The emergence of dengue as a virological challenge: from phantom disease to “pet” endemic, 1986-1987

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Abstract

This article analyzes how dengue presented a virological challenge during the 1980s in order to explore the role of virological studies in understanding this disease and constructing expertise in arboviral diseases. Although outbreaks were reported throughout the twentieth century, dengue was barely known in the Americas until the epidemic of dengue fever in Cuba in 1981. When the disease reached the Brazilian city of Nova Iguaçu (RJ) in 1986, it became the focus of attention for a team of virologists led by Hermann Schatzmayr, who mobilized efforts after the creation of the Flavivirus Laboratory at the Oswaldo Cruz Institute.

Keywords: dengue; virology; Instituto Oswaldo Cruz; epidemic; history.

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> One of the major obstacles in the fight against *Aedes* in Brazil is that it transmits two diseases considered phantoms: urban yellow fever, which has not existed in Brazil since [19]42, and dengue, which was an abstraction despite the fact that an epidemic has already occurred in Roraima, which Dr. Osanai will describe. The repercussions in the major centers were minimal, and unfortunately, even despite dengue in Roraima, we were unable to obtain the resources from governmental decision-making bodies necessary for a campaign to eradicate *Aedes* in Brazil (Leal, 1987, p.186).[1]

In 1981, cases of fever were reported in Boa Vista, Roraima, and later confirmed to be dengue by the virologists at the Evandro Chagas Institute (Instituto Evandro Chagas, IEC). From July 1981 to August 1982, 11,000 people were infected by serotypes 1 and 4 of the dengue virus, which probably entered the territory by land after originating in the Caribbean and northern South America. The main interpretation of this entire event was that the virus did not expand because *Aedes aegypti* was not found to be dispersed across the country in that context, and that combat against this vector was effective to eliminate it and contain the outbreak (Barreto, Teixeira, 2008, p.59).

A few years later, on April 30, 1986, after the first cases of dengue were registered in Nova Iguaçu, Rio de Janeiro, the Center for Studies at the Oswaldo Cruz Foundation's (Fundação Oswaldo Cruz, Fiocruz) National School of Public Health (Escola Nacional de Saúde Pública, ENSP) held a debate on the disease that was later transcribed and published in a dossier by the *Cadernos de Saúde Pública* journal (1987). The quote at the beginning of this article comes from the second invited speaker, Pedro Luis Tauil, who at the time was parliamentary advisor to the Brazilian Federal Senate and former director general of the Department of Eradication and Control of Endemic Diseases at the Superintendence of Public Health Campaigns (Superintendência de Campanhas de Saúde Pública, SUCAM), an agency dedicated to controlling or eradicating Brazil's main endemic diseases. His words clearly express the status of the disease when it reappeared in 1986: an abstraction, a "phantom disease."

As a disease caused by an arbovirus, which generally involve more complex cycles than other viruses, dengue presented an important challenge at that time. If (as Tauil said) the *Aedes aegypti* mosquito was a transmitter of phantom diseases, a new problem that was just becoming established, what was the importance of virological research from the study of this virus to prove that dengue was present?

As the virologist Pedro Fernando da Costa Vasconcelos, president of the Brazilian Society of Tropical Medicine, wrote in a short text reflecting on arboviruses, coronaviruses, and the emergence of SARS-CoV-2 in December 2019, only with scientific data produced where different disciplines interact (medical and veterinary science, ecology, and epidemiology) will it be possible to build mechanisms to prevent and control viruses, develop diagnostic methods, therapies, and vaccines, and understand how the disease functions (SBMT, 11 abr. 2020). According to this text, since humans will not stop entering "natural ecosystems," there are no other options than to invest in scientific understanding of the ecoepidemiology of arboviral diseases and zoonotic viruses, which have proliferated in the twenty-first century. But as he also says, national and international health authorities and politicians must learn to trust science.

If today, as Vasconcelos comments, "the whole world is asking what the next epidemic caused by arboviruses will be" (SBMT, 11 abr. 2020) while still wondering what direction the covid-19 pandemic will take, in the 1980s, it was dengue that generated uncertainties. In 1982, after the epidemic of dengue hemorrhagic fever (DHF) in Cuba, a technical group from the Pan American Health Organization (PAHO) estimated that five to eight years were needed to develop effective dengue vaccines (Martinez et al., 1987), which did not happen.

According to Dilene Nascimento, the lack of a dengue vaccine leaves only one strategy to fight the disease: eliminating its vectors. In her words, this makes the "history of dengue closely linked to the history of the mosquito and the fight against it to halt transmission of the disease" (Nascimento et al., 2010, p.212). Although the mosquito is considered the epidemic villain *par excellence*, as recent works in the historiography on mosquitoes maintain (Lopes, Silva, 2019), viruses create and establish their identity through their position in political and social contexts (Lopes, Reis-Castro, 2019). And to solidify this identity, it is essential to consider the ability to visualize, track, and identify viruses in humans as well as mosquitoes. The virus not only creates a new identity for the mosquito, but also connects with humans, identified from its pathological form. In this way, the insect that used to be the "yellow fever mosquito" becomes the "dengue mosquito." Advances in virological research and virology's ability to trace the movement of viruses thus requires us to reevaluate the reduction of dengue history to the history of the mosquito. One possible way to rethink these subjects is through what is called the ethnography of viruses. Recent works linked to the approach of "multispecies studies" have proposed a virus-centric analysis (for example, Lowe, 2010, 2017; Lowe, Münster, 2016). Celia Lowe (2017, p.92) points out invisibility as a specific characteristic of viral or microbial studies within multispecies ethnography. Viruses can only be inferred by the symptoms they cause, or recognized through science. Although the present work is not a multispecies ethnography study, reflections from this field can help point out the specific characteristics of viruses and mosquitoes in history, especially in relation to the discussion mentioned above about how viruses mark the identity of mosquitoes. This article will consequently attempt to define the importance of studying viruses as scientific objects in the case of dengue, and how this disease emerged as a challenge to Brazilian virology.

Firstly, I review the disease and identify the moment when dengue emerged globally as an arbovirus disease and became the object of the first virological studies. Then, I address the formation of the Department of Virology at the Oswaldo Cruz Institute (Instituto Oswaldo Cruz, IOC). Much of the documentation consulted for this research is found in the Hermann Schatzmayr Fund within the Archive and Documentation Department of the Casa de Oswaldo Cruz. Finally, I defend the idea that dengue emerged as a virological challenge when the disease was seen as a new problem. So, the objective of this article is to understand the role of virology in dengue's transition from a phantom disease to Brazil's "newest pet epidemic."

Between the 1970s and 1980s, the World Health Organization (WHO) published some "technical manuals" on dengue, its virus, and vectors, which targeted different experts. These publications were intended to serve as guides for diagnosing, treating, and combating dengue, especially for those "clinicians and other public health authorities that have been confronted with an epidemic of this disease for the first time" (Dengue..., 1987, p.7). The first, published in 1975, was triggered by the severe epidemics of the hemorrhagic form of the disease that occurred with greater intensity in Burma, Indonesia, Thailand, and other countries in Asia and the Western Pacific starting in 1972. The second revised manual was published in 1980 and meant to clearly present the topic of dengue so that the information could be used by professionals in primary health care services. In 1987, a third version of the WHO dengue manual was published; this version, greatly impacted by the 1981 DHF epidemic in Cuba, was intended to be a general update of the knowledge on dengue fever up to that time.

Other bulletins, manuals, and technical guides linked to WHO and published during the same period attempted to briefly summarize the problem of controlling *Aedes aegypti* in the Americas (Uribe, 1983), or the emergence of virus-caused hemorrhagic fevers such as DHF (Fiebres..., 1985). The texts addressed everything from the socioeconomic impact of dengue epidemics in Latin America and the Caribbean (since the sick were unable to work or study) to the severity of hemorrhagic epidemics and the ineffectiveness of programs to eradicate or control the vector mosquito. They also presented retrospective data on the global occurrence of dengue, isolation of its serotypes, the characteristics and classifications of the virus, the problem of immunity induced to a single serotype, in addition to epidemiology, treatment, and diagnosis. In an attempt to provide an overview of all the important characteristics of dengue, these texts used a proactive tone as they noted the need to investigate and develop new methods for detecting and determining the sequence of infection, "in particular, identifying the first and second viruses when only material obtained during the second infection is available (blood, serum, plasma, leukocytes)" (Fiebres..., 1985, p.25) in order to prevent severe forms of the disease.

In the mid-1980s, advanced techniques such as the MAC-Elisa immunoenzyme assay[2] became common in virology laboratories that maintained contact with the US Centers for Disease Control and Prevention (CDC), which were responsible for initial distribution of these tests. As a wide range of serological tests became available and knowledge was gradually constructed about the immune response to the dengue virus, laboratories such as the Flavivirus Laboratory at the IOC Department of Virology "molecularized" (Chadarevian, Kamminga, 2005) studies on the disease, which became more and more sophisticated.[3] But in the sphere of epidemiological studies, clinical studies, and entomology, numerous debates and tensions arose after each new epidemic of the disease.

In 1987, the infectologist Keyla Marzochi, who was responsible for clinical management, treatment, and study of dengue patients at Fiocruz's Evandro Chagas Hospital, published a text entitled "Dengue: a mais nova endemia 'de estimação'?" ["Dengue: our newest 'pet' endemic?"] in which she commented on the latest discussions among different technical groups and coordinating anti-dengue campaigns. In her opinion, the press made a reasonable contribution to alert the population, while neighborhood associations invited health agents to give lectures. Meetings and discussions were held at Fiocruz, with the Ministry of Health and participation by national authorities. In one of these debates (the same in which dengue was portrayed as a phantom disease), the difficulty of establishing consensus due to the contrasting opinions was clear. While some experts pointed out the seriousness of the situation and advocated rapid action by the authorities, others believed that the capital of Rio de Janeiro would not even be affected, based on studies that indicated a low rate of buildings infested by *Aedes aegypti*. But within a few days, the first cases of dengue in the southern region of the city began to appear (Marzochi, 1987, p.138).

As early as 1986, dengue came to be seen as a new Brazilian endemic disease by the experts who participated in the debates. At the same time, measures established by the Rio de Janeiro state Dengue Control Coordination (such as transforming dengue into a compulsory notification disease, or the determination to send specific dengue forms to state hospitals) did not solve the problem, due to failures in these processes. The Evandro Chagas Hospital at Fiocruz, which had a specific outpatient clinic for this disease since the start of the epidemic, still had not received any forms or formal information about the disease. A gap can be seen between the measures and actions taken by the public authorities and activities that were part of exchange between specialists in different areas, and indicates how the problem took shape: receiving little attention from the government while simultaneously becoming an interdisciplinary research agenda (Marzochi, 1987).

A review of the disease: between mosquitoes and viruses

Although the zika and chikungunya viruses were known since the 1950s, around the same time the dengue virus (Denv) was identified, unlike dengue they remained restricted to some African territories until at least 2013-2014. Dengue gained ground in the Americas throughout the twentieth century (or perhaps even earlier, according to older reports) to become an increasingly significant health problem. The disease was stabilized in the clinic alongside virology (Packard, 2016). Although it is commonly related to zika and chikungunya, during the 1980s dengue was more closely related to yellow fever, in research projects as well as in comparisons made in the sphere of public health. All these arboviral diseases (which today are more clearly delineated thanks to laboratory identification of their viruses) are transmitted by the same vector mosquito, *Aedes aegypti*, and, in historical analysis over the longer term, are often difficult to differentiate. Today, dengue is one of the world's main arboviral diseases. Approximately 2.5 billion people are at risk of infection, mainly in tropical and subtropical countries where climatic conditions are associated with political, social, and economic problems that make effective control of the disease vectors impossible (Valle, 2015).

According to Halstead (1992), the existence of a cyclozoonosis in which non-human primates in Southeast Asia support all four dengue serotypes leads to the view that this geographic region is "ground zero" for Denv. But the history of dengue during the eighteenth and nineteenth centuries, before two of the serotypes of the virus were isolated in mice in the 1940s, can only be inferred from reports and studies that focused on the clinical and epidemiological characteristics of the disease. Dengue was intertangled with the issue of febrile diseases (Packard, 2016), and, with the added challenge of the fragile documentation on this subject, any categorical consideration of the movement of the viruses and disease before that time becomes difficult. But considering the plausibility of using clinical and epidemiological observation clues, a "pandemic" character of the disease can be seen in the eighteenth and nineteenth centuries. Still, as can be seen from the historical accounts by Albert Sabin and Susumu Hotta, who worked with Denv in the 1950s, and from authors who studied the subject (Halstead, 1992; Kuno, 2007; McSherry, 2008), the Second World War was important not only for dengue virus research, but for the spread of the disease around the world.

In general, the historiography on the disease agrees that the first record of a dengue epidemic was made by the American physician Benjamin Rush, who called it breakbone fever in Philadelphia in the 1780s (McSherry, 1982, 2008; Rigau-Pérez, 1998; Halstead, 1992; Dick et al., 2012; Packard, 2016; Chandra, 2018). But supposed dengue epidemics were reported in the seventeenth century as well: in 1635, in Martinique and Guadeloupe in the Caribbean (Dick et al., 2012). And in a 1982 study, James McSherry attempted to establish a retrospective diagnosis of dengue for illnesses that affected a Scottish colony on the isthmus of Panama (related to the Darien scheme) in 1699 based on a report by Patrick MacDowall.

In 1779, knuckle fever was described in Batavia by the Dutch surgeon David Billon, as was knee trouble in Cairo. Although these two "diseases" were later associated with dengue due to their sudden onset with high fever, severe musculoskeletal pain, rash, and benign outcome, they could also have been chikungunya fever, especially due to the severe joint pain involved. The difficulty in establishing a historical distinction between dengue and chikungunya was analyzed by Donald Carey (1971) in "Chikungunya and dengue: a case of mistaken identity?". Carey pointed out the main differences between the two diseases and stated that knuckle fever and knee trouble were what today is known as chikungunya, while the breakbone fever described by Benjamin Rush in 1780 in fact was the first detailed historical record of dengue.

Throughout the nineteenth century, suspected cases of dengue were recorded in several countries such as Peru, the United States, Cuba, Brazil, Chile, and Argentina, as well as other regions of the Americas (Dick et al., 2012). The nineteenth-century records exclusively presented symptomatological and epidemiological aspects of the disease, and only rarely some speculations about etiology. Varied terms linked to the places where the disease erupted were widely used together or in place of the term "dengue" (Lara, 2019).

In a text published in 1952 in *the American Journal of Tropical Medicine and Hygiene*, Albert Bruce Sabin (1906-1993), who is better known for his work with the polio vaccine, detailed the main contributions to dengue research before and during the Second World War by the US Army medical corps.

In the Philippines, Percy Ashburn and Charles Franklin Craig obtained evidence proving the viral etiology of dengue, which had been under investigation in the region since 1906 after an epidemic struck Manila. Siler, together with Hall and Hitchens, demonstrated the period needed for the virus to develop in observed mosquitoes before it could be transmitted. In the same context, even before the 1930s, research in monkeys suggested the existence of a wild type of dengue. In 1931, James S. Simmons, St. John, and Reynolds established the role of *Aedes albopictus* in dengue transmission. The role *of Aedes aegypti* in transmitting the disease had already been known since the early twentieth century, first hypothesized by Thomas Lane Bancroft in Australia between 1905 and 1906 and then confirmed by Aristides Agramonte y Simoni in Cuba in 1908 (Lara, 2020). As for the virus, in 1934, Snijders, Postmus, and Schüffner conducted human experiments in the Netherlands and identified two different strains. In 1936, Shortt, Rao, and Swaminath cultivated the dengue virus in the chorioallantoic membrane of chicken embryos (Sabin, 1952, p.30). Sabin maintained that many studies were conducted before most virological techniques and more modern procedures were established.

American studies during the Second World War proved the existence of multiple immunological types of dengue. They also concluded that in regions such as New Guinea, fevers of unknown origin were caused by types of dengue virus, and above all, that "specific dengue immunity is associated with neutralizing antibodies to the virus, which can be used for diagnosis and epidemiological survey" (Sabin, 1952, p.49).[4] In addition to these studies (which during this period started to become more specialized, partly due to war-related demands like the need for an immunizing agent against dengue, similar to yellow fever), Japanese researchers reported many strains of the dengue virus. In the laboratory, these strains were adapted to a variety of research animals; three were confirmed as dengue, and two as Rift Valley fever and rabies (Sabin, 1952).

The teams led by Sabin and by Hotta and Kimura were the two groups responsible for the first and original isolations of the Denv-1 and Denv-2 serotypes of the dengue virus, with Kimura in 1943, Hotta in 1944, and Sabin and Scheringer in 1945. In the 1950s, the other two serotypes of the virus were isolated (Gubler, 2006; Kuno, 2007). Although the viral etiology of the disease had been suspected since the early twentieth century, the virus was not isolated until 1943. In Japanese studies, none of the twenty laboratory animal species were considered useful models due to the absence of dengue symptoms, a scientific problem that is still discussed today (Vieira, Schatzmayr, Schatzmayr, 2010). This difficulty led the Japanese scientists to isolate the virus by inoculating blood from volunteers in the acute phase of the disease in healthy volunteers (Gubler, 2006; Kuno, 2007).

During the 1960s and 1970s, the dengue virus was classified as a Flavivirus with Japanese encephalitis and yellow fever, and, together with the chikungunya virus was classified as an Alphavirus and joined the Togaviridae family (Hotta, 1978). The modern classification[4] of the dengue virus was an important factor for new laboratory studies that led to improved virological and epidemiological surveillance of the disease, generating a large quantity of data on global dissemination of the virus (Messina et al., 2014).

Sabin (1952) and Hotta (1978) were important actors in this process, because they were part of decisions in the public health sphere and also participated in the global process of disclosing proof of the disease from virological studies. At the same time that dengue virus was classified, its transmission mechanism was described and the relationship with symptoms was established. These scientists in the USA and Japan, as well as Hermann Schatzmayr at Fiocruz, played an important role during the period when virology was established as a science.

For Halstead (1992), the dengue "pandemic" of the twentieth century arose from the clash between ecological forces that emerged within the context of the Second World War and continued in an unprecedented manner from that time onward. The viruses circulated along with the Asian and American soldiers while at the same time city water supply systems were destroyed, war refugees lived in precarious temporary housing, the population grew due to high fertility, and migration between rural and urban areas all led to major growth in the area and population of *Aedes aegypti*. As Dilene Nascimento states, in Brazil there has been a movement between containment and reinfestation by the mosquito since 1958, when there was a drastic reduction, a return in 1967 due to garbage produced by the automobile industry, another reduction in 1973, and then a reinfestation three years later (Nascimento et al., 2010, p.212).

Without effective vector containment programs, dengue infections gradually increased from the post-war period onward. The achievements of campaigns to eradicate *Aedes aegypti* in the Americas (Magalhães, 2016) were undone by their interruption, and after the 1960 the dengue virus soon expanded in this region to reach Cuba, the Caribbean islands, Mexico, the United States, much of Central America, Colombia, Ecuador, Peru, Paraguay, Argentina, and Brazil (Halstead, 1992, p.292). In this way, the hyperendemicity of the disease and co-circulation of different strains and serotypes of the virus resulted in a new form of the disease, dengue hemorrhagic fever (DHF). This new form first occurred in Manila, the Philippines, between 1953 and 1954, and was recorded over the following decades in practically all of Southeast Asia; by the 1970s, it was one of the main causes of hospitalization and death of children in this region (Gubler, 2006). In the Americas, the first epidemic of DHF occurred in Cuba in 1981, causing the deaths of 158 individuals (one hundred children and 58 adults) and a total of 344,203 cases of the disease. That same year a dengue epidemic was also registered in Brazil in the city of Boa Vista, Roraima, but was soon contained and drew little attention on the national scale.

This review allows us to point out some continuities in the history of dengue. They are found in both the similarities of the symptomatological descriptions as well as considerations of the important role played by the environment in the proliferation of the disease. Places where miasmas emanated (according to the previously-held theory of miasmas, which considered emanations from decomposing plant and animal matter to be the focus of disease) almost always coincided with sites where mosquitoes reproduced and the virus circulated (Packard, 2016). What changes, from the historical point of view, is perception: it shifts from a strong emphasis on smell to understand and detect miasmas (Anaya, 2011) to a microbiological, entomological, and virological interpretation of the pathological phenomenon.

From 1981, dengue began to draw attention from some Brazilian scientists, such as the virologists at the Evandro Chagas Institute (IEC) in Belém, Pará. At the IEC there was already a tradition of arbovirus research since the 1950s, with the creation of the Belém Virus Laboratory by the Rockefeller Foundation (Andrade, 2019). In this way, infrastructure was built over decades, along with the expertise that permitted the first virological studies on dengue in Brazil, based on the Roraima outbreak. But only after the 1986 epidemic in Rio de Janeiro did the disease become the subject of major research projects, scientific debates, and political actions.

Although, as mentioned earlier, the mosquito appears in this story as a villain (Lopes, Reis-Castro, 2019), as the only research route (Nascimento et al., 2010), or as the focus of campaigns to eradicate *Aedes aegypti* (Magalhães, 2016), it is possible to argue that virology – since the 1950s, but especially in the 1980s (Rosa, 2016) – was important for the study of arboviral diseases and especially dengue.

The virologists at the Oswaldo Cruz Institute

The construction of the IOC Department of Virology at Fiocruz was the result of the virologist Hermann Schatzmayr's fight to obtain a suitably equipped space dedicated exclusively to the study of viruses, as well as worldwide social and political demand for virology laboratories that arose from the 1960s (Gazêta et al., 2005). The Oswaldo Cruz Foundation was in the middle of a period known as the "Fiocruz recovery" (Azevedo, 2007). Chaired from 1975 to 1979 by the economist Vinícius da Fonseca, projects such as the construction of Bio-Manguinhos in 1976 amid a meningitis epidemic and the global campaign to eradicate smallpox were important for the construction of a Center for Medical Virology at IOC in 1977, which became a department in 1980. In the 1970s, "bacteriology and virology – recognized as essential to public health for dealing with infectious diseases – were poorly developed in the spectrum of disciplines that characterized research" (Azevedo, 2007, p.66) at Fiocruz. Along these lines, with the support of the Brazilian National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) Fonseca drafted an assessment of scientific and technical conditions at the institution in order to develop a work plan.

The Center for Medical Virology (Centro de Virologia Médica, CVM), linked to the IOC, was created in 1977. It was led by Hermann Schatzmayr and dedicated to research and diagnosis for viral diseases. The CVM provided support for a graduate course in medical virology and was also intended to develop expertise in immunizations. A partner with the Mérieux Foundation in France, the center was offered "traineeships in other countries, two hundred thousand dollars to purchase equipment and pay wages for a specialist hired abroad. With these resources, Schatzmayr … brought a Brazilian virologist who had been working in London for many years, Gelli Pereira, along with his wife [Peggy], who was also a virologist" (Benchimol, 2001, p.340-341).

Part of the group of scientists that would be linked to the CVM had been involved in virus research since at least the 1960s, but in a less organized manner. The scientific trajectory of Hermann Schatzmayr, who directed the center and later the Department of Virology, is intertwined with the establishment of not only a new virus research center at the institution during the 1960s and 1970s, but also of the group of virologists who would join the fight against dengue in 1986.

Hermann Gonçalves Schatzmayr (1936-2010) was one of Brazil's leaders in virus science. In the 1950s he graduated in veterinary medicine from the Universidade Federal Rural do Rio de Janeiro, and later took a course in microbiology at the University of Brazil taught by professor Paulo de Góes, which earned him a scholarship in the university's virology laboratory (headed by professor Joaquim Travassos da Rosa, who later directed the IOC) and his first work on samples from the major influenza epidemic during 1957-1958 in Rio de Janeiro. Before joining the IOC in 1961, where he began to collaborate on research in a polio laboratory assembled with financial support from PAHO, Schatzmayr also studied at the University of Vienna in Austria; in 1966, he completed his doctorate at the universities of Giessen and Freiburg in Germany. Later he was appointed head of the Bio-Manguinhos unit in 1976, and the chair of Fiocruz between 1990 and 1992, during Fernando Collor government. At the IOC, in addition to creating the Center for Medical Virology and the Department of Virology he also acted as its coordinator for 30 years, working to fight polio, hepatitis, rubella, and other viral diseases. From the 1980s, he and his team were responsible for isolating serotypes 1, 2, and 3 of the dengue virus, which was systematically studied by the IOC Flavivirus Laboratory that was created in the midst of the 1986 epidemic. That same year, Schatzmayr and other virologists founded the Brazilian Society of Virology (Sociedade Brasileira de Virologia, SBV) in order to bring together Brazilian researchers. In the late 1990s, he combined research on dengue with studies of poxvirus in animals and humans. Until 1964, the year of the military coup, the PAHO laboratory had developed diagnostic methods and carried out comparative studies on replication of viruses in the Coxsackie and Echo group in mice, which permitted investigation of the role of these viruses in the etiology of poliomyelitis (Schatzmayr, Filippis, Friedrich, 2002, p.16). It is interesting to see not only the changes that began to take place in the laboratory from that time on in Schatzmayr's later statements to the researchers Anna Almeida and Marli Albuquerque for Casa de Oswaldo Cruz's Brazilian Biosafety Memory Project (Projeto Memória da Biossegurança no Brasil), but also internal and even generational political disputes among the IOC's groups of scientists.

> At that time, Lagoa's star began to rise; he was an extremely incompetent figure, did nothing in here, directed a viral tumor laboratory that did nothing at all. He never even showed up, he was only on paper, it was in the Cardoso Fontes building, where virology is now, in the upper part. The group on the right got strong, so Armando took over the institute and the first thing they did was to appoint Estácio Monteiro, a person connected with Dr. Lacorte, very connected to Dr. Rocha Lagoa, to head the laboratory where I worked. I rejected the man, because he knew nothing about it, he put 3 or 4 extremely incompetent people in there, I was disgusted in scientific terms (Schatzmayr, 23 abr. 1999).

José Guilherme Lacorte, Estácio Monteiro, and Joaquim Carvalho Loures comprised the main virus research group at IOC until the arrival of Schatzmayr. During the 1940s and 1950s, these scientists predominantly studied the flu and polio viruses and worked on other research agendas amid the excitement of post-war science, such as studies on the relationship between viruses and radioactivity, in the former Virus Section and Division.[5] Until the early 1970s, this group was still publishing articles in journals like *Memórias do Instituto Oswaldo Cruz* (Lacorte, Monteiro, Loures, 1971). Consequently, different virus study groups can be noted: one representing the former IOC, and the other still in its early stages. But the "scientific disgust" in Schatzmayr's account expresses not only a simple generational conflict or clash of research agendas, but the difficulties he faced when the IOC was directed by the controversial figure of Rocha Lagoa.

In 1966, Schatzmayr was invited to work in a virology laboratory that was being set up at ENSP (an institution that only came to be linked to the IOC after the 1970 creation of Fiocruz). In this new laboratory, together with Akira Homma, Schatzmayr established lines of research on enteroviruses, refining studies on the polio virus, and began research with viruses in water and sewage to develop environmental technologies that were passed on to other laboratories and companies such as the São Paulo State Environmental Company (Companhia Ambiental do Estado de São Paulo, CETESB) (Schatzmayr, Filippis, Friedrich, 2002). This same center also set up laboratories for rubella and viral hepatitis and served as the National Reference Laboratory to diagnose suspected cases of smallpox between 1968 and 1975.

During the late 1970s, when resources were scarce and ENSP's interests shifted to other areas, these virologists began to join another research center at IOC/Fiocruz, with plans by Vinícius da Fonseca to increase wages and construct a priority virus program. The creation of the Center for Medical Virology leveraged research and teaching activities, partnerships with universities, accreditation commissions for the first courses related to virology in Brazil, and international scientific cooperation with different virus research centers around the world. In 1980, the Center for Medical Virology became the Department of Virology. In 1981, the main laboratories and centers in the department included the study of the influenza and rabies viruses, enteroviral diseases, and viral hepatitis. That same year, the first contact with dengue was made: Schatzmayr sent an official invitation to the researcher Rita Maria Ribeiro Nogueira to participate in the "dengue diagnostic laboratory course" that was to be held from October 26 to November 13 of that year in Puerto Rico.

The course was communicated to the department by the Brazilian Ministry of Health's Public Health Laboratory Division in Brasília, on the recommendation of the Pan American Sanitary Bureau. Nogueira graduated from the Universidade Federal da Bahia in 1972 in medicine; she began her activities at IOC shortly after completing her medical training with a specialization in biology research in 1974. Since she entered the institution, Nogueira worked under the guidance of Schatzmayr, and was a student in the first class of the master's course in medical virology in 1977. The sources do not clearly state whether she actually completed the course. In an activity report for 1981, Rita Nogueira (20 nov. 1981) did not mention any such trip. But Schatzmayr's request, in the midst of the first epidemic of dengue hemorrhagic fever in the Americas and the first dengue epidemic in Brazil in Boa Vista, marks the very beginning of a closer look at the "new disease" at the Department of Virology, which would reconfigure some of the priorities of this research center from 1986.

Documentation related to the activities at the Department of Virology between 1982 and 1985 indicates that the research projects maintained the same thematic scope during this period. What is notable during this period is the interstate collaboration between laboratories, such as the virology laboratory training program in the state of Bahia (Schatzmayr, 5 ago. 1985), the participation of the IOC virology sector in a scientific agreement between France and Brazil, the first two national virology meetings (1982 and 1984), in which the department participated significantly, laboratory diagnostic courses, and international trips. In the “Future Prospects” section, the annual reports mentioned research on molecular biology, new diagnostic techniques, and studies involving rotaviruses, monoclonal antibodies, and adenoviruses. Despite the historical importance of the events of 1981, dengue was not mentioned in the department’s reports until 1986.

The emergence of dengue as a virological challenge (1986-1987)

Even though it occurred almost simultaneously with the DHF epidemic in Cuba, the Boa Vista episode does not seem to have sensitized public authorities in that context; it was seen as an isolated outbreak, while the vector mosquito continued to spread throughout Brazil. In the area of scientific research, the IEC’s serological investigation began in March 1982 with two patients presenting similar symptoms. Serological testing revealed a secondary response to flavivirus and were negative for 13 other types of arboviruses used in the same hemagglutination inhibition (HI) test. Days later, the results of other blood and serum samples indicated that the flavivirus was different from the ones known in Brazil at that time. The virus reacted to HI and CF (complement fixation) tests with dengue-immune sera 1, 2, 3, and 4, which were provided by the US National Institute of Health. “However, it was not possible to type the virus. Later, monoclonal antibodies were used ... and the agent was identified as dengue 4” (Rosa, Vasconcelos, Rosa, 1998, p.165).

This was the first connected effort by Brazilian virologists to face the dengue problem (which was still in Belém at that time), as well as the early use of a series of modern serological tests to isolate, identify, and type the virus. These different tests were being gradually introduced in Brazil; some were already in common use by the staff at the IOC Department of Virology by the late 1970s, such as immunofluorescence tests. But it is possible to show as early as 1981 how the use of monoclonal antibodies by the IEC team, for example, was fundamental for resolving research with the dengue virus. During the 1960s, immune system antibody secreting cell lymphocytes were shown to be “monospecific” because they secreted only one type of antibody, usually associated with a specific antigen. But the production of monoclonal antibodies was only first reported in 1975, when the biochemists César Milstein and Georges Köhler fused myeloma cells (carcinogenic lymphocytes) with cells taken from the spleens of immunized mice to generate an “immortal cell line” (hybridoma) capable of secreting monoclonal antibodies against a known antigen (Marks, 2015). In this way, researchers around the world soon began to explore the possibilities of these antibodies to purify biological products, identify new tumor markers, and (in the case of virologists) serotype viruses. These techniques were also replicated during the 1986 dengue epidemic in Rio de Janeiro, when virologists were responsible for isolating the virus, this time at the Oswaldo Cruz Institute.

A research note sent for publication on May 9, 1986 in the *Memórias do Instituto Oswaldo Cruz* announced the isolation of dengue virus type 1 from the serum of patients from Nova Iguaçu, in Rio de Janeiro (Schatzmayr, Nogueira, Rosa, 1986). The virus, which had been isolated in the cell lineage (C6/36) of the *Aedes albopictus* mosquito, confirmed that the symptoms of fever, headache, and exhaustion that were affecting the population of the Baixada Fluminense region were the result of infection by Denv-1.

The short text, signed by Hermann Schatzmayr and Rita Maria Ribeiro Nogueira from the IOC Department of Virology in collaboration with Amélia Travassos da Rosa, a researcher at the Evandro Chagas Institute virus laboratory, mentioned immunofluorescence techniques and the use of monoclonal antibodies, which are required to isolate the virus from human serum. Virus isolation was then confirmed by the CDC's dengue laboratory in San Juan, Puerto Rico. The cases of dengue were related not only to the first Brazilian cases reported in 1981 in the city of Boa Vista, but also to a 1923 article by the physician Antonio Pedro published in *O Brasil Médico* about a supposed dengue epidemic in Niterói, Rio de Janeiro, which attempted to establish a link between the symptomatological descriptions from the beginning of the century and the postulates of contemporary virology based on technological, epistemological, and specific institutional apparatus and an official notification system.

The scientific publication in question, which confirmed that the epidemic was dengue, simultaneously inaugurated the publications of the Department of Virology on the topic of dengue and was the result of previous work that brought together a kind of "epidemiological survey," links between different research centers, and close collaboration with health departments. Cooperation between IEC and IOC can be seen in the sharing of techniques and data on the 1981-1982 epidemic and the collaborative publications. When PAHO announced a course on laboratory diagnosis of dengue in Venezuela for March 1986, Schatzmayr sought support from IOC director Carlos Morel and Fiocruz president Sérgio Arouca to finance participation (as he did for Rita Nogueira in 1981) in order to bring the techniques and inputs needed for laboratory diagnosis of the disease to Brazil (Schatzmayr, Cabral, 2009, p.47). According to Schatzmayr, the diagnostic for dengue in Brazil was created by his group. "No one had experience with dengue here, no one had serum, there was nothing." When Nogueira returned from the course, she used the materials she brought back from Venezuela to test the sera collected from the suspected cases in Nova Iguaçu right at the beginning of the epidemic. "The nine were all positive. All type 1" (Schatzmayr, 14 mar. 2002).

Unlike the 1981-1982 epidemic in Boa Vista, the 1986 dengue epidemic drew more attention from newspapers and public authorities, not only because it was a major event in an important urban area of Brazil that later spread, but also because of the Brazilian context of redemocratization. Important events like the creation of the Unified Health System (Sistema Único de Saúde) were taking place at this time. The eighth National Health Conference was held in 1986; this event was responsible for launching the guidelines of what would become the Brazilian Unified Health System, and placed discussions on the right to health as a government duty squarely on the agenda. Dengue, which at first was confused with poisoning from a factory in Nova Iguaçu plant, was a novelty in the newspapers. In an article entitled "Dengue has already claimed 10,000 victims in RJ," the *O Fluminense* newspaper erroneously related the current epidemic to the one that had been "recorded in 1926," and got the name of the transmitting mosquito wrong, citing "*Aedes aegybti*, which was believed to be eradicated since 1965" (Dengue..., 25 abr. 1986).

The benign character of the disease was often emphasized. In the *Jornal do Brasil*, headlines like "Dengue causes fever but does not kill" were common during the first days of the outbreak (A dengue..., 25 abr. 1986). But the same newspaper also reported statements by the minister of Health at that time, Roberto Santos, and the former secretary and health advisor of the state of Rio de Janeiro Eduardo Costa, that indicated the difficulty of containing the outbreak; in their opinion, the SUCAM lacked what was needed to combat the disease. The newspaper revealed the precarious structure of the main agency: "SUCAM in Nova Iguaçu has only 80 agents to cover an area of 764 square kilometers and a population of 2 million inhabitants, most of whom live in unsanitary places that tend to be infested with the aedes aegypt [*sic*] mosquito" (Ministro..., 27 abr. 1986, p.20).

The way dengue fever was initially treated by the newspapers and authorities, whether as a new, benign, or transient disease, is related to a common comparison at the time related to fears that urban yellow fever would return. On the other hand, it contrasts with efforts during this period to construct a reference center for the study of the disease and the virus that causes it. The Flavivirus Laboratory at the IOC's Department of Virology was created as a direct response to the dengue epidemic when the disease emerged in Rio de Janeiro. The objectives of the laboratory, which was headed by the researcher Rita Nogueira, were to study the clinical, epidemiological, and molecular aspects of flaviviruses, particularly dengue and yellow fever. After the eruption of the 1986 epidemic and the initial work of identifying, isolating, and typing the virus, the laboratory began to study the molecular biology of viruses isolated throughout Brazil, from human cases as well as vectors, and also analyzed the molecular evolution of the samples. The lab soon became a reference center for confirming suspected cases of dengue and yellow fever and supporting epidemiological surveillance services in different Brazilian states such as Rio de Janeiro, Bahia, Espírito Santo, and Minas Gerais (Schatzmayr, Cabral, 2009, p.60).

The challenge caused by the emergence of dengue in 1986 had two main observable results: it profoundly reoriented the scientific trajectory of researchers at the Department of Virology like Hermann Schatzmayr, Rita Nogueira, and the researcher Monika Barth, and it broadened the understanding of dengue from a "phantom disease" to the "newest pet endemic" while building expertise in the study of arboviral diseases and molecular laboratory techniques such as C-reactive protein (CRP) testing.

Although Schatzmayr was involved in several other virological studies as head of the Department of Virology, dengue was one of his main objects of study from 1986 until his death in 2010. The Hermann Schatzmayr Fund contains a large quantity of dengue documentation among Schatzmayr's personal and professional documents, such as interviews, event certificates, official reports, serological records, and scientific articles. Rita Nogueira, who had studied enteroviruses until she was sent to participate in the international dengue course, took over the Flavivirus Laboratory and wrote her doctoral thesis on the laboratory profile of dengue epidemics caused by serotypes 1 and 2 of the virus, and during the 1990s and 2000s established numerous research projects on arboviral diseases. Another example of a career altered by dengue is that of researcher Monika Barth, the daughter of German zoologist Rudolph Barth (1913-1978) and wife of Schatzmayr. She had previously studied pollen morphology, but her work researching the morphology of several viruses via electronic microscopy was important to the development of virology at IOC. From 1986, Barth used her electron microscopy experience to systematically study the dengue virus, specifically the morphogenesis of the virus (how it formed within the cell). Her work in conjunction with the Flavivirus Laboratory connecting the morphological data with PCR tests and other techniques was ongoing throughout the 1990s and 2000s and clarified important points about the dengue virus cycle (Barth, 6 nov. 2019).

From 1986 to 1993, when there were two major epidemics in Rio de Janeiro, the Flavivirus Laboratory isolated dengue serotypes 1 and 2 for the first time in Brazil and sought to establish methodologies for diagnosing the disease in partnership with Fiocruz infectologists. In the mid-1990s, the research projects began to center on general studies on the virus, as well as assessing immune response to the disease, implementing viral sequencing techniques to genotype the dengue viruses circulating in Brazil, and the study of immunohistochemical techniques to diagnose fatal cases of the disease. From the late 1990s to 2010, in addition to genetic isolation and sequencing of the other serotypes of the virus (3 and 4) in subsequent dengue epidemics, these researchers mostly focused on experimenting with numerous molecular techniques and diagnostic tests. Laboratory research projects mostly involved evaluating different methods in the search for a more effective diagnostic option.

The research agenda, which contained studies on pathogenesis, molecular biology, viral characterization, and the constant evaluation and application of new techniques for improving laboratory diagnostics, was marked by solidification of the studies and ongoing work. When the disease emerged in 1986, yellow fever was an important biomedical model for work with dengue. But since the studies on dengue became more established, many differences between the two viruses and the diseases can be seen over the years. More recently, with the emergence of chikungunya and zika, dengue in turn has become the main biomedical model for the studies of these other arboviral diseases, although CHIKV (chikungunya virus) is not a flavivirus.

The group of virologists at IOC first published their work on this subject in 1986. In 1988, a more detailed study of Denv-1 was published. The virologists described in detail how they isolated dengue virus type 1 from a fatal human case and from adult female *Aedes aegypti* mosquitoes. The cytopathic effect generated by the virus in the cell was studied using electron microscopy, and the findings reported in the text. But the main emphasis of the article was to "defend" laboratory diagnosis of suspected dengue cases in all regions of the country where the vectors were found. To do so, they demonstrated and evaluated serological testing (immunoenzymatic assay) to capture the IgM antibody, also known as MAC-Elisa. This test was used for diagnostics as well as to assess circulation of the virus, and its results were considered "clear and reproducible" (Schatzmayr et al., 1988).

Prior to the development of the MAC-Elisa test, hemagglutination inhibition was the main serological testing method for dengue in Brazil used by the group of virologists at the Evandro Chagas Institute in 1981-1982. This test was highly sensitive and affordable, but problems with cross-reactions between the four serotypes of dengue virus in the early 1980s complicated its use for serological diagnosis of the disease (Figueiredo, 1998, p.159). After the introduction of MAC-Elisa in 1986, many Brazilian laboratories adopted the technique.

The work of the Flavivirus Laboratory, even before its official establishment, proved consistent over time. Both Hermann Schatzmayr and Rita Maria Ribeiro Nogueira not only built a new agenda that involved learning, applying, and improving modern techniques, but also became an undeniable hub for these studies. The well-arranged contributions from the Department of Virology (largely from its own head during the 1970s and 1980s) were instrumental to quickly establish a research center when dengue arrived in 1986, in conjunction with other Brazilian and international virology laboratories, experts from other areas, international agencies, and the ministry and secretaries of health. This center took advantage of the perfect moment to invest in a new research topic, as well as the evidence and even the intuition that dengue would become established as a chronic problem.

Final considerations

This article explored how dengue presented a virological challenge and mobilized efforts by virologists and scientists linked to the IOC Department of Virology. It examined the main impacts of this disease on this research center, on the careers of scientists, on the incorporation of new laboratory techniques for the study of viruses and particularly arboviral diseases, and on the way virology positioned itself with regard to new problems in the sphere of public health. This study brings new sources to the historiography and presents some novelties as well as analytical possibilities, and primarily emphasizes the role of viruses and virology in discussions on disease and public health. The process analyzed here can explain the rapid and consistent response of Fiocruz virologists to more recent public health crises such as zika, chikungunya, and covid-19. The transition of the idea of dengue from a phantom disease to the "newest pet endemic" is a good example, because of the important role of virus science in this process. Arboviruses circulate among different species including mosquitoes and humans, and have a complex cycle that virologists explored to understand dengue, resulting in better explanations of the disease that emerged at that time as well as the incorporation of new tests and laboratory methods; this, in turn, generated expertise for Brazilian virology that today is reflected in the predominance of arbovirological studies in virology congresses, for example. Dengue hemorrhagic fever is still a major challenge at the present time, with new outbreaks every year due to the co-circulation of the four serotypes of the virus.

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NOTES

[1] [Translator's note] In this and other citations of texts from Portuguese, a free translation has been provided.

[2] The MAC-Elisa (IgM antibody capture enzyme-linked immunosorbent assay) is an assay to document serological response that was developed by the CDC in Puerto Rico and has been used since 1986; it is considered the most useful, simplest, and fastest test for surveillance and diagnosis, since it generally requires only one serum sample. The assay uses specific antigens from the four dengue serotypes to capture

the IgM antibody in serum samples. The immune response in a dengue infection produces IgG and IgM antibodies, which are directed against proteins in the virus envelope. IgM develops from the fifth day of the onset of the disease, so work with these tests takes into account the stage of infection. Over the years, this test has become an important diagnostic tool for dengue, since it has sensitivity and specificity of 90-98%, even though it can only be used five or more days after the onset of fever (Teste..., 2010).

[3] The term molecular is linked to the emergence of a "molecular vision" of life, health, and disease that is related to advances in molecular biology in the study of nucleic acids, proteins, DNA, and genes between the 1950s and 1970s, and the Human Genome project in the 1990s (Chadarevian, Kamminga, 2005). Since the 1990s there has been extensive literature on the subject (Kay, 1993; Rheinberger, 1995); the 2005 book by Chadarevian and Kamminga offers an excellent effort to systematize this discussion.

[4] There is an interesting discussion on the topic of modern classification of viruses and the epistemological implications. According to Gregory Morgan (2016), the first attempts to build a viral classification scheme in the 1960s focused on the structural properties of the virion. Over time, the International Committee on Taxonomy of Viruses (ICTV) included evolutionary history as an important factor. The definition of viral species created by ICTV was based on monophilia, but according to Morgan (2016), the existence of horizontal genetic transfer in various groups of viruses poses a challenge to this definition. This author defends the idea of radical pluralism in virus classification systems, because some viruses can easily be members of more than one species, and the very concept of a species is quite problematic in the case of viruses.

[5] In 1942, a new regime promulgated by the Vargas government reorganized the technical and administrative services at the IOC to create eight divisions: Microbiology and Immunology, Viruses, Medical Zoology, Physiology, Chemistry and Pharmacology, Pathology, Endemic Studies, Hygiene, and two sections (Auxiliary and Administration). From 1944, the Virus Division was headed by the bacteriologist Cássio Miranda, director of the IOC between 1953 and 1954, while the Virus Section linked to the division was put under the responsibility of José Guilherme Lacorte, who had already held this post. Before that, the study of viruses at the IOC was led by José de Castro Teixeira (1906-1944) (Lara, 2020).

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