From Bombay to Rio de Janeiro: the circulation of knowledge and the establishment of the Manguinhos laboratory, 1894-1902

SILVA, Matheus Alves Duarte da. From Bombay to Rio de Janeiro: the circulation of knowledge and the establishment of the Manguinhos laboratory, 1894-1902. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v.25, n.3, jul.-set. 2018. Available at: <http://www.scielo.br/hcsm>.

Abstract

In order to understand the 1900 establishment of the Federal Serum Therapy Institute of Manguinhos and its earliest scientific work, we must analyze the circulation of knowledge and international disputes surrounding antiplague serums and vaccines. This article discusses the development of the first antiplague serum, in Paris, and the trials conducted in India, which started in 1897. It also examines the invention of an antiplague vaccine in Bombay around the same time and the ensuing controversy involving it and the French serum. The article then explores the pathways by which these objects reached Brazil and also looks at how local issues there meshed with the international scientific dispute, ultimately justifying reconfigurations of the two objects in Rio de Janeiro.

Keywords: bacteriology; Pasteur Institute of Paris; Federal Serum Therapy Institute; antiplague serum; antiplague vaccine.

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Received on 12 Jun. 2017.
Approved on 25 Sep. 2017.

Translated by Diane Grosklaus Whitty.

http://dx.doi.org/10.1590/S0104-59702018000400003

India, August 1898. In a lengthy letter, Paul-Louis Simond (1858-1947), a French physician sent to Bombay to test the Pasteur Institute's antiplague serum, informed Émile Roux (1853-1933), vice-director of the Pasteur laboratory, of the conclusion reached by his mission: "It seems to me that, to return to India, it is necessary either that the [British] government asks you for serum or that you are certain that great progress has been made in the [curative] value of the serum" (Simond, 31 ago. 1898).[1] In the next paragraph, Simond laid out the reasons for his caution: "I told you that the [British] administration [in India] is headed towards failure. It has adopted two supposedly scientific methods to combat the plague: Haffkine's preparation [vaccine] and Lustig's serum" (31 ago. 1898).

Two years later, a similar controversy would arise in Rio de Janeiro, pitting different antiplague serums and the modified Haffkine vaccine against each other. The discussion there centered on the efficacy of the antiplague serums and vaccines, how to produce them, and whether they could be used concomitantly. The backdrop of this controversy was the Federal Serum Therapy Institute (Instituto Soroterápico Federal, ISF), which had recently opened at Manguinhos. The primary goal of the present article is to analyze the circulation of knowledge about antiplague serums and vaccines and attendant controversies, moving from Bombay to Rio de Janeiro.

In recent decades, the establishment of the ISF has been a recurring subject of interest in discussions of the history of science in Brazil. Nancy Stepan (1976, p.70)[2] reports that when the plague first appeared in Brazil, in October 1899, the municipality of Rio de Janeiro, then the federal capital, "decided ... to establish a small laboratory where vaccines and serums against plague could be produced at small cost." She summed up the history of the products to be made there with these words: "by 1896, an antiplague vaccine had been developed by Haffkine, and by 1898[3] Yersin employed the first antiplague serums ... By 1900, control of bubonic plague was possible through the use of vaccines, serums, and the elimination of the rat" (p.68). There are a number of problems with Stepan's analysis: it does not mention any disagreements about different antiplague serums; it presents these serums and vaccines as complementary; and it does not question the efficacy of any of them, leading the reader to infer that the antiplague serums and vaccines produced at the ISF were precisely the same as those made a few years earlier by Yersin and Haffkine and, further, that Brazil opted to make these particular products simply because they had proven efficient.

In a comparative study of the history of the Federal Serum Therapy and Butantan institutes, Benchimol and Teixeira (1993, p.13-14) write that, at the outset of the plague epidemic in Brazil, in the port of Santos, "public health authorities faced the challenge of obtaining curative serum, which only the Pasteur Institute in Paris manufactured for export, but not in large enough quantities to meet world demand. Anticipating the inevitable, the São Paulo state government and the municipality of the Federal District decided to establish their own facilities for the production of antiplague serums and vaccines." The authors go on to explain that the role of the two laboratories was, theoretically, "to import ready techniques and knowledge to defeat a public health crisis" (p.14). Yet, as we learned in the quotation from Simond, knowledge regarding antiplague vaccine and serums was not "ready" in 1898. Would the products be ready a few months later?

In a more recent study on Oswaldo Cruz and the ISF, Henrique Cukierman (2007, note 7, p.81-82), writing in a note, casts doubt on the efficacy of the antiplague serum at the moment the disease reached Brazil. However, Cukierman does not enter into an analysis of the historicity of the product, and so he states, in part reproducing the discourse of the figures who were involved in fighting the disease in Brazil, "if there is plague, the construction of local antiplague serum facilities will be wholly justified" (p.50). This author was also one of the first to identify a possible dispute between antiplague serum and vaccine in Brazil. But he devotes little space to this controversy in his discussion and ultimately aligns with those who favored the serum; as to the vaccine, he states that "some had reached a consensus about serum therapy as far as its less troublesome and most reliable results" (note 9, p.83). Cukierman goes on to write that "when we refer to the serum factories, it is implied that we are referring to the less controversial and most noted product of the serum 'and' vaccine factories" (note 9, p.83; emphasis in the original). However, there was nothing straightforward about the preparation of serum "and" antiplague vaccine, nor was there any consensus about antiplague serum therapy.

In his analysis of a controversy surrounding the antiplague serum made at Manguinhos, Jorge Augusto Carreta (2011) takes the matter of the product's efficacy further, for example, pointing to the doubts expressed by Brazilian doctors in 1899 about methods for making and administering the serum (p.687) and, later, how accidents with the Manguinhos serum raised concerns about its efficacy (p.690-691). However, since Carreta's study looks only at this laboratory, it is unclear whether these problems derived from inadequate adaptation of the technique by the Brazilians or from the curative power of the antiplague serum itself.

In short, these earlier studies viewed the two products made by the ISF at Manguinhos, that is, antiplague serum and antiplague vaccine, as finished products upon their arrival in Brazil. The present article interrogates this position through an analysis of the history of antiplague serum and antiplague vaccine from the moment of their conception through their large-scale production in Rio de Janeiro; it tracks the two products as well as the people and knowledge that circulated with them and observes the transnational construction of knowledge about both. As employed here, the concept of circulation does not focus merely on the movement of an idea, practice, person, or scientific object but primarily on the changes and reconfigurations that transpire during this process. As theorized by Kapil Raj (2013, p.343; emphasis in the original): "by circulation we understand not the 'dissemination,' 'transmission,' or 'communication' of ideas, but the processes of encounter, power and resistance, negotiation, and reconfiguration that occur in cross-cultural interaction." Further according to Raj (p.344), the concept of circulation "suggests a more open flow and especially the possibility of mutations and reconfigurations."[4] Grounded in this frame of reference, I intend to show that: (1) in 1899, there was not just one antiplague serum but rather a number of them; (2) the efficacy of both the antiplague serum and vaccine was then a matter of controversy; (3) the two products were not necessarily complementary; and (4) in public health terms, there were disagreements over the concomitant use of the two products in Rio de Janeiro, and the solution devised by the ISF involved the reconfiguration of knowledge produced in different places.

The article is divided into two parts. The first, covering 1896 to 1899, focuses on the encounter in Bombay between Pasteur Institute staff members, on the one hand, and Alessandro Lustig (1857-1937) and Waldemar Haffkine (1860-1930), on the other, and on the emerging controversy over different antiplague serums and vaccines. The second part analyzes the early years of the ISF (1900-1902) in order to ascertain which serums and vaccines reached Brazil, how this circulation occurred, and how the products were made in Rio de Janeiro. My analysis has been based on some of the private documents of the French researchers who were sent to India, such as letters, field notebooks, and scientific papers, along with documents by Lustig and Haffkine. In examining the Brazilian context, I have highlighted both the work of Camillo Terni (1863-1934), one of the scientists behind circulation of the antiplague vaccine in Rio de Janeiro, as well as Oswaldo Cruz's scientific correspondence and the early research and work conducted by the ISF.

Antiplague vaccine and serums in India

Alexandre Yersin (1863-1943) arrived in Bombay on March 5, 1897 (Yersin, 6 mar. 1897). Born in Switzerland, Yersin worked as an assistant at the Pasteur Institute but left the Paris laboratory in 1890 to serve as a physician in the French colony of Indochina (Mollaret, Brossollet, 1993, p.97). While based there, in 1894 he was commissioned by the French government to investigate the appearance of the bubonic plague in Hong Kong, where he would identify its bacillus.[5] During his stay, he cultured plague microbes that were shipped to Paris for further research (Yersin, 1894). One year later, working with other researchers, Yersin published a paper about the first experiments with antiplague vaccine and serum in *Annales de l'Institut Pasteur* (Yersin, Calmette, Borrel, 1895). The antiplague vaccine had been produced using a new technique, in which bacteria were heated to a temperature of 50°C prior to inoculation in guinea pigs. The results of the animal trials did not seem very promising, since the vaccine often times weakened and killed the animals. Given these findings, the vaccine was eventually abandoned (p.590-591). The authors went on to describe their attempts to make antiplague serum using new techniques that had been developed for preparing antidiphtheria serum: several weeks after a horse was inoculated with live bubonic plague cultures, some of its blood was drawn to make serum. The remedy had proven promising since it both cured and immunized guinea pigs; in other words, it acted as a vaccine, in a process known as serum-vaccination (p.591-592).

At that point, the preparation of antiplague serum was thus following the steps of antidiphtheria serum. Launched in 1894 in Germany and France, the drive to develop an antidiphtheria serum met with swift success, as discussed in recent studies; it represented a milestone in the history of bacteriology as a shift from preventive medicine based on vaccines to curative medicine based on serums (Gradmann, 2008, p.151). Moreover, this new development suggested that serum therapy could be generalized to the treatment of other diseases (Gachelin, 2007, p.52). The relatively rapid stabilization of antidiphtheria serum can in part be attributed to the fact that there were large numbers of patients in European hospitals and it was easy to conduct human trials (Gachelin, 2010). However, French researchers faced a different challenge when it came to antiplague serum: although

the bubonic plague presented a threat, it was not found in Europe, meaning the same tests could not be conducted there and it was impossible to determine whether the serum that cured guinea pigs could also cure humans. In consideration of this, Yersin returned to Indochina, where the threat of the disease was real; he founded a laboratory in the city of Nha Trang and began making antiplague serum. In 1896, a plague epidemic broke out in Guangzhou, China, which is where Yersin (1896, p.195-196) conducted his first human trials of the remedy, curing 24 of 26 cases. Following news of these successful tests, the city of Bombay invited Yersin to administer his preparation among the thousands of people struck with bubonic plague there starting in September 1896 (Ministère..., 1896-1898).[6]

When Yersin got off the train in Bombay, however, he was not carrying "the" antiplague serum in his baggage but rather two types of serums. The first of these, which had been used in Guangzhou, was referred to as the old serum; the new serum was made in both Paris and Indochina. While the old serum relied on live cultures, the new one was prepared from dead cultures, that is, cultures that had been destroyed by heat. The change was made because the horses died much more frequently when inoculated with active plague bacilli (Yersin, 1897, p.366-367). Yersin rapidly detected a second difference between the two products: the new serum displayed a higher mortality rate than the previously tested one. During the first series of trials conducted in Bombay, in which Yersin employed the old serum made at his laboratory in Nha Trang, 19 of the 57 treated people passed away, yielding a mortality rate of 38% (Yersin, mar. 1897). Yersin was apparently excited by these numbers, since he told his mother that "the obtained results were good and will be even better when we have a more active serum" (Yersin, 19 mar. 1897). During the second series of trials (Yersin, abr. 1897), using the new serum produced in Nha Trang, Yersin's hopes were not confirmed; 13 of 19 people died, leading him to state that "this serum produced no results, it did not have the slightest antitoxic effect; this is due to the current procedure for immunizing horses in Nha Trang, which is not good; I believe the horses in Paris were immunized using another procedure and that they provide a good serum" (Yersin, 15 abr. 1897). In a letter to Émile Roux, Yersin (24 abr. 1897) exhibited greater caution than he had in his confident remarks to his mother: "if you do not have a more active serum, I believe that in the interest of serum therapy in India, the experiment should be suspended and only resumed under very good conditions." Taken together, the results of the three series of trials, including new testing conducted with the Paris serum,[7] differed from the findings in China, given that the overall mortality rate reached 50%. An analysis of the numbers found in Yersin's letters to his mother and in his field notebook indicates that he did not doubt the serum's curative power, instead attributing the discrepant results to the limited availability of the preparation, to patients' advanced stage of illness, and, in the case of the serum sent from Paris, to the need to stabilize it, since it was not yet "active enough" (Yersin, 30 abr. 1897).

During the three months he spent in India, Yersin not only tested the serum's curative power but also used it as a vaccine capable of immunizing people against the plague. As he explained to Roux, serum-vaccination was a way to make use of the serum sent from Paris; since it was "necessary to inject high doses of it [to obtain a cure], which is not practical," he believed "it would be better to use it preventively" (Yersin, 24 abr. 1897). But when Yersin began administering the serum-vaccine, he and Haffkine came into conflict.

Waldemar Mordecai Haffkine was born in Odessa, in what was then the Russian Empire. There he obtained a degree in zoology and worked with Elie Metchnikoff. For political and religious reasons, he went into exile in France, where, thanks to his former professor, he began working as a librarian at the Pasteur Institute. Yersin was at that time an assistant at the Paris laboratory, where he and Roux were conducting research on diphtheria. When Yersin left for Indochina the first time, in 1890, Haffkine took over his duties at the laboratory (Kumar, 1999, p.241-245). In 1893, Haffkine also headed to Asia, specifically to India, where he tested the cholera vaccine he had developed in Paris (p.245-246). Since Haffkine was based in the country, the British authorities sent him to Bombay in 1896 to ascertain whether the disease then sweeping the city was the bubonic plague and, if so, find some way to contain it. After Haffkine (1903, p.1-10) officially detected the disease, he developed a vaccine that was used on a broad scale throughout India starting in January 1897.[8] Grounded partially on his previous cholera research, Haffkine's preparation was an effort to combine in one vaccine bacilli killed by heat and the toxin they secreted in the culture media (Haffkine, 1897).

The description found in Haffkine's biography might lead us to believe that he would be a logical choice as Yersin's intermediary in Bombay, since the two were old acquaintances from the Pasteur Institute. However, in a paper on the serum experiments in India, Yersin voiced harsh criticisms of Haffkine's vaccine. He said it was dangerous because it caused fever and intense pain and could hasten the death of patients who were incubating the disease; furthermore, the immunity it offered was very short-lasting. Given these problems, he recommended immunization with antiplague serum (Yersin, 1897, p.370-371). As Yersin saw it, antiplague serum and Haffkine's vaccine were thus not complementary, and the French product should be used for both curing and preventing the plague. Haffkine saw things the other way around. According to the Russian, at the time that the French serum was being used in India, the city of Bombay asked him to test Yersin's serum. After reaching conclusions "of an entirely negative character" about the curative power of the antiplague serum, Haffkine (1903, p.20) declared that the product did not work and that the vaccine developed by him should be the prime tool for controlling the bubonic plague in India.

Biographers of both scientists have described this dispute, but only from one side or the other.[9] In his study of Haffkine, Selman Waksman (1964, p.47) contends that Yersin's critique of the Russian researcher stemmed from the latter's conclusion that the results of the Pasteur Institute team could not be confirmed. Mollaret and Brossolet (1993), in their study on Yersin, assert that the controversy sprang essentially from the fact that Yersin believed Haffkine's vaccine was merely a copy of the one developed and then abandoned by the Pasteur Institute in 1895; thus, he felt it unfair for the Russian to claim to have invented it. While this argument may be correct as far as the stance taken by Yersin, both authors are ignoring Haffkine's later efforts to prove he was the true inventor of the antiplague vaccine.[10]

In my interpretation, Haffkine and Yersin's conflict in India involved both scientific and social issues. On the one hand, their disagreement had to do with the dual-purpose nature of the French antiplague serum, which both cured and prevented; the vaccine might

relegate the serum to a purely curative role, which Haffkine also questioned. Haffkine's vaccine thus presented a challenge to the institutional politics of the Pasteur Institute, which, as a private company, earned part of its funds selling products like antidiphtheria serum (Hess, 2008); the institute hoped to do the same with antiplague serum, not only in India but primarily if the disease were to reach Europe (Roux, 20 out. 1897). To a lesser extent, Yersin's preference for the French serum can be seen as deriving from two factors: he considered himself the inventor of the product and he was the director of the Nha Trang laboratory, whose main purpose was to make this serum. In Haffkine's case, professional success was likewise entwined with the fate of the developed product, since he received some tenuous support from the British government to maintain his laboratory for the manufacture of antiplague vaccine.

The construction of knowledge about the bubonic plague and competition over how to control and cure the disease entered a new phase when Yersin was replaced by Paul-Louis Simond, who arrived in India in June 1897 and stayed until August 1898. One of the earliest letters that Roux (20 out. 1897) mailed to his former student set the tone for Simond's mission: "The plague will last in India, so we must take advantage of it, not to conduct large-scale treatment, because we do not have enough serum, but to conduct 'successive tests with various types of serums'" (emphasis added). In other words, the goal was not to cure the people of India but to stabilize the Pasteur Institute serum vis-à-vis other remedies, which would only be possible through human trials. When Roux mentioned diverse types of serums, he was referring to the way horses were immunized in Paris, that is, using dead or live cultures and, in the latter case, microbes of varying degrees of virulence.

Recent studies on antidiphtheria serum, which have been concentrated in France and Germany, have examined extensive efforts to standardize its manufacture, the role of the social groups involved in the process (Hess, 2008), and some of the limitations encountered, since, as stated by Simon (2008, p.195), "the horses were not reliable machines or even standardized animal." However, the situation was more complex in the case of antiplague serum, since it was not a matter of standardizing a process for making a remedy known or believed to be efficacious, unlike the serum against diphtheria. In India between 1897 and 1898, the French were looking to determine which of the different techniques for making antiplague serum would yield a product that could cure plague victims. In Simond's research, the range of antiplague serums made at the Pasteur Institute yielded different findings, and more disappointing results were often obtained through serum therapy than when patients were treated with other remedies. Referring to experiments conducted from June 1897 through February 1898, Simond (1897-1899, p.37) justified the diversity of the findings in his field notebook:

> 340 plague sufferers were treated by me or under my direction. ... The proportion of cures within the entire set of these cases was 42%, to wit, 58% mortality. But we cannot draw any conclusions whatsoever from these general numbers because they refer to patients from all social categories, the serum was most often administered on the 3rd or 4th day,[11] and 'the serums that were employed displayed variable activity' (emphasis added).

Meanwhile, British physicians were reaching conclusions about the French serum. They claimed that it could not cure and that Yersin had probably forged part of the data published on serum therapy in China. As Simond (24 maio 1898) wrote to Roux, this criticism was starting to spread, and certain British public health authorities threatened to block further testing of the French serum, prompting Simond to conclude that "if we return to Karachi when the [disease] resurges, probably next March [1899], we will either have to engage in open warfare with the British physicians holding public health power or beg them to let us work in government hospitals" (Simond, 31 ago. 1898).

Simond's issues were not limited to criticisms by the British. When he reached India, other international missions were also arriving in Bombay to study the disease (Condon, 1900, p.371).[12] An Italian mission, for example, was led by Allesandro Lustig, who, together with Gino Galeotti (1867-1921), had developed an antiplague serum at the University of Florence's Institute of Experimental Pathology; it was tested in India beginning on June 12, 1897 (Lustig, 1899, p.12). The two Italian physicians stayed there until September 1897, and Galeotti returned with a new supply in March of the following year. From March to June 1898, the serum was tested on 175 ailing people in Bombay and achieved a cure rate of 42%, exactly the same as that obtained using the Pasteur Institute serum around the same time (Galeotti, Polverini, 1898; Lustig, Galeotti, 1901, p.206-208). But the Italians used a different method to prepare the serum. According to Lustig and Galeotti (1897, p.1.027), in a paper published in the *British Medical Journal*, Yersin's technique was "slow, and sometimes dangerous for the animals," and so they proposed that before immunizing the horses, the bacteria should be dissolved in a caustic potassium solution to destroy the microbes. Hydrochloric acid would then be added, causing precipitation and the formation of a powdered substance. According to the authors, it was this substance, with its "nucleo-proteids," that was injected in the horses; they claimed it was safer and easier to dose.

Although Simond (31 ago. 1898) failed to determine which of the various techniques used to make antiplague serum in Paris were the most efficacious, at the end of his mission he stated categorically that Lustig's serum was "worthless." But the British authorities did not agree and decided to support production of Lustig's serum. With funding from the municipality of Bombay, Galeotti and another Italian physician, Giovanni Polverini, set up a laboratory in the city in October 1898, where they made antiplague serum using the techniques developed in Florence (Galeotti, 1899, p.1). As to the French serum, Bhalchandra Krishna (1898, p.1), president of the medical society at Grant College in Bombay, effectively summarized how Yersin's and Simond's stay in India was perceived, writing in November 1898:

> Europeans *savants*, either individually or in deputations, on behalf of their respective Governments visited Bombay during the last two years, and certainly contributed in a large measure to the general knowledge of the disease; but it is also certain that no help whatever has yet been obtained from those important studies, either in the combatting of the disease generally or in its treatment. An intense and deeply sympathetic interest was excited by the arrival of Dr. Yersin, of the Pasteur Institute in Paris, who came with the object of giving a trial to his curative remedy for plague. ... The results of the trials given to it here in Bombay are known to all of you.

This disappointment would soon contaminate the view of Lustig and Galeotti's serum as well. In late 1898, following a fatal accident in Vienna, Italy temporarily banned research with the bubonic plague bacillus; the Municipal Laboratory in Bombay consequently became the sole producer of the serum. Treatment with the serum produced by the Italians in Bombay began on February 1, 1899; by May 31, 218 tests had been conducted, with a cure rate of 34% (Polverini, 1899, p.4). Polverini explained this difference and justified the investment by the municipality of Bombay; as he saw it, the product made in India employed the same techniques as in Florence and the discrepancy in results could be attributed to local factors. He wrote:

> It may be due to the increased virulence of the disease in 1899, and to the confidence with which the most desperate cases were subjected to the treatment by Dr. Choksy, the Medical Superintendent of the Arthur Road Hospital; or it may be explained by the fact that the horses have been bled only twice, as there are strong reasons to believe that the serum improves with every bleeding. The race of the horses and the climatic conditions in India might also lessen the resistance of the animals to the immunizing injections, and impair their faculty to produce the substance which is the curative agent of the serum (Polverini, 1899, p.4).

The discussion surrounding these differing results sparked a debate over what could be considered an efficacious antiplague serum. According to Polverini (1899, p.20), expecting a total cure would be "an exaggeration which could only have been indulged in by those who were ignorant of the clinical features of plague." Taking this into account, plus the fact that 20% of all cases eventually recovered thanks solely to ordinary treatment, Polverini suggested that the goal should be a 50% cure rate, at least until the antiplague serum could be deemed a finished product. If this criterion of efficacy were accepted, stated Polverini (p.20), one could argue that the Bombay serum was headed in the right direction.

Circulation and reconfigurations in Rio de Janeiro

It was within this international scientific context, marked by uncertainties regarding the preparation of antiplague serums and their efficacy along with questions about whether they should be used concomitantly with antiplague vaccine, that the first cases of the bubonic plague were identified in Brazil, in the port of Santos, in October 1899. That same month, Baron Pedro Affonso (1845-1920), owner of the Municipal Vaccination Institute (Instituto Vacínico Municipal), invited Oswaldo Cruz (1872-1917), a physician who had recently returned from a stay at the Pasteur Institute in Paris, to work with him with the goal of making antiplague serum at a new laboratory in the federal capital (Franco, 20 out. 1899).

However, as I have argued here, there was more than one method for preparing antiplague serum. A fine illustration of this fact is found in the letters exchanged by Cruz and Alexandre Besredka (1870-1940), one of the researchers who continued to work with the plague in Paris after 1898. Unfortunately, we do not know what questions were posed by Cruz, but they can be inferred from Besredka's replies. In a letter dated December 30, 1899, Besredka stated:

> I have little to add to what you already know thanks to recent publications on the method for preparing antiplague serum. The matter of plague toxins is still being studied, and so far it has not moved beyond the realm of laboratory research, and it should be said that up to this point, we have not made much practical use of it. The best serum, as you know very well, is the one obtained with live cultures ... In the next issue of the *Annales* [*de l'Institut Pasteur*] ... you will find the paper by Calmette and Salimbeni on the plague in Porto [Portugal]. There you will find very valuable information on antiplague serum therapy.

Besredka's reply was probably not the most encouraging if Cruz was only interested in replicating knowledge produced by the Pasteur Institute, since he indicated that there were different ways of preparing the serum and that there was uncertainty surrounding the issue of toxins. The reply probably also piqued Cruz's curiosity about the paper by Albert Calmette (1863-1933) and what it might have to add about serum therapy. When Cruz most likely read the article some days later, he must have realized that it contradicted Besredka to some extent, since the best serum, according to Calmette, was not serum produced by inoculating horses only with live culture but by inoculating them with a mixture of live and dead cultures. This modification was based on experiments performed by Yersin and Simond in India, which showed that serum made solely from dead cultures was "not active enough to treat the disease" (Calmette, Salimbeni, 1899, p.867). Further along in the paper, Cruz would be informed that the serum produced via this new method had been used to treat 142 people in Porto, with a mortality rate of 14%; he would also read that over 600 other people had been serum-vaccinated and that the ensuing immunity did not last more than 15 days (p.903). At the end of the article, Cruz would learn that Calmette had tested Haffkine's vaccine on animals and found some "drawbacks;" in addition to causing fever, as well as pain at the injection site, the vaccine could hasten and intensify the disease in animals that were incubating the plague. The article proposed a technique for addressing these drawbacks; this method had not been tested on humans and was not laid out in the text, but it would involve mixing antiplague serum with the vaccine (p.905).

At the time that this article was published in France, Camillo Terni, an Italian physician and director of the Bacteriological Institute of Messina, was disembarking in Brazil to study the bubonic plague under commission to the government of his country; there he stayed until September 1900. In January 1900, he was one of those responsible for confirming the first case of plague in Rio de Janeiro (Terni, Gomes, Franco, 1900, p.42-43). During the following months, he conducted research at a laboratory ceded by the General Directorship of Public Health (Diretoria Geral de Saúde Pública, DGSP), located at Paula Cândido Hospital in the Jurujuba Beach neighborhood in the city of Niterói, a facility where suspected and confirmed cases of the plague were received and isolated (Guimarães, 20 abr. 1900, p.1).

An article released in the journal *Brasil Médico* in May 1900 featured a lecture given by Terni on April 15 at the National Academy of Medicine (Academia Nacional de Medicina) in Rio de Janeiro. Terni began his talk by presenting his method for preparing antiplague vaccine, which had originally been described in a paper published in Italy in October 1899 (Terni, Bandi, 1899). He sought to convince his Brazilian audience of its efficacy (Terni, 1900). According to Terni, Haffkine's process was slow and immunization generally occurred

only 12 days after inoculation (Terni, 1900, p.145). To address these problems, he proposed that instead of culturing the bacillus in test tubes, as Haffkine did, it should be injected into the peritoneal cavity of guinea pigs, which would develop peritonitis in a few hours. The animals would be sacrificed within 48 hours, and the bacteria that were drawn from the peritoneum would undergo fractional sterilization over a period of two days (p.145). Based on trials conducted with animals and humans, Terni held that his vaccine offered the advantages of "being much more active than Haffkine's. . .so much so that it [could] be inoculated in smaller amounts and [would] display a much faster vaccinating effect," usually between the 4th and 5th days (p.146).

The second part of Terni's lecture focused on antiplague serum. Beginning with an examination of Yersin's technique, Terni (1900, p.147) stated that this method of "immunization, which is too slow because its material is not very active, causes serious suffering in the animals (horses), due not to the action of the proteids and toxins in the plague germ but to the action of all the other pyrogenic products that the germ generates in the culture medium and which are foreign to the infectious process of the plague bacillus." In regard to Lustig's technique, Terni said that "the same drawbacks are found ... while the results, in terms of serum quality, are inarguably greater" (p.147). In view of these problems, he proposed a third method, which consisted of inoculating the animals with Terni-Haffkine antiplague vaccine to prompt immunity and permit subsequent inoculation with live cultures. Yet he admitted that "the results obtained so far with serum therapy against such a serious and insidious illness as the plague are still too meager to encourage enthusiasm" (p.148). Farther on, he concluded that, "with current methods, it is not possible to obtain ... a serum with great curative power" (p.152). If the curative power of the serum was not a cause for excitement, its prophylactic effect was "not very practical," leading Terni to conclude that serum-vaccination could "not yet offer positive results like vaccination" (p.151).

This lecture can be viewed, on the one hand, as the intersection and reconfiguration in Rio de Janeiro of different types of knowledge about the prevention and cure of the plague, knowledge that had been produced in different places. Terni inverted the proposals of Yersin, Simond, and Calmette, ranking Haffkine's vaccine – as modified by him – as the chief weapon for containing the plague, thereby negating any possibility that serum could be used as an immunizer. Yet he had a more nuanced view than Haffkine, who felt antiplague serum had no curative value. According to Terni, it did have curative value and could be refined, as long as his preparation method, which differed from the methods used by the Pasteur Institute and by Lustig, were adopted. This is in fact what happened in Rio de Janeiro. During the epidemic of 1900, two serums were employed in the federal capital: the one imported from Paris and Terni's, in part brought from Italy and in part made at the laboratory in Jurujuba (DGSP, 1904, p.24).

On the other hand, Terni's presence in Brazil represented a problem for the project of the two serum therapy institutes, both in Rio de Janeiro and São Paulo. After reading Terni's harsh criticisms of the antiplague serum, especially the French model, Vital Brazil (1865-1950), director of the São Paulo institute, wrote to Cruz: "How can one reconcile the illustrious professor's disbelief in serum therapy for the plague with the enthusiasm that

leads him to advocate his process of immunization and rank it above the others?" (Brazil, 5 jun. 1900). To which Cruz replied: "There is tremendous enthusiasm here: everyone has accepted the communicated facts without discussion or critique. Our colleagues sing praises, and vaccinations are occurring on a broad scale! They are also happier than we are, as the St. Thomas's of science" (Cruz, 14 jun. 1900).[13] Cruz had the opportunity to come face-to-face with the Italian a few days later, at a session of the 4th National Congress of Surgery and Medicine, held in Rio de Janeiro. Terni, who was in attendance, heard Cruz make the following remark: "To judge from the conclusions of [Albert] Calmette, [antiplague] vaccination is dangerous during the period of an epidemic, because it has been observed that inoculating animals with the vaccine makes the recipient sensitive to the plague. The reference is to Haffkine's vaccine, the only one about which he deems himself able to speak" (Congresso..., 24 jun. 1900, p.1). Terni's reply was immediate: "The vaccine is offered as a preventive measure, therefore implying that the individual receiving it is not infected" (p.1).

This disagreement with Terni prompted Cruz to once again turn to his friend Besredka, in Paris, for information. Unlike on the previous occasion, however, Besredka (13 nov. 1900) could not help him: "Unfortunately, I do not have any information that might be of use to you, simply because we do not prepare lymph [plague vaccine] at the Institute, we make only [antiplague] serum." But this reply arrived a bit late. On July 31, 1900, Cruz, who weeks earlier had been a critic of the antiplague vaccine, initiated the first experiments aimed at making the vaccine at the newly established ISF. The inauguration of antiplague vaccine research at Manguinhos was in fact possible thanks to Terni, since vials of vaccine that he had made in Jurujuba were shipped to the ISF. During the first months, Cruz (31 jul.-31 dez. 1900) and his assistants studied this and other techniques for making antiplague vaccine. They studied antiplague serum at the same time, and the various vaccines were used to immunize horses, a process partly in keeping with Terni's recommendations. On October 30, 1900, the first vials of antiplague vaccine prepared at Manguinhos were delivered to the General Directorship of Public Health (Cruz, 31 jul.-31 dez. 1900). This would be Manguinhos's only product until February 1901, when it began to deliver antiplague serum (Cruz, 27 fev. 1901).

From 1900 to 1902, antiplague vaccine was produced at two places in Rio de Janeiro. At the Bacteriological Laboratory of the General Directorship of Public Health, Antonio Alves Guimarães, who had worked with Terni in Jurujuba, prepared the vaccine according to the Italian's technique; by end 1901, around 20,000 people in Rio de Janeiro had been inoculated with this vaccine (Aragão, 1902, p.17-18, 24-25). Terni's vaccine was also produced for a short time at Manguinhos, but it was then replaced by another, created there based on the proposals for modifying Haffkine's vaccine that had been presented by the German Commission in India.[14] The Germans had suggested using a solid culture medium, agar, and inoculating only with bacterial bodies. According to Cruz (1901, p.445), this approach was better because it enabled: "(1) Vaccine inoculation solely with dead microbial bodies, free of other inert, foreign elements; (2) The possibility of achieving rigorous dosing; (3) Speed and safety in preparation." However, Cruz also felt that the Germans had not codified these changes, something that would be done at Manguinhos.[15]

Terni's vaccine, on the other hand, was criticized for a number of reasons. When guinea pigs were inoculated at Manguinhos, immunity appeared between the 10th and 12th days and not the 4th or 5th day, as Terni had stated. Furthermore, dosing was hard, since pus and epithelial cells came mixed in with the fluid removed from the peritoneal cavities of the guinea pigs. Lastly, the process was expensive because it required one guinea pig to be sacrificed for every 50 to 60cc of immunizing fluid produced (Cruz, 1901, p.444-445).

These criticisms of Terni's vaccine also meant rejecting his serum, since the two were connected. According to Antônio Cardoso Fontes (1903, p.55), assistant to Oswaldo Cruz, the process for making antiplague serum adopted in Rio de Janeiro began with inoculation with an emulsion of sterilized cultures, partially relying on the techniques used to make antiplague vaccine there. This step was followed by the gradual administration of increasingly virulent live cultures.[16] In general lines, Manguinhos relied on the reconfiguration devised at the Pasteur Institute after the failed mission to India. However, the French laboratory had not released detailed information on its new approach, forcing staff at Manguinhos to establish their own standards, both for the virulence of plague cultures and for the periods when inoculation and bleedings should take place (Vasconcellos, 1909, p.15-16). As mentioned earlier in the case of antidiphtheria serum, the effort to achieve standardization at Manguinhos was at times stymied because it was impossible to standardize the horses, which died as a result of the plague injections (Fontes, 1903, p.57-58).

The great innovation introduced by the ISF[17] was to make both antiplague serum and antiplague vaccine in one same laboratory, contrasting with the procedure in Bombay and Pais, the two main locations for knowledge production on the plague. The Brazilian institute's simultaneous production of both remedies would translate into the vaccination policy defended by Cruz. Yet even though he had created a new vaccine, Cruz would still criticize its efficacy, raising concerns similar to those posed by Pasteur Institute staff members in India. Accordingly, Cruz (1901, p.465), in the instructions accompanying the Manguinhos vaccine, advised that "in epidemic periods, the procedure should be to immunize using vaccine serum, injecting from 2 to 5cc of antiplague serum simultaneously with the appropriate vaccine dose." This technique was not the same as simple serum-vaccination as previously advocated by the French but called for the concomitant application of serum and vaccine for the purposes of immunization. The argument behind this combined use was the fact that the vaccine afforded immunity only after the 8th day, while the serum offered instant albeit short-lived immunity (Fontes, 1903, p.29-30).

However, as I have argued from the beginning, simultaneous production of antiplague serum and vaccine at Manguinhos was not something simple and should be understood, firstly, as an extension of what Terni had proposed and put in practice in Jurujuba. Secondly, by making both products at Manguinhos, Cruz was in a way acknowledging lowered expectations about the serum's prophylactic power, as Pasteur Institute staff members themselves, after the mission to India, admitted that the immunity it afforded did not last long. In the third place, in asserting that the serum could offset the vaccine's deleterious effects, Cruz was both lending new import to the product at a time when there was no consensus about its curative power and also reaffirming the ISF's prime goal. By modifying and producing antiplague vaccine at Manguinhos and linking it with

antiplague serum, Cruz was actually taking two positions. In terms of the local context, he was positioning himself against Terni, showing that the latter's vaccine was not efficacious and that, accordingly, neither was his serum. In terms of the international context, Cruz was conveying the idea that the antiplague vaccine, as an object, was useful yet dangerous, and should thus be administered in conjunction with antiplague serum.

Final considerations

By tracing the history of the production of antiplague vaccine and serum in Rio de Janeiro, starting from the experiences in India, we have been able to rethink the establishment of the Federal Serum Therapy Institute. As we saw in the first part of this article, the British authorities in Bombay adopted the following policy for controlling the bubonic plague: the Pasteur Institute serum was rejected and Lustig's serum was made locally; at the same time, Haffkine's vaccine was administered on a broad scale but not in association with the serum. More specifically, the present analysis of the French mission in India has helped us understand subsequent changes to the Pasteur Institute's antiplague serum, related to preparation technique, immunizing effect, and even to the reigning image of its efficacy. At the same time, we saw that the French believed that Haffkine's vaccine was dangerous and should not be used to contain a bubonic plague epidemic, and these arguments would initially be advanced in Brazil to justify rejection of the product. Lastly, this analysis of the Bombay debates over the various serums and antiplague vaccine has shed light on the global panorama of competition in efforts to cure and prevent the plague, where the Federal Serum Therapy Institute took part.

Considering the scenario that played out in India, it cannot be argued that the decision to make antiplague serum in Brazil was based merely on the efficacy of the Pasteur Institute's product, because this would mean ignoring the attendant uncertainties and the range of existing serums. The Brazilian decision becomes clearer if, on the other hand, we bear in mind Polverini's and others' discussion over the role of antiplague serums as remedies that might save a relevant percentage of plague victims and if we also allow for the prospect that antiplague serum therapy might be stabilized and refined. Therefore, when analyzing the establishment of the Manguinhos Laboratory, we must take the global context of plague serum therapy into account.

The making of the first products at Manguinhos was also contingent on local considerations and on interactions between this laboratory and knowledge produced in various parts of the world. As shown in the second part of this article, while Lustig's serum never reached Rio de Janeiro, another antiplague serum, Terni's, competed with the French model until 1901. Yet Terni's presence in the Brazilian federal capital held even greater significance. An awareness of his challenge to the project spearheaded by Oswaldo Cruz – first questioning the value of antiplague serum therapy and then the French model of serum – is essential to understanding the earliest steps that were taken by the ISF. As we have seen, the first product made there was a modified antiplague vaccine, which can be interpreted as a response to Terni's success in Rio de Janeiro. Furthermore, production of this vaccine by the ISF occasioned the most important reconfiguration of knowledge on the

bubonic plague to be produced at Manguinhos in these early years, that is, the preparation and concomitant application of antiplague serum and vaccine. Yet this reconfiguration must be understood as having resolved a local controversy within a larger international dispute. In short, the intersection of this international scientific context – crystalized in Bombay but with ramifications in France and Italy – with issues encountered in Rio de Janeiro is another element to be born in mind when writing the history of Manguinhos.

ACKNOWLEDGEMENTS

The author wishes to thank Daniel Demellier, archivist at the Pasteur Institute in Paris, for help with sources; the anonymous peer reviewers and editors for their suggestions and critiques; and Kapil Raj, Dominique Pestre, Daniel Dutra, and Marcella Souza for their comments during both research and writing. He is especially grateful to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes) for funding his full doctoral studies abroad (Processo: 99999.001241/2015-00), of which this article is a product.

NOTES

[1] In this and other citations of texts from non-English languages, a free translation has been provided.

[2] This and other citations in English of Stepan (1976) were sourced from Stepan, *Beginnings of Brazilian science: Oswaldo Cruz, medical research and policy (1890-1920)*, New York: Science History Publications, 1981.

[3] In point of fact, the Pasteur Institute's antiplague serum was first tested on humans in 1896 (Yersin, 1896).

[4] For an in-depth discussion of the concept of the circulation of knowledge, see also Raj (2007), especially pages 225 and 226. For an analysis of transnational approaches in the history of science, the dialogue between this field and other historiographic agendas, and a critique of the idea of circulation, see Fan (2012, p.251-253).

[5] There was to be a dispute over credit for this discovery with Japanese researcher Shibasaburo Kitasato. On this controversy, see Howard-Jones (1975).

[6] There is an extensive bibliography on bubonic plague epidemics in India at the close of the nineteenth century. For an analysis of the demographic impact of the disease and ensuing social tensions, see Klein (1988). For a discussion centered on the clash between the colonial state and European medicine, on the one hand, and the colonized, on the other, see Arnold (1993). For a critique of this interpretation and a study of physicians in India who practiced Western medicine, see Mukharji (2011). For a comparative study of the epidemic in Bombay and public health measures employed there vis-à-vis other infected ports, see Echenberg (2007). In addition to this research, we can also cite Chakrabarti (2012), who, in an exploration of the institutionalization of bacteriology in India, examines the testing of antiplague serums and vaccines in Bombay, although the period of analysis is later than the one explored in this article.

[7] The serum sent from Paris was tested on 71 people and the cure rate was 45% (Yersin, maio 1897).

[8] In August 1899, the British government established the Plague Research Laboratory (PRL) to produce antiplague vaccine; it was directed by Haffkine. Prior to then, Haffkine's laboratory had been located at different addresses and had been supported primarily by Aga Khan, political and religious leader of the Khojas. For a chronology of the foundation of the laboratory, see Condon (1900, cap.3).

[9] In an article on Haffkine's work in India, Kumar (1999) describes the disputes between him and certain British physicians, primarily regarding standardization of the vaccine. However, the text makes no mention of the controversy between the French and Haffkine.

[10] Haffkine and other members of the PRL were to argue that he was the inventor of the vaccine, not only because he had created the product but also because he had developed a way to detect its purity by observing the appearance of stalactite-like shapes in the culture broth (Haffkine, 1897; Condon, 1900; Bannerman, 1904). In point of fact, this information is missing from the 1895 paper by Pasteur Institute staff members.

[11] With this comment, Simond meant to argue that the patients were virtually terminal upon arrival, but the British accused both him and Yersin of actually preferring to treat these patients because an individual who had survived until the 4th day had better chances of recovering, with or without the help of serum, and this would boost product statistics.

[12] By 1900, official missions had been dispatched from Egypt; the Austro-Hungarian, Russian, and German empires; Italy; and Ceylon (Condon, 1900, p.371).

[13] An analysis of these letters can also be found in Cukierman (2007, p.78-79), although his conclusions differ from those reached here.

[14] Terni's vaccine was produced at the Butantan Institute for a time and was then replaced by the process developed at Manguinhos (Fontes, 1903, p.54).

[15] This vaccine was described by Henrique Vasconcellos (1922, p.58), Oswaldo Cruz's colleague, as "the first bacteriological product made according to all techniques in Brazil. The inception of scientific bacteriology in our land inarguably dates to this occasion."

[16] Immunization with dead and live cultures was also adopted in the early years of the Butantan Institute. In March 1903, however, Vital Brazil (cited in Fontes, 1903, p.51) advised that he was testing another process, which consisted of "starting straightaway with the injection of live germs sensitized by specific serum." In 1905, Manguinhos abandoned the step of inoculation with dead cultures in order to refine the process of serum preparation (Vasconcellos, 1909, p.16).

[17] The Butantan Institute followed Manguinhos's example and also made serum and vaccine. However, as stated by Vital Brazil (cited in Fontes, 1903, p.54) "vaccination in S. Paulo has been on a very small scale, limited to a small portion of personnel subordinated to the Directorship of Sanitary Services (Diretoria do Serviço Sanitário)."

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