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Title: Vaccine development as a ‘doable problem’: The case of the meningococcal A vaccines 1962-1969

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Abstract

During the period from 1962 to 1967, the development of a meningococcal A vaccine could be considered as feasible despite all the drawbacks of working with cerebrospinal meningitis A. In this paper, I analyse why and how this programme for vaccine development was put into place, and in particular how the problem was perceived as feasible. Deploying the concept of Doable Problems developed by Joan Fujimura, I examine the complex range of factors that led to the outcome of the trial in Yako in 1967. Thus I show how the different protagonists were mobilized and their work organized at different levels in order to produce and test a vaccine. Indeed, a number of elements seemed to stand in the way of successfully producing a vaccine, but the collaboration of the different actors under the aegis of the WHO provides interesting lessons about the management of this kind of project. Seen in a wider historical context, this approach could provide ideas and lessons for approaching current questions in vaccination from a new perspective.

Keywords: Cerebrospinal meningitis A; Institut Mérieux; World Health Organization; Doable problem; Meningococcal vaccine; Africa

1. Introduction

In the early 1960s, following numerous warnings, the World Health Organization (WHO) classed cerebrospinal meningitis A (CSMa) as a public health priority in Africa. In light of its increasing resistance to sulfa-drugs, active immunization appeared to be the best approach to combatting this deadly disease, leading to new initiatives to produce an effective vaccine. The production of this vaccine implied the collaboration of several organisms under the aegis of the WHO: the Institut Mérieux in Lyon, a team from the Institut de Médecine Tropicale du Service de Santé des Armées (IMTSSA) in Marseille, and the Laboratory of Hygiene of Ottawa. During the period from 1962 to 1967, a prototype vaccine was prepared and tested in Yako, Upper Volta. Although this trial demonstrated the safety of this vaccine, it could not prove its efficacy because the predicted meningitis epidemic did not occur. For 2 years after this episode, the Institut Mérieux vaccine continued to be quite widely distributed in Africa to test different properties, but never its efficacy as a prophylactic.

Historians have paid little attention to the development of the meningococcal A vaccine. Similarly, pharmaceutical companies tended to regard CSMA vaccines as scientifically and commercially less exciting than other drug projects (Graham, 2016, p. 420). The vaccine would target a disease that at that time attracted little attention in Europe and North America (more exposed to the C strain of the bacterium). Indeed, developing this vaccine project presented a number of drawbacks for pharmaceutical laboratories: CSMA was a disease which affected a poor continent (Africa); there were no animal models for testing the vaccine, meaning that it would need to be tested directly on humans; if a company did choose to produce such a vaccine, it would have to invest a great deal of money without any guarantee concerning the returns on investment. Furthermore, meningococcal vaccine trials had been carried out at the beginning of the twentieth century with poor results (Cvjetanović, 1968, pp. 124-125). Despite all these drawbacks, a number of actors engaged themselves in the development of such a vaccine. In this article, I draw on a range of historical sources including published scientific literature and archives (Institut Mérieux, WHO and IMTSSA), to construct an explanatory narrative of the development of the meningococcal A vaccine.

To analyse this episode, I deploy a schema proposed by Joan H. Fujimura, the concept of ‘Doable Problems’ (Fujimura, 1987). According to Fujimura, a problem is doable if there is an alignment between three levels of work organization: experiment, laboratory and the social world. Fujimura has argued that: “The first level is the *experiment*, or the set of tasks which are carried out in the laboratory. The second level is the *laboratory* wherein many different experiments and other tasks are carried out. The third level is the larger *social world* in which experiments and laboratories are situated”. Another definition states that: “These levels include the experiment as a set of tasks; the laboratory as a bundle of experiments and other tasks; and the social world as the work of laboratories, colleagues, sponsors and other players, all focused on the same family of problems” (Fujimura, 1987, p. 258). While Fujimura gives a description of these three levels, she does not provide precise guidelines concerning which tasks should be classified at which level. In this situation, it was not easy to see how to classify certain tasks that could be interpreted as being at one level or another. In these cases, I opted for what seemed the most appropriate level. Thus, I classed ‘the research and tinkering work’ at the level of experiment, including, for example, cultivating the meningococcus, developing a production technique, etc. I classed ‘the collaborative contacts between the different protagonists’ at the laboratory level considering that this was appropriate for work done in partnership, such as when one protagonist makes something for another. Finally, I classed ‘large scale operations or events’ at the level of the social world,

including such tasks as negotiating a new trial, enrolling new partners, etc. The alignment of these three levels is possible thanks to the articulation which operates between them. Defining articulation poses fewer problems, notably once the necessary work of assigning levels has already been carried out. As Fujimura explains: “Articulation is the work of pulling together everything that is needed to carry out tasks: planning, organizing, monitoring, evaluating, adjusting, coordinating and integrating activities” (Fujimura, 1987, p. 258). Another definition states that: “Articulation works include the seemingly mundane, taken-for-granted work of purchasing chemicals for reagents, negotiating with sponsors and collecting information about the latest results of competing laboratories” (Fujimura, 1987, p. 260).

Deploying this concept, I examine the complex range of factors that led to the outcome of the trial in Yako. Here, I will be considering not only certain technical developments in the vaccine production but also the wider social aspects of the ongoing project including various collaborations, discussions, the circulation of products, meetings, trials and setbacks. Thus I show how the different protagonists were mobilized and their work organized at the different levels in order to produce and test a vaccine. Indeed, a number of elements seemed to stand in the way of successfully producing a vaccine, but the collaboration of the different actors under the aegis of the WHO provides interesting lessons about the management of this kind of project.

Work on the history of vaccines has usually focused on the politics of vaccination (Brunton, 2008; Holmberg, Blume, & Greenough, 2017), protest movements (Porter & Porter, 1988; Durbach, 2004; Walloch, 2015), or the technical aspects of production (Moulin, 1996; Blume, 2008), and while Fujimura’s ‘Doable Problems’ approach has been deployed in various contexts (Palmer, 2006; Lassen, Bønnelycke, & Otto, 2015) there is no example of its application to the history of vaccines. There are many intriguing elements in this history, such as the role of the Yako trial, which was initially conceived to provide conclusive proof of the efficacy of the Institut Mérieux vaccine. The present paper examines this and other unusual elements that attest to the complex reality of the development, production and use of the vaccine. The approach has the advantage of making a place for setbacks in the analysis rather than just following the path to the successful vaccine. Seen in a wider historical perspective, this approach could provide ideas and lessons for approaching current questions in vaccination from a new perspective.

2. Historical background

2.1. *The cerebrospinal meningitis A*

Cerebrospinal meningitis is a disease that has been known since antiquity (Hansen & Freney, 1998, p. 213), but it was the Swiss doctor Gaspard Vieusseux (1746-1814) who provided the benchmark description in his account of an epidemic that struck Geneva in 1805 (Vieusseux, 1805), noting that the disease affected especially children and young people. Anton Weichselbaum (1845-1920), a Viennese doctor, determined the etiological agent of the cerebrospinal meningitis in 1887 (Weichselbaum, 1887), using methylene blue to determine the morphology of the bacteria and Gram staining to classify the bacteria as gram-negative, he gave it the name of *Diplokokkus intracellularis meningitis*. The diagnosis of the disease was helped by the lumbar puncture technique developed by Heinrich Irenaeus Quincke (1842-1922) in 1890 (Foster, 1970). Charles Dopter (1873-1950) developed the first classification of meningococci in 1909 (Anon, 1950), a classification that evolved a few years later to reflect the various observations that had been made. Serotherapy was also used with some success, but it caused important and dangerous anaphylactic reactions (Artenstein & LaForce, 2012, pp. 4701-4702). With the discovery of antibiotics and sulfa-drugs, the disease was brought under control for several years (Lapeyssonnie, Vandekerkove, & Causse, 1969, p. 587).

Cerebrospinal meningitis is a ubiquitous disease which affects especially children and young people (Saliou & Debois, 2002, pp. 326-327). The meningococcus bacterium (now named *Neisseria meningitidis*) is a germ that affects exclusively humans and CSMA epidemics occur predominantly in Africa, especially in the 'meningitis belt', an area stretching from Senegal to Ethiopia (Lapeyssonnie, 1968, pp. 716-717). The disease represents a major problem for researchers and trials of prophylactic measures: it is almost impossible to predict where an epidemic will occur. It is also difficult to predict for any given area whether an epidemic will take place, making African meningitis epidemics appear capricious and insidious (Le Viguelloux, 1974). There is, however, an epidemic season which extends from September to May and a region affected by an epidemic one year is not likely to be affected the following year. The unpredictability of the outbreaks from year to year constituted an important difficulty in the organization of vaccine trials. There was another obstacle in the organization of trials: CSMA epidemics were short, with an ascending and descending phase, so it was necessary to vaccinate at the right time. CSMA represented a public health problem in Africa during the second half of the twentieth century; every year, tens of thousands of cases were reported, with a case mortality rate of 10-15% (Lapeyssonnie, 1983, p. 12). While

it was necessary to diagnose and treat the disease quickly, it nevertheless responded well to sulfa-drugs. Of course, such a therapeutic approach was difficult to put in place in African countries where there were limited medical facilities and long distances separated villages, towns and cities (Ghipponi, Darrigol, & Faucon, 1968, p. 504).

2.2. Early version of the vaccine

CSMa was brought to wider attention thanks to the efforts of Léon Lapeyssonnie (1915-2001), a French military doctor trained at the Military Medical School in Lyon (Chastel, 2002). This school, specialized in tropical medicine, had become the center for training military doctors who would pursue careers in the French colonies. Following the example of Eugène Jamot, Léon Lapeyssonnie worked for several years in the French colonies of West Africa, studying the incidence and prevalence of African trypanosomiasis (Dutertre, 2002). During this period he encountered CSMa on several occasions when an epidemic broke out in the area. In 1960, following an urgent request from Michel Debré, the French Prime Minister, Léon Lapeyssonnie was sent to Niger at the head of a team of military doctors, to fight a deadly epidemic of CSMa (Lapeyssonnie, 1961). It took the team two months to bring this epidemic under control and as a result of this episode, Lapeyssonnie started to issue alerts concerning the disease and its complex epidemiology. Now attached to the Institut de Médecine Tropicale du Service de Santé des Armées in Marseille, Lapeyssonnie was made available to the WHO for a consulting mission on an epidemiological study of CSMa in Sub-Saharan Africa.

Léon Lapeyssonnie worked for the WHO from 1961 to 1962 during which time he carried out missions in three different regions in Africa (covering Niger, Upper Volta, Nigeria, Chad and Sudan). These 3 missions allowed him to study the epidemiology of the disease in the countries concerned. He used his analysis of the different methods for the prophylaxis and treatment of the disease to develop a research programme for combatting CSMa. In 1963, after 2 years of work, Léon Lapeyssonnie published an important monograph on CSMa in the bulletin of the WHO (Lapeyssonnie, 1963), which remains a reference concerning the disease and its epidemiology even today. The work carried out by Lapeyssonnie, combining field data and archives, provided a detailed if not exhaustive description of the complex epidemiology of the disease. Here, he highlighted the public health problem posed by CSMa in Africa, especially in the ‘meningitis belt’. Furthermore,

Lapeyssonnie's work underlined the danger of resistance to sulfa-drugs and the need to develop an effective vaccine to avoid this problem. The sulfa-drugs had been used for the first time against meningitis in 1937 (Martin & Delaunay, 1937), and because they were generally very effective they continued to be used widely and indiscriminately until the 1960s. The first cases of resistant strains appeared in 1962 in the United States, but for cerebrospinal meningitis B and not A (Feldman, 1967). Nevertheless, these cases worried African CSMa experts who predicted that in case of a meningitis epidemic carried by sulfa-drug resistant strains the drugs would be ineffective, leading to a major public health disaster. Trials of vaccines against CSMa had been attempted in the early part of the twentieth century, but they had proved inconclusive (Faucon, 1968a, p. 162). While not entirely original, Lapeyssonnie's emphasis on the danger and risks of CSMa in Africa made the problem more difficult to ignore.

The WHO took note of Lapeyssonnie's warnings about CSMa, and launched a campaign against the disease, including the development of a vaccine. The first choice of the WHO for vaccine production was Louis Greenberg (1914-2001) and the Laboratory of Hygiene of Ottawa based on his experience in vaccine production (Greenberg, 1963). Greenberg developed two different vaccines; one being a whole bacterial vaccine (2W), and the other an enzyme-lysed clear vaccine (1L). For this, he used four strains of CSMa, three from Lapeyssonnie's missions, and the other one provided by the National Institutes of Health in the United-States. The vaccine strains were grown in a Frantz medium, for 24 hours at 37°C. Following incubation, phenol was added and the organisms were heat-killed at 56°C for one hour (Greenberg & Cooper, 1963, p. 3). The Greenberg vaccines were tested by the WHO in Niamey in Niger in March 1963, after the country's Ministry of Public Health gave its authorization for a test on human subjects (Greenberg & Cooper, 1965, p. 21). There were no animal models available for assessing the quality and efficacy of the vaccine before testing it on humans, and so the principal aim of this trial was to demonstrate the safety of the vaccine. Léon Lapeyssonnie organized the trial: 215 children (Yantala and Canada Schools) were injected once subcutaneously with 1 ml of vaccine, 109 with 1L vaccine, 106 with 2W vaccine. Both vaccines prepared by Louis Greenberg were well tolerated (Lapeyssonnie & Digoutte, 1963, p. 3). Despite these positive results, Louis Greenberg and the Laboratory of Hygiene of Ottawa abandoned its production of the meningococcal A vaccine, obliging the WHO to find another partner, although Greenberg continued to collaborate with the WHO (and later the Institut Mérieux) right up until 1968.

2.3. *The Institut Mérieux vaccine*

After Greenberg's withdrawal from the programme, the WHO invited the Pasteur Institute in Paris to produce the vaccine and they declined in the following terms: "Unfortunately, the consensus is that in light of the remarkable effect of the sulfa-drugs on meningococcus, there is no need to produce a new vaccine" (IMTSSA, 005-500). The Pasteur Institute did not, it seems, take the risk of resistance to the sulfa drugs seriously. The second choice of the WHO for the vaccine production was the Institut Mérieux of Lyon, an option suggested by Lapeyssonnie who had met Charles Mérieux (1907-2001) a few years earlier and with whom he had already discussed the issue of resistance to the sulfa drugs (Mérieux, 1997, pp. 168-169). While CSMA was not part of the Institut Mérieux's area of 'field expertise', Mérieux nevertheless accepted the WHO's proposal for developing a meningococcal A vaccine, knowing that he could count on the help of Léon Lapeyssonnie and his team at the IMTSSA, with their extensive experience of the meningococcus bacteria in Africa.

There followed many exchanges between the Institut Mérieux and the IMTSSA concerning the preliminary steps of vaccine development, with the IMTSSA providing the Institut Mérieux with strains of the bacterium, as it had for Greenberg. Moreover, the WHO kept in close contact with the institute and followed the progress of the vaccine with interest. Nor were exchanges limited to those between the Institut Mérieux and the IMTSSA, or between the Institut Mérieux and the WHO, as the WHO also worked directly with the IMTSSA to implement the appropriate conditions for the success of this enterprise. In September 1964, the WHO organized a special meeting concerning *Neisseria* in Geneva (IMTSSA, 005-508), the first that it had organized specifically for the meningococcus. The meeting brought together different specialists of the disease to discuss different issues such as the bacteriology of meningococcus, the epidemiology of the disease and its incidence in the meningitis belt. All the participants agreed on the necessity for international cooperation, especially with African laboratories, in order to keep abreast of the epidemiology of the disease on the continent. Following this meeting, the WHO worked with the IMTSSA to organize two missions in Africa. Two military doctors from IMTSSA (R. Faucon and M. Vandekerkove) were sent to draw up an inventory of African laboratories, institutes, and health facilities which could potentially collaborate in the study of the disease (IMTSSA, 005-553; IMTSSA, 005-429a). The idea was to use these local facilities to help with the diagnosis

of CSMA and assist in applied research on the disease. These missions also had the specific objective of assessing the conditions for conducting a vaccine trial, and for this the WHO and the IMTSSA identified the Centre Muraz¹, in Bobo-Dioulasso, Upper Volta (today's Burkina Faso) as a partner for a collaboration. The Centre Muraz was the largest institute under the direction of the Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies (OCCGE), an organization set up to combat a range of diseases in Africa (African trypanosomiasis, leprosy, malaria, bilharzia, etc) and which included several countries in the meningitis belt. The Centre Muraz had been working for a number of years on CSMA and had already been identified as a potential partner by Lapeyssonnie during his missions for the WHO in 1961-62. The Centre Muraz accepted the WHO's offer to collaborate on the CSMA vaccine (a partnership for which it was paid) and was asked to 'prepare the terrain' for a vaccine trial. This preparatory period concluded with another meeting in Geneva in November 1966 to discuss the upcoming trial, with representatives from the WHO, the IMTSSA, the Institut Mérieux and Louis Greenberg (IMTSSA, 005-535).

The rise of sulfa-resistant strains of CSMA in Africa was making the development and testing of a meningococcal vaccine more urgent. In December 1966, R. Faucon, headed a team of doctors and technicians on a mission to Morocco at the request of the Moroccan government. This team was mandated by the French Ministry of Foreign Affairs to help the local health authorities in Fez to control a major meningitis epidemic in which 90% of the CSMA strains were resistant to sulfa drugs (Faucon & Zannotti, 1969). Though Morocco was outside the meningitis belt, this was the highest level of sulfa-resistance that had been observed. Although the epidemic ended quickly with relatively few victims it was the herald of Lapeyssonnie's predictions concerning the sulfa-drug resistance of the meningococcus A. While resistant strains had been regularly observed during epidemics in Africa and in the laboratory, this epidemic was the first to be massively carried by resistant strains. Although the city of Fez had the capacity to fight this epidemic, even without sulfa-drugs, experts feared the disastrous consequences of such an epidemic in the poor and isolated villages of the meningitis belt.

Three years were needed from the beginning of the collaboration between the WHO and the Institut Mérieux before a vaccine was ready for testing at the beginning of 1967,

¹ Founded in 1939, the Centre Muraz was based in Bobo-Dioulasso, Burkina Faso. Its role was to oversee the prevention, diagnosis and control of communicable and non-communicable diseases in the country. To this end, it promoted and carried out health research and training, providing expertise in medical biology, human sciences and public health. The Centre Muraz, <http://www.centre-muraz.bf/>, accessed 24 December 2018.

much longer than the time taken for the Greenberg vaccine. During these 3 years the Institut Mérieux vaccine had evolved significantly. Originally (in 1963), the vaccine was based on 10 strains isolated by Léon Lapeyssonnie during his missions, while the 1967 vaccine contained 24 strains² killed by heat and isolated by different correspondents of the IMTSSA (including R. Faucon and M. Vandekerkove) in different countries of the meningitis belt. In February and March 1967, a vaccine trial was organized by the WHO in partnership with the Centre Muraz and the IMTSSA in Yako (Upper-Volta) to evaluate the safety and the efficacy of the Institut Mérieux vaccine (Sansarricq, 1968). The remaining stocks of the Greenberg vaccine were used for comparison with the Institut Mérieux vaccine, as this vaccine had already demonstrated its safety during the 1963 vaccine trial in Niamey. To complete this trial set-up, an anti-typhoid vaccine was used as a control³. The Yako region was chosen for many reasons, including the partnership with the Centre Muraz in Upper Volta and the good relationships between the WHO and the OCCGE (of which Upper Volta was a member), which facilitated the organization of this trial. The Yako region presented a number of advantages for a trial, including a dense, stable and cooperative population, relatively plentiful medical facilities and comprehensive authorities willing to provide their support (Sansarricq, 1967, p. 2). As already mentioned, CSMa did not strike in the same place two years in a row, and so in addition to the vaccine production project, the WHO was developing a network of laboratories to monitor CSMa epidemiology, essentially in Africa. Though it was difficult to predict where the disease would appear with certainty, it was possible to guess where the next epidemic would occur with a fairly high degree of probability. From 1963 to 1966, the incidence of CSMa in Upper Volta was considered by the experts to be non-epidemic, leading the monitoring network to predict an epidemic here in 1967 (during the CSMa season).

In total, 18891 people were vaccinated (about 6000 people for each vaccine). Some reactions were observed for the Institut Mérieux vaccine, but these were not considered to be serious, and the safety of the vaccine was considered proven. However, the efficacy of the vaccine could not be evaluated, because the meningitis epidemic expected to break out in Yako did not take place (Lapeyssonnie, 1970, p. 625). Following this episode, many doses of the vaccine were sent to different African countries (Morocco, Upper Volta, Mali) but were

² The Institut Mérieux considered its vaccine would be more effective if it contained as many meningococcus A strains isolated during epidemics in Africa as possible.

³ This vaccine was used to check that there were no specific reactions due to the meningococcal vaccine inoculation.

used to test other features of the vaccine such as the effects on germ carriers and the morbidity rate⁴. In 1967, a few months after the Yako trial, the first Cerebrospinal Meningitis International Seminar was organized by the WHO and the OCCGE (IMTSSA, 005-429b). This meeting brought together health representatives from across the meningitis belt, in the premises of the Centre Muraz. Following the success of this meeting, a second seminar was held in 1968 in Niamey and Bobo-Dioulasso (Faucon, 1968b). These seminars represented a double interest for the protagonists implicated in the development of a meningococcal vaccine. First, these seminars allowed them to focus on progress in the control of CSMa, discussing such issues as resistance to the sulfa-drugs, vaccine production, and diagnosis of the disease. Second, with the participation of representatives of the countries of the meningitis belt, these seminars helped in the construction of a ‘favourable environment’ for future vaccine trials. Although they had no immediate plans to evaluate the efficacy of the Institut Mérieux vaccine, the WHO and its partners continued to mobilize against the public health problem represented by the CSMa in Africa.

3. Analysis

Before analysing the Yako trial and its consequences, I want first to briefly recall the main features of the ‘Doable Problems’ approach⁵. According to Fujimura, the doability of a problem should be understood in terms of the alignment of three levels of work organization: experiment, laboratory and social world. The alignment of the three levels of work organization takes place thanks to the process of articulation.

The Yako trial was an important event in the history of the development and production of the meningococcal vaccine, and it can be considered a point of no return in the process. Since the recruitment of the Institut Mérieux for the vaccine development in 1963, the WHO and its partners had done everything possible to obtain encouraging or even decisive results. Despite all the means put in place to successfully demonstrate the efficacy of the vaccine, nothing had happened as planned. Following the non-appearance of the epidemic predicted for Yako, and hence the absence of results from this trial, nothing was really

⁴ The morbidity rate is the frequency or proportion with which a disease appears in a population. The purpose of this experiment was to see whether the use of the vaccine had an effect on this rate.

⁵ More details can be found in the introduction, see above.

undertaken again to prove the efficacy of the Institut Mérieux vaccine. Despite the efforts of the protagonists who thought that it was feasible to produce an effective meningococcal vaccine, no such vaccine was produced during this period. Thus, while the configuration would lead us to think that producing an effective meningococcal vaccine was a doable problem at this time (1963-67), I think the correct interpretation is to see the problem as not doable due to a lack of alignment of the different levels.

According to Fujimura, if a problem is not doable, this is due to a failure to execute essential tasks at one or more levels, or a lack of articulation between the different levels. At the experiment level, the Institut Mérieux had developed a production technique for the meningococcal vaccine. As seen above, this technique took some time to be developed, and evolved during the process. Moreover, the CSMA was not part of the ‘field expertise’ of the Institut Mérieux. This being said the Institut Mérieux could count on Lapeyssonnie and the IMTSSA, with their expertise on the meningococcus bacteriology, to help them carry out this task, and the WHO also helped in the initial steps of the development process. These last two elements can also be assigned to the laboratory level. Two other collaborations were important at this laboratory level and for the organization of the Yako trial. Despite abandoning vaccine production, Louis Greenberg continued to collaborate with the WHO and the Institut Mérieux until 1968, donating his stock of vaccines to the WHO for comparison with other vaccines⁶ and travelling to Lyon in 1964 to help the researchers at Mérieux to develop activity tests for their vaccine. The last significant appearance of Louis Greenberg in this story was in 1968 when he talked about his vision of the qualities required of a good vaccine at the second Cerebrospinal Meningitis International Seminar on the CSMA. Remaining at the laboratory level, I can cite the special meeting on *Neisseria* in Geneva in September 1964, the two missions organized in Africa by the WHO and the IMTSSA (the missions led by Faucon and Vandekerkove, not counting Lapeyssonnie’s), and the discussion organized in Geneva in November 1966 that brought together all the protagonists involved in the vaccine development (in order to discuss the upcoming trial). All these ‘tasks’ had an influence on the understanding of the disease as well as the interest and feasibility of the Yako trial. It was during the missions that the Centre Muraz was enrolled to ‘prepare the terrain’ for a vaccine trial. Turning now to the social world level, the organization of the Yako trial was probably the most significant achievement at this level. The realization of this trial in Yako was partly due to the recruitment of the Centre Muraz which operated in Upper Volta, but it

⁶ During the Yako trial, Greenberg’s vaccine was used as a standard for the comparison with the Institut Mérieux product and Greenberg even provided some unused labels for the vials of vaccine for future trials.

was also due to the good relationship between the WHO and the OCCGE (which included Upper Volta and coordinated the Centre Muraz). Thus, we see a network of relationships at this level supporting the trial with the Mérieux vaccine. Moreover, the CSMA epidemic which struck Fez in 1966-67 certainly weighed in favor of developing an effective meningococcal vaccine, providing another motor for a trial to prove the efficacy of the Institut Mérieux vaccine. This epidemic, carried principally by sulfa-drug resistant strains, confirmed the seriousness of Lapeyssonnie's warnings. Furthermore, the appearance of this epidemic outside the meningitis belt heightened the danger of CSMA, as it signaled its capacity to spread to the entire African continent, and even into other parts of the world (Faucon & Zannotti, 1969).

I have passed in review the various tasks, assigning them to what I consider their appropriate level. These tasks seem to be in place and the 'problem', namely demonstrating the efficacy of the vaccine, should have been doable on Fujimura's model had there been an alignment of the three levels of work organization. However, it seems there was a lack of articulation between these levels, and I hypothesize that this was partly due to the non-appearance of the CSMA epidemic. There needed to be an epidemic in Upper Volta in order for the Yako trial to perform its function in the development of the Mérieux vaccine. The Yako trial had two distinct goals: to prove the safety of the Institut Mérieux vaccine and to prove its efficacy. The proof of the safety of the vaccine did not require an epidemic, as researchers and their partners needed only to observe the reactions to vaccination. The proof of efficacy, on the other hand, depended on the outbreak of an epidemic so that the rates of infection and mortality between the unvaccinated and vaccinated groups could be compared. By not appearing as predicted, the African meningitis lived up to its reputation as being capricious and insidious (Le Viguelloux, 1974). Without the epidemic it was impossible to prove the vaccine's efficacy, and this corresponds to a lack of articulation. I am not claiming that the non-appearance of the CSMA epidemic is the exclusive explanation for this lack of articulation, but I believe that it is the factor that triggered the misalignment at this point. Without articulation, the three levels cannot be correctly aligned, and the 'problem' of demonstrating the efficacy of the vaccine could not be made doable. I can hypothesize that the appearance of the epidemic would have allowed the evaluation of the vaccine efficacy (without it necessarily being positive), and this would have provided the missing element for a good articulation. The problem would have been rendered doable and perhaps resolved (one way or the other).

However, it is important to distinguish between what protagonists presumably saw as a problem and our explanation in terms of non-alignment. For the protagonists involved in demonstrating vaccine efficacy, the non-appearance of the CSMa epidemic could be considered as a problem that did not allow them to demonstrate the efficacy of the vaccine. From the perspective of our analysis, the non-appearance of the CSMa epidemic is one among a number of different elements in the lack of articulation which triggered the misalignment of the levels of work organization. Here I want to insist on the point that the objective pursued by the protagonists was the same as the ‘doable problem’ highlighted in this episode using Fujimura’s analytical framework: to develop an effective vaccine against CSMa which demanded the demonstration of vaccine efficacy.

The fact that the trial at Yako did not produce any results (positive or negative) does not explain why no subsequent attempt was made to evaluate the efficacy of the vaccine despite its largescale distribution (85000 doses) to different African countries (Morocco, Upper Volta, Mali) and the testing of other features, such as its effects on germ carriers and the effect of the vaccine on the morbidity rate. Evaluating the efficacy could be difficult for a number of different reasons: the non-appearance of the disease as predicted (as we saw in Yako), a lack of organization in the field, or the vaccination being carried out too late (during the declining phase of the epidemic). But what is striking is that no clear request was ever made to evaluate the efficacy of the Institut Mérieux vaccine, meaning that there was no attempt to repeat the Yako project in any of these 3 countries (Morocco, Upper Volta and Mali).

I believe that what we are witnessing here, after the Yako trial, is a situation that Fujimura has termed ‘uncertainty’. According to Fujimura: “Uncertainty decreases doability because it inhibits researchers’ abilities to plan ahead which, in turn, means that much of the work is carried out on an *ad hoc basis*. *Ad hoc* articulation for alignment usually takes more time and effort and generally decreases the efficiency of garnering and using resources at all levels of work organization” (Fujimura, 1987, p. 276). In the case of the Yako trial, the null outcome of this venture introduced this kind of uncertainty, and while the protagonists could have overcome it by organizing another trial – sufficient doses were distributed – thereby rendering the problem doable, this was not done. The uncertainty seems to have reduced the doability of the problem as Fujimura predicts. After the Yako trial, the WHO focused its attention on organizing two Cerebrospinal Meningitis International Seminars in 1967 and 1968, thereby federating research on CSMa with the possible aim of finding an alternative to the Institut Mérieux vaccine. An alternative was found in 1969 thanks to the enrollment of

Emil C. Gotschlich, a Rockefeller Institute researcher who had developed a polysaccharide vaccine for cerebrospinal meningitis C (Gotschlich, Goldschneider, & Artenstein, 1969). The idea was to use the same technique to develop a polysaccharide vaccine against CSMa, and for this the WHO approached the Walter Reed Army Institute of Research and the Rockefeller Institute to produce the new vaccine, suggesting a lack of confidence in the technique used by the Institut Mérieux to produce the vaccine or maybe in the Institute itself. As Bychenko Cvjetanović, in charge of microbial diseases at the WHO (and the principal interlocutor with the Institut Mérieux) wrote to René Triau, medical director of the Institut Mérieux, concerning a polysaccharide vaccine: “As far as the polysaccharide meningococcal antigen of group A is concerned, I am in contact with the Rockefeller Institute in New York and the Walter Reed Army Institute of Research, Washington. These institutions are able to prepare the vaccine and I have requested them to offer this vaccine to us. I am now awaiting their reply which I hope will be a positive one. However, should they for some reason be unable to produce this antigen, we would be glad if you could produce the necessary vaccine” (Institut Mérieux, box D11). Following the refusal of these other institutions, the WHO returned to the Institut Mérieux for a collaboration with Gotschlich to develop a vaccine.

In early 1963, the Institut Mérieux was using heat-killed strains of meningococcus to produce the vaccine, and while this was justified in terms of the immunological knowledge at the time, the domain was developing rapidly and by 1967 or 1968 the Mérieux technique could already be seen as outdated. As Cvjetanović put it during the second Cerebrospinal Meningitis International Seminar in 1968: “We still lack a solid, scientifically controlled immunological basis for the production of the vaccine. Vaccines have been prepared based on the immunological knowledge of the moment” (Cvjetanović, 1968, p. 123). After the Yako trial, the Institut Mérieux vaccine was used for testing features related to the disease just like the Greenberg vaccine had been used after it had been abandoned. Louis Greenberg had already remarked on the difficulty of developing a vaccine for CSMa: “One of the greatest difficulties in developing a meningococcal vaccine is that we do not know the antigen or antigens that produce immunity. We are working in the dark” (Greenberg, 1968, p. 136).

The people working for the WHO were not the first to doubt the viability of the approach, while Louis Greenberg had abandoned the production of his meningococcal vaccine for many different reasons, one of them was his loss of confidence in the possibility of proving the efficacy of his vaccine. As he said during the second Cerebrospinal Meningitis International Seminar in 1968: “It has been almost 6 years since we started working on an anti-meningococcal vaccine. It has been 5 years since Lapeyssonnie injected his first subject

with it. Up until now, some 10000 people have received our experimental vaccine [...] and I don't feel any closer to knowing the antigenic value of our vaccines in light of the combined results of all the studies from these last years" (Greenberg, 1968, pp. 137-138). Shortly thereafter, he wrote: "To date, all we can say is that we have a vaccine which protects mice and which is known to be pyrogen-free. If anyone would like to have a vaccine to protect mice, we have it" (IMTSSA, 005-543). Cvjetanović also wrote to Triau concerning the vaccines sent to Mali after the Yako trial: "I doubt whether any new scientific information will be obtained from this immunization but I hope that at least there will be no adverse reactions due to lack of sterility or other mistakes" (Institut Mérieux, box D11). Thus, during the period from 1962 to early 1969, developing an effective meningococcal vaccine did not seem to be a doable problem, partly due to the technique used to develop it.

The situation of uncertainty lasted from 1967 (after the Yako trial) until 1969 (the enrollment of Gotschlich). During this period, the situation of uncertainty kept the problem in a state of non-doability. As seen above, the technique used by the Institut Mérieux can be considered as an important element (or even the key element) of uncertainty. Technically speaking, there were no grounds for condemning this vaccine; it could not demonstrate its efficacy because of a natural accidental phenomenon (the non-appearance of the epidemic). Perhaps the non-occurrence of the Yako trial left a bitter impression: "a sizeable fraction of the population was vaccinated and ultimately this experiment failed because this area was not affected by meningitis for the next two years. A lot of money, a lot of energy and a lot of time was spent there for nothing" (Lapeyssonnie, 1970, p. 625). But for the WHO, it was clear that the vaccine was at fault: "It has already been mentioned that immunological knowledge about cerebrospinal meningitis is rather limited. Previous studies do not provide evidence of a beneficial effect of vaccines. [...] collective laboratory research will be organized at the international level to elucidate the basic immunological processes of this disease. Perhaps then it will be possible to prepare better types of vaccines and submit them to field trials to evaluate their effectiveness?" (Cvjetanović, 1968, p. 128). So, when Gotschlich's new technique for preparing the vaccine arrived in 1969, having already proved its efficacy with another strain and which additionally used a specific meningococcal antigen, the situation of uncertainty was unblocked. This event was probably perceived by the WHO as an opportunity to revive the production of a meningococcal A vaccine. Furthermore, it was a valid pretext for switching from an old 'outdated' technique to a new modern technique. It was probably also an opportunity for the Institut Mérieux to maintain its place as a producer, although this was also linked to the refusal of the Walter Reed Army Institute of Research and the Rockefeller

Institute to produce the vaccine. With the emergence of this new technique using the polysaccharides of the meningococcal bacterium to prepare the vaccine, the development of an effective vaccine against CSMA was again perceived as a doable problem by the institutions and researchers involved.

4. Conclusion

During the period from 1962 to 1967, the development of the meningococcal vaccine was above all a history of collaborations. As Stuart Blume has argued, the period between the 1940s and the 1970s was a ‘Golden Age’ in which such a collaboration was still relatively straightforward (Blume, 2017, p. 90). A public health organization (the WHO), a private pharmaceutical company (the Institut Mérieux), a military research institute (the IMTSSA), a public health institution (the Centre Muraz) and a public laboratory (Laboratory of Hygiene of Ottawa, Louis Greenberg) worked together to develop a prototype meningococcal vaccine. Knowledge and even useful biological materials circulated freely, without having to navigate the jungle of intellectual propriety that has characterized modern biotech vaccine programmes since the 1980s (Blume, 2017, pp. 94-95). Nevertheless, as we have seen, this proved not to be a ‘good’ period for producing an effective meningococcal A vaccine.

Fujimura’s concept of ‘doable problems’ offers a promising approach for analysing how a problem, however complex it may be, can be considered as ‘doable’ for certain actors involved. As I have underlined, there were a number of evident difficulties concerning the development of this meningococcal vaccine: CSMA was a disease which affected a poor continent (lack of potential markets), there was no animal model available for testing the vaccine (therefore it needed to be tested on humans), so the company which chose to develop a vaccine would have to invest a lot of money without any guarantee of success. Meningococcal vaccine trials were undertaken at the beginning of the twentieth century but with disappointing results. Moreover, there was already an effective treatment (the sulfa-drugs) that had only failed in a few isolated cases prior to the Fez epidemic of 1966-67. However, certain actors took the risk of trying to develop a meningococcal vaccine, which I suppose means that at the time of engaging in the project they saw this problem as doable.

This approach has allowed us to identify the complex range of factors that led to the trial in Yako, including many social factors such as the collaborations, formal meetings, informal discussions, and the circulation of materials. As we have seen, despite the fact that

all the necessary elements seemed to be present for demonstrating the efficacy of the vaccine, a lack of articulation – subsequent to the non-appearance of CSMA epidemic in Yako – ‘disaligned’ the levels. Following Fujimura’s approach, however, we should not simply blame the non-appearance of the CSMA epidemic, but rather try to identify a larger misalignment. Indeed, as I have argued, the period following the Yako trial should be understood as a period of ‘uncertainty’. This period of uncertainty was partly due to the lack of trust in the technique used by the Institut Mérieux to develop the vaccine, an ‘old technique’ which seemed to be outdated. Indeed, when the Institut Mérieux launched its vaccine development in the early 1960s, the technique used – a whole cell vaccine, using intact germs killed by heating – was the only known technique for working on the meningococcus and a meningococcal vaccine, but over five years later this was no longer the case. This situation of uncertainty, in addition to the lack of articulation kept the project in a state of non-doability until 1969 and the enrollment of Emil C. Gotschlich and the production of a new meningococcal polysaccharide vaccine (Erwa, Haseeb, Idris, Lapeyssonnie, Sanborn, & Sippel, 1973). This situation of uncertainty can also provide elements of answer where archives or scientific data are missing. No scientific data had demonstrated the inefficacy of the whole cell vaccine produced by the Institut Mérieux. However, it was apparently not considered very highly. While a demonstration of its efficacy was possible, it had never been attempted. No rational explanation can be advanced for this absence of a relevant trial. But as seen above, the notion of uncertainty can provide elements like ‘the lack of trust in the technique used’ or ‘the perception of a technique as outdated’ to try to explain this state of affairs.

What is the interest of this approach in the context of the wider history of vaccines as the area is currently configured? There are a large number of publications on the social aspects of vaccines, but they usually focus on people’s behavior with respect to vaccination, foregrounding notions such as ‘hesitancy’, ‘resistance’ or ‘acceptance’. The politics of vaccination is also well represented with a tendency towards considering a ‘global vision’ looking at what kind of decision is taken in light of the national or international context. Stuart Blume has probably been the best representative of this approach over the past ten years (especially in the Netherlands), and has brought this reflection together in his most recent book (Blume, 2017). The histories covering the technical aspects of the development and production of the vaccines have tended to concentrate on a ‘history of progress’; how was a given vaccine developed, using what technique, and when. In this context, the doable problems approach brings neglected aspects of vaccine development to the fore, including

many social factors such as the collaborations, formal meetings, informal discussions, and the circulation of materials.

A vaccine cannot be produced without a producer. A vaccine cannot be tested without a 'terrain' for a trial. The organization of a trial requires negotiations, exchanges, and partnerships. It is necessary to find the right collaborator, the right place, the right technique. The doable problems approach allows us to analyse these factors, divided into the three levels of work organization. The concept of articulation with its alignment of levels allows us to understand and explain why at one point, when everything seemed in place, the project failed to take off. This approach is neither a predictive nor a teleological approach, but rather a learning approach. If a problem was not doable, understanding why this was the case can be helpful for overcoming similar problems later on. Thus, for example, on the history of the meningococcal A vaccine, we can see that following the null results from Yako, all the subsequent trials were organized in conditions of a 'declared epidemic'.

Fujimura's approach contributes to bringing to light the steps that need to be taken to make a problem doable. Although often recounted in terms of a success story, vaccine development is rarely as straightforward as these narratives suggest. Approaching this specific episode via an analysis in terms of doable problems allows us to identify the very real difficulties of vaccine development, production and use. Finally, I want to stress that the development and production of a vaccine is not just a matter of applied science, social factors have to be brought into the analysis to understand these processes. The history of vaccines is too often presented as a narrative of progress, which means that any deviation from this narrative presents a problem. This leads to an inability to put the vaccine in perspective as just one element in public health policy, and serves to fuel the excessive expectations of the general public concerning these products. I believe that better understanding the stories of vaccines in their complex detail will help to put them back in perspective as tools in fight against disease. The history of vaccines alone cannot solve the current problems related to vaccination, especially the crisis of confidence and the hesitancy which affect a majority of vaccines indifferently in many countries⁷, but a historical approach to vaccines less oriented towards scientific progress and instead highlighting the difficulties of the venture where social aspects have to be taken into account can help to reposition the vaccine in its complex reality.

⁷ The Vaccine Confidence Project, <https://www.vaccineconfidence.org>, accessed 24 December 2018.

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