccine and serum were produced in a far more integrated, interdependent global context, where scientific data was disseminated by teams of researchers and institutions subject to state policies and by international health organisations. Noguchi's vaccine and serum never stopped being a backup tool for the campaigns launched in the Americas and Africa, waged in the belief that yellow fever was transmitted by a single vector to just one vertebrate host in a few identifiable key centres. The history of leptospirosis as a globally acknowledged health problem was largely separate from the history of the disintegration of Noguchi's theory of yellow fever. His serum and vaccine seem to have been used most widely in Africa, where the vector eradication campaign did not take off as it did in the Americas. Despite the vast apparatus set in motion by the International Health Board on both sides of the Atlantic, there does not seem to have been much difference between the artisanal production methods for Noguchi's and Freire's immunological products. Both left the scene on the eve of a sea change in the approach to yellow fever.

Beginning in 1928, the development of a new vaccine, the only weapon possible against sylvatic yellow fever, required more complex production processes involving laboratories and specialists from the fields of microbiology, biochemistry, virology, and immunology. Successive vaccines were given to increasingly large numbers of people, surpassing one million by 1938.

The creators of the viral vaccines continued to test their products hastily on humans. Nevertheless, the clinical studies and observations performed by USA and Brazilian specialists in response to cases of low immunity or encephalitis and jaundice after immunisation with the vaccine manufactured after 1937 were very sophisticated. Obviously,

the control procedures were far from ideal if we take as a benchmark the standards adopted after the Second World War for research ethics and human experimentation.

The 1930 revolution marked the beginning of a period of national developmentalism that prevailed until the 1980s. Throughout successive periods of authoritarian and democratic political rule, industrialisation grew apace, while the state adopted a successful strategy of national development derived from a strong alliance between the industrial bourgeoisie and the state apparatus.

Developmentalist economic policies mostly benefited urban groups who were protected by labour laws and the increasingly comprehensive health care and welfare system. The main target of the yellow fever vaccine was rural populations, and it became an important component of national agencies tackling endemic diseases in the interior. Mediating the relationship between city and countryside, the vaccine was valuable in the expansion of internal frontiers, a process symbolised by the inauguration of the new capital city, Brasília, on 21 April 1960 during the administration of Juscelino Kubitschek (1956–61). It was during this period that the elimination of *Aedes aegypti* from Brazil and other countries in the Americas was also announced. The yellow fever vaccine was an important facilitator of the large-scale enterprises in agriculture, livestock farming, mining, energy, and infrastructure that were pursued after the 1964 coup d'état.

The yellow fever laboratory served as a cornerstone for important transformations in other vaccines at Fiocruz, which is still the largest supplier in the country and a key player in the health policies adopted since the creation of Brazil's Unified Health Service (SUS), a sort of national health system, an outcome of the new 'Citizen's Constitution' passed in 1988, in which health care was defined as a right of citizens and a duty of the state.

The vaccines and therapeutic agents produced by Fiocruz explain to a large extent the strategic role it plays in SUS. Its future depends on successful connections between these industrial activities and on the ability of Fiocruz research areas to respond to the challenges of innovation in the increasingly competitive world of Big Science, which commands astronomical budgets, increasingly complex national and international networks and teams, and equipment, techniques, and laboratories that must be constantly upgraded. Although new types of

vaccines are on the horizon, not least for parasitic diseases, the procedures involved are increasingly complex and new paradigms are emerging at the interface between technical/scientific and socio-economic issues concerning yellow fever and other diseases, involving vaccinology, molecular biology, genetics, entomology, ecology, and public health.

Notes

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