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Vaccine Development and Collaborations: Lessons from the History of the Meningococcal A Vaccine (1969–73)

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Abstract: Based on a wide range of historical sources, including published scientific literature and archives (Institut Mérieux, WHO and IMTSSA), this article examines the history of the development of the meningococcal A vaccine between 1969 and 1973. It explores the social factors of vaccine development including various collaborations, informal discussions, the circulation of products and materials, formal meetings, trials and setbacks to highlight the complex reality of the development, production and use of the vaccine. Inscribed in a 'Golden Age' of vaccine development and production, this episode not only adds to the scholarship on the history of vaccines, which has tended to focus on a narrative of progress, but also considers the sharing of knowledge through collaborations, and the risks involved in the development of a vaccine. Finally, this perspective reveals the uncertainties and difficulties underlying the production of an effective vaccine.

Keywords: Cerebrospinal meningitis A, Institut Mérieux, World Health Organization, Collaborations, Meningococcal vaccine, Africa

Introduction

Cerebrospinal meningitis A (CSMa) is endemic in much of Africa and can become epidemic. The germ, the meningococcus, now named *Neisseria meningitidis*, is exclusively human and especially affects children and young people with high mortalities.[1] For a long time largely neglected, the disease was brought to wider attention as a public

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[1] Pierre Saliou and H. Debois, 'Quelles stratégies vaccinales contre les épidémies africaines de méningite à méningocoque', *Bulletin de la Société de Pathologie Exotique*, 95, 5 (2002), 327.

health problem thanks in particular to the efforts of the French military doctor Léon Lapeyssonnie (1915–2001). Lapeyssonnie worked for several years in the French colonies of West Africa, studying the incidence and prevalence of African trypanosomiasis.[2] During this period he encountered CSMa on several occasions when an epidemic broke out in the area, and was able to note the impact of the disease on working life and health activities in the countries. As a result of these episodes, Lapeyssonnie started to issue alerts concerning the disease and its complex epidemiology.[3] Attached to the Institut de Médecine Tropicale du Service de Santé des Armées (IMTSSA) in Marseille, Lapeyssonnie was assigned to the World Health Organization (WHO) for a consulting mission on an epidemiological study of CSMa in Sub-Saharan Africa. 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). In 1963, after two years of work, Lapeyssonnie published an important monograph on CSMa in the *Bulletin of the WHO*, which remains a reference concerning the disease and its epidemiology even today.[4] Here, he highlighted the public health problem posed by CSMa in Africa, especially in an area stretching from Senegal to Ethiopia that he named the 'meningitis belt' where CSMa epidemics predominantly occurred.[5] Furthermore, Lapeyssonnie's work underlined the potential danger of resistance to sulfa-drugs and the need to develop an effective vaccine to avoid this problem. In fact, trials of vaccines against CSMa had been attempted in the early part of the twentieth century, but they had proved inconclusive.[6] The sulfa-drugs had been used for the first time against CSMa in the early 1940s,[7] and because they were generally very effective they continued to be used widely and indiscriminately until the 1960s; yet, if CSMa epidemics carried by sulfa-drug resistant strains occurred it could lead to a major public health disaster. 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 research programme against the disease, including the development of a vaccine. The WHO's choice for production of the vaccine 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.[8] With the help of the WHO, Léon Lapeyssonnie and his team at the IMTSSA, the Institut Mérieux developed a vaccine,[9] which was tested in 1967 during a vaccine trial in Yako, Upper Volta (today's Burkina Faso).[10] Although this trial demonstrated the safety of this vaccine, it could not

[2] J. Dutertre, 'General Medical Officer Lapeyssonnie "The Man of Big Endemics"', *Bulletin de la Société de Pathologie Exotique*, 95, 5 (2002), 307–9.
[3] Léon Lapeyssonnie, 'À propos de la récente épidémie de méningite cérébrospinale au Niger. Activité d'une mission médicale française (3 mars 1961–7 avril 1961)', *Médecine Tropicale*, 21, 2 (1961), 172–4.
[4] Léon Lapeyssonnie, 'La méningite cérébrospinale en Afrique', *Bulletin of the World Health Organization*, 28, suppl (1963), 1–114.
[5] Léon Lapeyssonnie, 'Étude épidémiologique comparée de la méningite cérébrospinale méningococcique dans les régions tempérées et dans la ceinture de la méningite en Afrique', *Médecine Tropicale*, 28, 6 (1968), 716–17.
[6] R. Faucon, 'Bases de la prophylaxie antiméningococcique', *Médecine Tropicale*, 28, 2 (1968), 162.
[7] R. Martin and A. Delaunay, 'L'action du para-amino-phényl-sulfamide (1162F) dans les méningites purulentes à streptocoques et accessoirement à méningocoques', *Presse Médicale*, 45 (1937), 1406–9.
[8] Charles Mérieux, *Virus Passion* (Paris: Robert Laffont, 1997) 168–9.
[9] The vaccine was based on twenty-four strains killed by heat and isolated by different correspondents of the IMTSSA in different countries of the meningitis belt.
[10] Léon Lapeyssonnie, 'De quelques problèmes pratiques posés par les essais contrôlés sur le terrain d'un vaccin antiméningococcique', *Médecine Tropicale*, 30, 5 (1970), 625.

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prove its efficacy because the predicted meningitis epidemic did not occur.[11] However, the development of an effective meningococcal A vaccine became more urgent: in the same year of this trial, a major CSMa epidemic struck in Fez, Morocco, in which 90 per cent of the strains were resistant to sulfa-drug.[12] Although the epidemic ended quickly, with relatively few victims, it was the herald of Lapeyssonnie's predictions concerning sulfa-drug resistance in meningococcus A.[13]

The history of meningococcal A vaccine development (1963–73) is inscribed in a specific period described by Stuart Blume as a 'Golden Age' of vaccine development and production. During this period (between the end of the 1940s and the end of the 1970s),[14] vaccine development and production was still shared between public- and private-sector institutions, often in open collaboration. Their relationships were typically rooted in a common commitment to public health, whether or not allied with the need to make a profit. Knowledge was freely available and freely exchanged. Patents played little or no role in vaccine development at this time and flows of strains or know-how were scarcely hindered by commercial interests.[15] Thus, it is typical of this period that meningococcal A vaccine development (1963–67) started with a collaboration between a public health organisation (the WHO), a private pharmaceutical company (the Institut Mérieux) and a military research institute (the IMTSSA).

By discussing the development of the meningococcal A vaccine (1963–73) in this specific period, this study will contribute to our knowledge in three different ways. First, it contributes to existing work on the history of vaccines. Since the publication of Louis Galambos' *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895–1995* (Cambridge: Cambridge University Press, 1995), a number of authors have written books[16] and articles[17] on this subject, as well as organising dedicated

[11] The disease represented a major problem for researchers and trials of prophylactic measures: it was almost impossible to predict where an epidemic would occur. It was also difficult to predict for any given area whether an epidemic would take place, making African meningitis epidemics appear capricious and insidious.

[12] R. Faucon and P. Zannotti, 'La méningite cérébrospinale à Fès en 1966–67. I. La méningite cérébrospinale au Maroc', *Médecine Tropicale*, 29, 2 (1969), 151–60.

[13] CSMa epidemics were usually short, with an ascending and descending phase.

[14] This period could be marked at the beginning by the John Enders' success in growing a polio virus on a tissue culture in 1948. The early 1980s were profoundly transformed by dramatic changes (fall of the Berlin Wall, collapse of the Soviet Union, economic crisis, extreme ideological commitment to liberalisation and privatisation), which affected vaccine development.

[15] Stuart Blume, *Immunization: How Vaccines Became Controversial* (London: Reaktion books, 2017), 90–1.

[16] Karen L. Walloch, *The Antivaccine Heresy: Jacobson v. Massachusetts and the Troubled History of Compulsory Vaccination in the United States* (New York: University of Rochester Press, 2015); Christine Holmberg, Stuart Blume and Paul Greenough, *The Politics of Vaccination: A Global History* (Manchester: Manchester University Press, 2017); Blume, *ibid*.

[17] Sanjoy Bhattacharya, 'International Health and the Limits of its Global Influence: Bhutan and the Worldwide Smallpox Eradication Programme', *Medical History*, 57, 4 (2013), 461–86; Dora Vargha, 'Between East and West: Polio Vaccination across the Iron Curtain in Cold War Hungary', *Bulletin of the History of Medicine*, 88, 2 (2014), 319–43; Gareth Millward, 'A Disability Act? The Vaccine Damage Payments Act 1979 and the British Government's Response to the Pertussis Vaccine Scare', *Social History of Medicine*, 30, 2 (2016), 429–47; Gareth Millward, '"A Matter of Commonsense': The Coventry Poliomyelitis Epidemic 1957 and the British Public', *Contemporary British History*, 31, 3 (2016), 384–406; Jeremy K. Ward, 'Rethinking the Antivaccine Movement Concept: A Case Study of Public Criticism of the Swine Flu Vaccine's Safety in France', *Social Science & Medicine*, 159 (2016), 48–57; Farah Huzair and Steve Sturdy, 'Biotechnology and the Transformation of Vaccine Innovation: The Case of the Hepatitis B Vaccines 1968–2000', *Studies in History and Philosophy of Biological and Biomedical Sciences*, 64 (2017), 11–21; Mary Augusta Brazelton, 'Engineering Health: Technologies of Immunization in China's Wartime Hinterland, 1937–45', *Technology and Culture*, forthcoming (2019).

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meetings.[18] Most of these studies have focused on the politics of vaccination, protest movements or the innovative aspect of vaccine production.

Second, this study contributes to the scholarship on cerebrospinal meningitis A. The history of the development of the meningococcal A vaccine has been largely ignored, despite the WHO classifying CSMa as a public health priority in Africa during the second half of the twentieth century. In light of its increasing resistance to sulfa-drugs, active immunisation appeared to be the best approach to combatting the disease, leading to new initiatives to produce an effective vaccine. However, pharmaceutical companies tended to regard CSMa vaccines as scientifically and commercially less interesting than other drug projects.[19] The vaccine would target a disease that at that time attracted little attention in Europe and North America. Indeed, developing this vaccine presented a number of drawbacks for pharmaceutical laboratories: CSMa was a disease that affected a poor continent (African countries represented poor potential markets); the *Neisseria meningitidis* is a germ that affects exclusively humans, so no animal model was available for testing the vaccine (therefore it needed to be tested on humans); and 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. Meningococcal A vaccine trials had been carried out at the beginning of the twentieth century with poor results.[20] 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.[21] In the context of the specific period presented above, it is interesting to analyse the stakes and the motivations of the actors engaged in the development of such a vaccine.

Finally, this examination of the development of the meningococcal A vaccine provides a new perspective on the complex reality of the development, production and use of the vaccine. In this article, we 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. In this study, we will be considering not only certain technical aspects in the vaccine's production, but also the wider social factors of the vaccine's development including various collaborations, informal discussions, the circulation of products and materials, formal meetings, trials and setbacks. In the specific period described above, the collaborations of the different actors under the aegis of the WHO provide interesting lessons about the management of this kind of project. Seen in a wider historical context, this history provides reflections on the current situation of vaccine development and production.

The Meningococcal A Polysaccharide Vaccine

After the trial in Yako in 1967,[22] many doses of the prototype vaccine developed by the Institut Mérieux were sent to different African countries (Morocco, Upper Volta, Mali) to test different features of the vaccine, such as the effect on germ carriers and the effect of

[18] Workshop on 'Vaccination between Research, Health Politics, and Nation: Lessons learned from historical examples on vaccination campaigns and vaccination development' held at the East Anglia University Medical School in Norwich, UK, in October 2013; Workshop on 'Vaccines: Values, Present and Past' held at the Uppsala University Department of History of Science and Ideas in Uppsala, Sweden, in November 2017.

[19] Janice Graham, 'Ambiguous Capture: Collaborative Capitalism and the Meningitis Vaccine Project', *Medical Anthropology*, 35, 5 (2016), 420.

[20] Faucon, *op. cit.* (note 6), 162.

[21] Faucon and Zannotti, *op. cit.* (note 12), 151–60.

[22] Lapeyssonnie, *op. cit.* (note 10), 625.

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the vaccine on the morbidity rate,[23] but until 1969 no subsequent attempt was made to evaluate the efficacy of the vaccine.

When the Institut Mérieux agreed to the request of the WHO to develop a meningococcal A vaccine, CSMa was not part of the Lyon institute's area of expertise. Nevertheless, the Institut Mérieux accepted the WHO's request, knowing that it could count on the help of Lapeyssonnie and his team at the IMTSSA with their extensive experience of the meningococcus bacteria in Africa.[24] Between 1963 and 1967, the Institut Mérieux developed a prototype heat-killed whole cell vaccine containing twenty-four strains isolated by IMTSSA correspondents in different countries of the meningitis belt.[25] At that time, the use of heat-killed meningococcal strains to produce a vaccine might have seemed outdated. However, this was justified in terms of the immunological knowledge of the time. As Bychenko Cvjetanović, in charge of microbial diseases at the WHO (and the principal contact with the Institut Mérieux), put it during the second Cerebrospinal Meningitis International Seminar in 1968 in Niamey and Bobo-Dioulasso: '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'.[26] The prototype vaccine developed by the Institut Mérieux could not demonstrate its efficacy during the trial in Yako because the expected CSMa epidemic did not occur. After this event, without clear scientific evidence and without any clear reason, there was a loss of confidence in the technique used by the Institut Mérieux to produce the vaccine (or maybe in the institute itself). This production technique was definitively abandoned in 1969 after the WHO and the Institut Mérieux were informed of the existence of an effective vaccine against cerebrospinal meningitis C (CSMc).[27]

The vaccine in question had been developed by Emil C. Gotschlich, a Rockefeller Institute researcher. The vaccine developed by Gotschlich was based on the polysaccharides present on the meningococcal capsule.[28] Polysaccharides are chemical substances which have an antigenic power if their molecular weight reaches 100 000 daltons (Da).[29] The antigenic power of such polysaccharides – the ability to be recognised as an antigen by the immune system – had been highlighted by Michael Heidelberger based on research on the pneumococcus bacterium.[30] Inspired by Heidelberger's work, Gotschlich had extracted polysaccharides from the meningococcal capsule, with a detergent called Cetavlon, which would go into the composition of his vaccine.[31] Gotschlich started his work on

[23] Archives of the Institut Mérieux, box D11, D11_2, 3_08/06/67; Archives of the Institut Mérieux, box D11, D11_2, 5_21/11/67; Archives of the Institut Mérieux, box D11, D11_3, 2_11/03/69.

[24] Archives of the Institut Mérieux, box D11, D11_1, 1_12/11/63.

[25] Archives of the Institut Mérieux, box D11, D11_2, 3_08/06/67.

[26] B. Cvjetanović, 'Les vaccins antiméningococciques étudiés par l'Organisation Mondiale de la Santé: A. Les vaccins antiméningococciques', *World Health Organization, BD/CSM/68.9, II^{ème} séminaire interrégional sur la méningite cérébrospinale, Niamey, 13–17 février 1968, Bobo-Dioulasso, 19–24 février 1968*, 123.

[27] Archives of the Institut Mérieux, box D11, D11_3, 1_04/03/69.

[28] Until then, the meningococcal vaccines developed were based on the whole cell technique using several strains of meningococcus, killed by heat and alcohol.

[29] In the field of biochemistry, the dalton represents the mass unit of atoms. By way of comparison, one protein amino acid represents about 110 Da, a protein greater than 12 kDa, and a DNA base with deoxyribose and phosphate (one nucleotide) about 330 Da.

[30] Andrew W. Artenstein and Marc F. LaForce, 'Critical Episodes in the Understanding and Control of Epidemic Meningococcal Meningitis', *Vaccine*, 30 (2012), 4702–4.

[31] Emil C. Gotschlich, Teh Yung Liu and Malcom S. Artenstein, 'Human Immunity to the Meningococcus: III. Preparation and Immunochemical Properties of the Group A, Group B, and Group C Meningococcal Polysaccharides', *The Journal of Experimental Medicine*, 129, 6 (1969), 1350–1.

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the polysaccharide vaccine at the Walter Reed Army Institute of Research before being recruited to the Rockefeller Institute.[32] CSMc was of interest to the US army because the disease affected new recruits in training camps where the misuse of antibiotics had led to the appearance of resistant strains.[33] In fact, the US army's concern about meningococcal C resistance in training camps was the same as the WHO's with meningococcal A resistance in the African meningitis belt. The vaccine developed by Gotschlich had soon shown its efficacy during a trial organised by the US army shortly after its development.[34]

When the Institut Mérieux and the WHO heard about Gotschlich's technique, they saw an opportunity. The Institut Mérieux took advantage of the WHO's influence and asked to be put in contact with the Rockefeller Institute.[35] A few months after this request, members of the Institut Mérieux and the Centre International de Référence pour les Méningocoques du Pharo (abbreviated as Pharo)[36] were invited to the WHO's Geneva headquarters for an exchange with Professor Krause of the Rockefeller Institute.[37] The American institute agreed to share its technique, including Gotschlich's close collaboration with the Institut Mérieux, the WHO and Pharo for developing a meningococcal A vaccine.[38] Gotschlich's first visit to the Institut Mérieux took place in July 1969, and it was organised to help the Lyon institute to cultivate the meningococcus bacterium in order to correctly extract the polysaccharides used in the composition of the vaccine.[39] This work between Gotschlich and the Institut Mérieux continued throughout the summer by written correspondence, focusing especially on the best parameters to adopt (agitation, aeration, temperature and pH) for meningococcal cultivation.[40] This first step of collaboration allowed the Institut Mérieux to extract polysaccharides, which were then sent to Gotschlich in New York for analysis.[41]

We can stop for a few moments to question the risk of developing such a vaccine. As noted in the introduction, developing this vaccine presented a number of drawbacks for pharmaceutical laboratories. Nevertheless, CSMa was a public health problem in Africa in the second half of the twentieth century. Every year, tens of thousands of cases were reported, with a mortality rate of 10–15 per cent.[42] But the problem of meningococcal A strains resistant to sulfa-drugs had been highlighted only a few times. In fact, in Africa between 1963 and 1973, the only epidemic carried mostly by drug-resistant meningococcus A was the one that occurred in Fez in 1966–7.[43] Thus, the vaccine had been developed to avoid a health disaster that never really took place. The problem was

[32] Artenstein and LaForce, *op. cit.* (note 30), 4704.
[33] M.S. Artenstein and R. Gold, 'Current Status of Prophylaxis of Meningococcal Disease', *Military Medicine*, 135, 9 (1970), 735.
[34] M.S. Artenstein, R. Gold, J.G. Zimmerly, F.A. Wyle, H. Schneider and C. Harkins, 'Prevention of Meningococcal Disease by Group C Polysaccharide Vaccine', *New England Journal of Medicine*, 282, 8 (1970), 417–20.
[35] Archives of the Institut Mérieux, box D11, D11_3, 2_11/03/69.
[36] The Pharo, located in Marseille, was a centre created in 1966 by the WHO. The creation of this centre was an element of the research programme launched by the WHO to fight against the CSMa after the work of Lapeyssonnie. Lapeyssonnie's team of the IMTSSA was the hard core of this centre.
[37] Archives of the Institut Mérieux, box D11, D11_3, 4_11/06/69.
[38] Archives of the Institut Mérieux, box D11, D11_3, 5_09/07/69.
[39] Archives of the Institut Mérieux, box D11, D11_4, 1_11/07/69.
[40] Archives of the Institut Mérieux, box D11, D11_4, 3_01/08/69.
[41] Archives of the Institut Mérieux, box D11, D11_4, 4_25/08/69.
[42] Léon Lapeyssonnie, 'Épidémiologie de la méningite cérébro-spinale à méningocoques: le point de vue de Sirius', *Médecine Tropicale*, 43, 1 (1983), 12.
[43] Faucon and Zannotti, *op. cit.* (note 12), 151–60.

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probably a little bit more complex. The use of sulfa-drugs was certainly more expensive than an active immunisation, and it required having stockpiles of sulfa-drugs in Africa.[44] Moreover, to cure an individual the disease had to be quickly treated with these drugs. In Africa, the distances between villages, or between villages and towns, or between population groups and health organisations were immense.[45] Furthermore, the sulfa-drugs could only treat the disease, not control it. Finally, an effective meningococcal A vaccine was considered a good approach to fighting the public health problem represented by CSMa in Africa.

Only two months after the start of collaboration between the Institut Mérieux and Gotschlich, in September 1969, the WHO organised a round table on CSMa in Marseille in partnership with Pharo. This event brought together more than twenty participants involved in the fight against CSMa, including the protagonists mentioned so far.[46] The WHO used it to address some issues related to the disease: from now on, Gotschlich's technique would be the only one used to develop a meningococcal vaccine,[47] and the WHO was already looking for a zone to perform a vaccine trial. Four countries had been targeted to host this trial: Mali, Sudan, Nigeria and Morocco. The first three countries were included in the meningitis belt, while Morocco had been chosen because of the 1966–67 Fez epidemic. The WHO intended to perform this trial in December 1969, and Pharo, in partnership with the Centre Muraz, were in charge of setting up a protocol.[48] The Centre Muraz was the most important laboratory under the leadership of the Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies (Organization of Coordination and Cooperation for the fight against the Great Endemics, abbreviated OCCGE). This organisation promoted research against many diseases affecting the African continent (African human trypanosomiasis, leprosy, malaria, bilharzias, etc.), and included many meningitis belt countries in its ranks. The WHO had good relations with OCCGE, which led to the completion of the Yako trial in Upper Volta in 1967. Certainly, the CSMa Marseille round table launched the meningococcal A polysaccharide vaccine.

After assessing the risks related to the production of this vaccine, we can question the interests and stakes for the main protagonists. The WHO had a prominent position in decision-making and interventions around infectious diseases. It was a global health institution, playing a key role in public health strategies, including the planning, implementation and funding of health programmes. Therefore, launching a research programme to fight CSMa was completely within its remit. Pharo was created through the WHO programme to facilitate collaborative research on CSMa, whatever the means mobilised against the disease. The centre assisted laboratories involved in the isolation and identification of meningococcal strains, provided reference strains, and conducted resistance experiments of strains with sulfa-drugs. It seemed inevitable – almost like a duty – for the centre to be involved in the development of a meningococcal A vaccine. For Gotschlich, who had developed an effective vaccine to fight CSMc, participating in

[44] Léon Lapeyssonnie and J.P. Digoutte, 'La vaccination antiméningococcique: intérêt et conditions d'utilisation', *WHO unpublished document*, 16 September 1963, 3.
[45] P. Ghipponi, J. Darrigol and R. Faucon, 'Un problème d'épidémiologie pratique en Afrique sahélienne: recherche de porteurs rhinopharyngés de méningocoques', *Médecine Tropicale*, 28, 4 (1968), 504.
[46] Archives of the WHO, box C11-87-2, 'Informal Meeting on Cerebrospinal Meningitis Organized by the WHO International Reference Center for Meningococci with WHO Participation – Marseille, September 1969' (1969), 1.
[47] *Ibid*., 2–3; The whole cell technique used in the past by the Institut Mérieux would never be used again.
[48] Archives of the Institut Mérieux, box D11, D11_5, 1_22/07/69.

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and helping to develop a meningococcal A vaccine was therefore a continuation of his work. It would also allow him to increase his expertise on polysaccharide vaccines. In the course of his work, Gotschlich had only succeeded in extracting and demonstrating the immunogenicity of polysaccharide A. Collaborating with the Institut Mérieux and the WHO could perhaps offer him the opportunity to demonstrate also the efficacy of a meningococcal A polysaccharide vaccine, and thus be associated with this success. If this venture succeeded, his name would be associated with communications and publications. If it did not, Gotschlich would not have lost very much except maybe his time. Finally, for his help with the development of the vaccine, he had been paid only $3500 per year by the WHO.[49] A symbolic sum, this nominal subsidy was probably used to contribute to some technical costs.

It is more difficult to analyse the Institut Mérieux. The Lyon institute was not the WHO's first choice for developing this vaccine. Louis Greenberg (1914–2001) of the Laboratory of Hygiene of Ottawa was chosen in 1962 for his expertise in vaccine production.[50] He quickly developed an enzyme-lysed clear vaccine, which proved its safety during a vaccine trial in Niamey, Niger, in March 1963.[51] Despite these positive results, Greenberg abandoned meningococcal vaccine production for reasons that have not been clearly established.[52] Presumably it became financially impossible for a public laboratory to maintain vaccine production.[53] The WHO's second choice was the Institut Pasteur in Paris, which 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'.[54] Thus, the Institut Mérieux was the third choice, an option suggested by Lapeyssonnie who knew the institute's president, Charles Mérieux. As explained at the beginning of this section, CSMa was not part of the Lyon institute's area of expertise. It developed and produced the vaccine almost for free: it received a grant of only $1000 from the WHO, an even more symbolic subsidy than for Gotschlich.[55] This grant constitutes the only financial support that the Lyon-based company would receive during the vaccine's development. When the Institut Mérieux agreed to the request of the WHO, it had no guarantee of any return on investment. Finally, when the Institut Mérieux agreed to the request of the WHO, it seemed like a risky bet.

Following the recommendations of the WHO during the CSMa round table, the Institut Mérieux had to start producing stockpiles of meningococcal A polysaccharide vaccines.[56] But before the use of the vaccine during a trial, its safety and its immunogenicity needed to be demonstrated. To meet this demand, Gotschlich developed a specific protocol for a pilot trial to be carried out on children.[57] Indeed, the immunogenicity of the polysaccharide A

[49] Archives of the WHO, box C11-181-15(A), 'Collaboration Laboratory Study of Polysaccharide CSM vaccines' (1974).
[50] Louis Greenberg, 'A New Approach to Bacterial Vaccines', *Canadian Medical Association Journal*, 89, 9 (1963), 396–402.
[51] Lapeyssonnie and Digoutte, *op. cit.* (note 44), 1.
[52] Archives of the Institut Mérieux, box D11, D11_1, 1_12/11/63.
[53] Archives of the IMTSSA, box 2013 ZK 005-500, 'Letter to B. Cvjetanović from Louis Greenberg', 9 September 1963.
[54] Archives of the IMTSSA, box 2013 ZK 005-500, 'Letter to B. Cvjetanović from Pierre Mercier', 8 November 1963. The doctor, Pierre Mercier, was the deputy general secretary of the Institut Pasteur in Paris.
[55] Archives of the WHO, box C11-181-10, 'Grant to Institut Mérieux, Lyon, in respect of production of cerebro-spinal meningitis vaccine' (1969).
[56] Archives of the Institut Mérieux, box D11, D11_5, 1_22/07/69.
[57] Archives of the Institut Mérieux, box D11, D11_7, 4_15/10/69.

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was known for adults,[58] but no experiments had been carried out on children, the sub-population the most widely affected by CSMa.[59] This pilot trial was organised in Dakar, Senegal, by Professor Michel Rey, director of the Infectious Diseases Clinic of the Faculty of Medicine and Pharmacy, and collaborator with the WHO.[60] For Gotschlich and the WHO, satisfactory results during this experiment were the precondition for any future vaccine trial, and especially the trial scheduled for December 1969. So in October 1969, the Institut Mérieux sent twenty vials of meningococcal A polysaccharide vaccine batch V1 S004 to Dakar. Serum samples taken after vaccination were sent to Gotschlich for analysis.[61]

In parallel with the work done by the Institut Mérieux and Gotschlich, the WHO negotiated with the African states to organise a vaccine trial in December 1969. In fact, before the round table in September 1969, the WHO had established links with the Sudanese government, one of the four countries being targeted.[62] Negotiations with Sudan started in April 1969 – before the collaboration with Gotschlich started – during an inter-regional seminar on the CSMa organised by the WHO in Khartoum.[63] Sudan had been targeted by the WHO because its level of endemic CSMa was high, enabling vaccine experimentations, and because Khartoum, the capital city, had good medical and scientific infrastructures.[64] To build links with Sudanese authorities, the WHO contacted Doctor Kalcić, one of their own epidemiologists working in the capital. Kalcić had been approached not only because he worked for the WHO but also because he had overseen a pertussis vaccine trial in Slovenia, making him a good candidate for organising a trial of the meningococcal vaccine.[65] But despite the WHO's intervention, the government of Sudan did not agree to the trial. This refusal was related to political considerations. Indeed, during the few months of negotiations the Minister of Health had changed. The new minister was clearly not as favourable as his predecessor to a WHO intervention in Sudan.[66]

Although Sudan refused, an agreement was reached with Mali – another one of the four countries targeted at the round table – to conduct a trial in December 1969.[67] For this experiment, following discussions as the round table, the Institut Mérieux had prepared 40 000 doses of vaccine batch V1 S004 and an equal quantity of placebo.[68] However, the Malian vaccine trial never took place. The Dakar pilot trial was inconclusive and the

[58] Emil C. Gotschlich, Irving Goldschneider and Malcom Artenstein, 'Human Immunity to the Meningococcus: IV. Immunogenicity of Group A and Group C Meningococcal Polysaccharides in Human Volunteers', *The Journal of Experimental Medicine*, 129, 6 (1969), 1367–84.
[59] Saliou and Debois, *op. cit.* (note 1), 327.
[60] Archives of the WHO, box C11-181-13, 'Subvention à la Faculté Mixte de Médecine et de Pharmacie, Dakar, en vue d'études sur les vaccins contre la méningite cérébrospinale: étude immunologique des vaccins contre la méningite cérébrospinale à utiliser dans les essais sur le terrain' (1970).
[61] Archives of the Institut Mérieux, box D11, D11_7, 5_17/10/69.
[62] Archives of the WHO, box C11-446-2SUD, 'Proposed Field Trial of Cerebrospinal Meningitis Vaccine' (1969).
[63] Archives of the WHO, box C11-440-3(69), 'WHO Inter-Regional Seminar on Cerebrospinal Meningitis Control – 1969' (1969); Archives of the IMTSSA, box 2013 ZK 005-511, 'Letter to Léon Lapeyssonnie from B. Cvjetanović', 21 March 1969. Cvjetanović was the head of Microbial Diseases at WHO.
[64] Archives of the WHO, *op. cit.* (note 62).
[65] Archives of the WHO, *op. cit.* (note 62).
[66] Archives of the WHO, *op. cit.* (note 62).
[67] Archives of the WHO, box C11-181-9, 'Subvention au Ministère de la Santé Publique et des Affaires Sociales, Koubala, Mali, en vue d'un essai pratique contrôlé d'un vaccin polysaccharidique contre les méningocoques du groupe A et étude sur les porteurs de méningocoques' (1969).
[68] Archives of the Institut Mérieux, box D11, D11_8, 3_31/10/69.

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meningococcal A polysaccharide vaccine batch V1 S004 showed no immunogenicity.[69] Following this disappointment, the WHO had wanted to quickly arrange another pilot trial in Dakar with a new batch of vaccine, but Rey was no longer available. Furthermore, a yellow fever epidemic broke out in Mali in early December, and the country's health authorities were no longer interested in a meningococcal vaccine trial.[70] With the vaccine's immunogenicity problem, the impossibility of carrying out a new pilot trial and the need to find another country in which to perform a full vaccine trial, the protagonists had to think again.

Finding a Solution

According to Gotschlich's analyses of sera from Dakar, the vaccine's lack of immunogenicity was due to a degradation of the polysaccharides. As presented in the previous section, the polysaccharides have a suitable antigenic power – the same thing as immunogenicity – only if their molecular weight was 100 000 Da or more. Degradation led to a decrease in their molecular weight and, therefore, their antigenic power. This degradation seemed to be a feature of the meningococcus cultivated in the high-capacity fermenters used by the Institut Mérieux. Gotschlich had not used the same type of machines when he worked on the meningococcal C polysaccharide vaccine and so had not been confronted with this problem.[71] To confirm this hypothesis, Gotschlich asked the Institut Mérieux to send him a new batch of vaccine (lot V2 S0011) in order to perform supplementary analyses.[72] In addition to the technical help provided by Gotschlich, Pharo proposed to execute the same analysis to provide a second opinion.[73] At the end of January 1970, Doctor Vandekerkove from Pharo went to the Institut Mérieux to study the method for producing the meningococcal polysaccharide vaccine in more detail. During this visit, he had brought back vaccines of the batch V2 S0011 to Marseille to carry out analyses concerning the degradation of polysaccharides.[74] The analyses performed by the technicians at Pharo gave the same conclusion as Gotschlich: there had been a depolymerisation – or a degradation – of polysaccharides contained in the vaccine, and this depolymerisation resulted in a decrease in molecular weight below 100 000 Da.[75] To solve the immunogenicity problem, the manufacturers needed to solve the problem of the depolymerisation of polysaccharides. Gotschlich was the first to propose a solution. He compared the vaccines produced by the Institut Mérieux with the batch A-5 produced by the Walter Reed Army Institute of Research.[76] Indeed, Gotschlich and his associates at the Rockefeller Institute had already evaluated the immunogenicity of polysaccharide A in 1969. There was a decrease in molecular weight for the batch A-5 as well as for the vaccine produced by the Institut Mérieux. However, this decrease was larger in the vaccine produced by the Institut Mérieux. To try to understand where the problem was coming from, Gotschlich asked Robert Donikian, head of the Bacteriological Division at the Institut Mérieux, to check the manufacturing process, the sterilisation and the lyophilisation performed on the vaccine in

[69] Archives of the Institut Mérieux, box D11, D11_8, 10_10/12/69.
[70] Archives of the Institut Mérieux, box D11, D11_8, 11_10/12/69.
[71] *Ibid*.
[72] Archives of the Institut Mérieux, box D11, D11_8, 12_11/12/69.
[73] Archives of the Institut Mérieux, box D11, D11_8, 16_22/01/70.
[74] Archives of the Institut Mérieux, box D11, D11_10, 2_17/02/70.
[75] Archives of the Institut Mérieux, box D11, D11_10, 3_17/03/70.
[76] Gotschlich, Goldschneider and Artenstein, *op. cit.* (note 58).

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the Lyon laboratories;[77] but this investigation did not reveal anything suspicious. Unable to detect concretely at which stage of the production chain the problem arose, Gotschlich decided to put in place a new manufacturing process for the vaccine.[78] In the future, this new manufacturing process should avoid the degradation of the polysaccharides contained in the vaccine, and therefore the decrease in immunogenicity of the latter.

While the Institut Mérieux, Pharo and Gotschlich attempted to solve the immunogenicity problem, the WHO sought a place to conduct a pilot trial. Obtaining satisfactory results in such a trial was the prerequisite for a large-scale trial to demonstrate the efficacy of the vaccine. With Rey unavailable in Dakar, the Centre Muraz – which had been in charge of setting up the protocol for the cancelled trial of December 1969 – in Bobo-Dioulasso, Upper Volta, appeared to be the best option. Indeed, Doctor Jean Étienne of the Meningitis Section of the Centre Muraz had requested the vaccine from the Institut Mérieux. Cases of CSMa had become more and more numerous since the end of 1969, especially in Bobo-Dioulasso, and Étienne feared that an epidemic would break out in 1970: 'However, it would be prudent to have the necessary products now, so that immediate action can be taken in the event of confirmed epidemics'.[79] The Institut Mérieux replied:

> It seems difficult to deliver to the Centre Muraz directly. The actual manufacture was made at the request of WHO and under its aegis, and it does not seem possible to distribute it freely. Perhaps the Centre Muraz could contact WHO to participate in the campaign that this organization has undertaken.[80]

At this moment, the interests of Étienne and the WHO did not seem to converge. While Étienne wanted the vaccines to be ready in case of an epidemic, the WHO wanted the Centre Muraz to use these vaccines for a pilot trial. Thus, at the request of the WHO, the Centre Muraz could only use the vaccine to perform a trial. In other words, it was forbidden from using the vaccine for a general immunisation programme:

> In the meantime, the Centre Muraz, Bobo Dioulasso, has requested us to provide them with the vaccine for use in case of an outbreak of CSM. Dr Triau has replied that the vaccine will be sent only if the center will agree to carry out a controlled field trial, and that it will not be released for mass immunization.[81]

But before vaccines were sent to the Centre Muraz, the WHO wanted Gotschlich to go there to supervise. As indicated by Doctor Triau to Étienne: 'Upon receipt of your letter, I telephoned Dr Cvjetanović (WHO) in Geneva. He thought it desirable that Dr Gotschlich should visit the Centre Muraz as soon as possible.'[82] Cvjetanović had also written to Gotschlich to inform him of this suggestion: 'Since this study will require very close observation and supervision, I think it would be best if you yourself could go to Upper Volta to carry this out.'[83] But this request was unsuccessful. Étienne was insistent about the need for the vaccine in Upper Volta: 'Our intervention system is in place, and we are missing only the main element: the vaccine. Anyway, I draw your attention to the fact that we must do something under penalty of losing the confidence of the Governments and no longer be able to do anything thereafter.'[84] Finally, WHO relented, and in February 1970 the Institut Mérieux sent vials of vaccine to the

[77] Archives of the Institut Mérieux, box D11, D11_11, 1_09/04/70.
[78] Archives of the Institut Mérieux, box D11, D11_11, 3_18/05/70.
[79] Archives of the Institut Mérieux, box D11, D11_8, 8_04/12/69.
[80] Archives of the Institut Mérieux, box D11, D11_8, 9_08/12/69.
[81] Archives of the Institut Mérieux, box D11, D11_8, 11_10/12/69.
[82] Archives of the Institut Mérieux, box D11, D11_8, 10_10/12/69.
[83] Archives of the Institut Mérieux, *op. cit.* (note 81).
[84] Archives of the Institut Mérieux, box D11, D11_8, 14_14/12/69.

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Centre Muraz.[85] Nonetheless, as seen above, the vaccine's immunogenicity problem would not be solved until several months later. So, it was hard to imagine that the Centre Muraz could obtain satisfactory results. Without any guarantee concerning the immunogenicity of the meningococcal A polysaccharide vaccine produced by the Institut Mérieux – at least until the new manufacturing process had been applied – the vaccine trial scheduled for December 1969 was postponed to the following year by the WHO.[86]

At the beginning of summer 1970, the Institut Mérieux produced a new batch of the meningococcal A polysaccharide vaccine, V4 S0053, which was sent to Gotschlich for analysis.[87] Gotschlich's conclusion was that the batch produced using the new manufacturing process no longer had the decrease in the molecular weight that had been seen in batches V1 and V2.[88] Following these positive results, vials of this new batch were sent to Rey – available again – in Dakar to perform a new pilot trial to evaluate the immunogenicity of the vaccine.[89] After the completion of the pilot trial in Dakar, serum was recovered from the vaccinated subjects and sent to Gotschlich, who confirmed the immunogenicity of batch V4 S0053.[90] These results in hand, the WHO now had to find a country that would agree to a full vaccine trial. This condition was fulfilled in September 1970 at the WHO Regional Assembly in Accra, Ghana. During this meeting a delegation from Nigeria – still one of the four countries targeted during the 1969 round table in Marseille – informed the WHO of the possibility of carrying out a vaccine trial.[91]

With the preparation of a new trial in Nigeria to demonstrate the efficacy of the meningococcal polysaccharide vaccine, the Institut Mérieux started the production of a new batch (V5 S0087). After toxicity and the sterility tests had been carried out by the Institut Mérieux, the vaccine was sent to Rey in Dakar to evaluate the immunogenicity as had already been done for lots V1 and V4. Serum from the vaccinated subjects was sent to Gotschlich to perform the final analyses and in early January 1971, batch V5 had passed all the tests performed by the Institut Mérieux, Rey and Gotschlich.[92] In parallel to this preparation, Étienne from the Centre Muraz performed two surveys in December 1970 and January 1971 on behalf of WHO to strengthen data on post-vaccination reactions and pathways of vaccine immunisation. The surveys were completed in Bougoula in the region of Sikasso, in Mali and in Bobo-Dioulasso in Upper Volta, with lot V3 produced by Gotschlich in the Rockefeller Institute and lot V4 of the Institut Mérieux.[93] After the completion of these experiments, the serum of the vaccinated subjects was recovered and sent to Gotschlich and Pharo for analysis. The results showed that post-vaccination reactions were uncommon, there was no difference between different pathways of

[85] Archives of the Institut Mérieux, box D11, D11_8, 19_29/01/70.
[86] Archives of the Institut Mérieux, box D11, D11_8, 15_05/01/70.
[87] Archives of the Institut Mérieux, box D11, D11_12, 2_19/06/70.
[88] Archives of the Institut Mérieux, box D11, D11_12, 4_01/07/70.
[89] Archives of the Institut Mérieux, box D11, D11_12, 8_27/07/70.
[90] Archives of the Institut Mérieux, box D11, D11_12, 9_19/08/70.
[91] Archives of the IMTSSA, box 2013 ZK 005-553, 'Vaccination contre la Méningite Cérébro-spinale' (1970), 1–8.
[92] Archives of the Institut Mérieux, box D11, D11_13, 12_12/01/71.
[93] Archives of the IMTSSA, box 2013 ZK 005-227, 'Rapport sur la mission effectuée à Bougoula (République du Mali) par le Docteur Jean Étienne Médecin-Chef de la Sous-Section Méningite, Centre Muraz, Bobo-Dioulasso)' (1971); Archives of the IMTSSA, box 2013 ZK 005-227, 'Rapport sur l'enquête effectuée à Bobo-Dioulasso (Haute-Volta) concernant le vaccin antiméningococcique par le Docteur Jean Étienne Médecin-Chef de la Sous-Section Méningite, Centre Muraz, Bobo-Dioulasso' (1971).

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immunisation (subcutaneous and intradermal) and the safety and immunogenicity of the vaccines were considered good.[94]

With this new collaboration between Gotschlich, the WHO, the Institut Mérieux and the Pharo, polysaccharides and the different batches of vaccine circulated freely; just like the people who were involved in the development of the vaccine. It was clearly an advantage for the Institut Mérieux to be able to rely on other people or organisations to perform the trials with the vaccine. They also relied on others to highlight technical problems with production. In fact, each protagonist seemed to have a specific role in the development of the vaccine. As presented in the introduction, this history is a history of collaborations included in a specific period highlighted by Stuart Blume as a 'Golden Age' of vaccine development and production.[95] These collaborations principally occurred between the WHO, a public health organisation, the Institut Mérieux, a private pharmaceutical company, the Pharo, a military WHO research centre, and Gotschlich, a Rockefeller Institute researcher. We could further add WHO collaborators such as the Centre Muraz and Doctor Jean Étienne, or Professor Michel Rey in Dakar. The WHO, the Institut Mérieux, the Pharo and Gotschlich are considered as the main protagonists involved in the development of the meningococcal A vaccine because they were directly implicated in developing the vaccine. The WHO initiated the CSMa research programme (and eventual development of a vaccine); the Institut Mérieux was the producer; Gotschlich developed the production technique and provided technical assistance; Pharo, relying on Lapeyssonnie's team at the IMTSSA, provided technical assistance too.[96] The other collaborators we presented above, if they played a meaningful role, mainly helped in implementing trials.

The vaccine trial was organised in January–February 1971 in Lagos, Nigeria, by the WHO, and Institut Mérieux produced more than 50 000 doses of meningococcal A polysaccharide vaccine batch V5 S0087 for the latter.[97] During this trial, 14 426 children were vaccinated, 7187 with the vaccine and 7239 with tetanus toxoid as a control.[98] However, the results of this trial were not statistically significant: eight cases of CSMa occurred among vaccinated subjects, against five cases in those who received the tetanus toxoid.[99] While the immunogenicity problem that hampered the vaccine trial in Mali was now considered to be resolved, the vaccine developed by the Institut Mérieux with the help of the WHO, Gotschlich and Pharo still did not seem to be effective in preventing CSMa.

The Last Bow

The vaccine seemed to have a problem again, just as it had before the cancelled Malian trial. However, this time the problem was quickly identified: the heat-sensitivity of the

[94] Archives of the IMTSSA, box 2013 ZK 005-640, 'Immunogénicité et innocuité du vaccin antiméningococcique polysaccharidique A – Enquêtes de Bougoula (Mali) et Bobo-Dioulasso (Haute-Volta): Résultats finaux par le docteur Jean Étienne' (1971).

[95] Blume, *op. cit.* (note 15), 90–1.

[96] Between 1963 and 1967, the Lapeyssonnie team of the IMTSSA provided the meningococcal strains that composed the whole cell meningococcal vaccine developed at that time by the Institut Mérieux.

[97] Archives of the Institut Mérieux, box D11, D11_13, 14_12/01/71.

[98] Archives of the WHO, box C11-181-14, 'Grant to the Federal Ministry of Health, Lagos, Nigeria, in respect of controlled field trial of cerebrospinal meningitis vaccine' (1971).

[99] W.R. Sanborn, Z. Bencić, B. Cvjetanović, Emil C. Gotschlich, Tom M. Pollock and J.E. Sippel, 'Trial of a Serogroup A !'eningococcus Polysaccharide Vaccine in Nigeria', *Progress in Immunological Standardization*, 5 (1971), 497–505.

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vaccine. In fact, this problem had already been raised by Gotschlich at the time of setting up his new manufacturing process. Gotschlich had sent the following instruction to Donikian (head of the Bacteriological Division at the Institut Mérieux) concerning the application of his new manufacturing process: 'Please remember to keep the material in a freezer before and after lyophilisation. Minus 20 C is OK.'[100] Donikian had replied: 'Well received your letter of May 18th. Let's draw your attention to the impossibility of keeping the freeze-dried bottles at $-20\,^{\circ}\mathrm{C}$. At this temperature, the caps are permeable to air and the bottles will no longer be under vacuum. Please review this problem and give an answer.'[101] Surprisingly, no answer was given, and the problem seemed to have been ignored until the Lagos vaccine trial. In brief, the vaccines were not stored at the correct temperature before use (a temperature ranging from $+4\,^{\circ}\mathrm{C}$ to $-4\,^{\circ}\mathrm{C}$). In Lagos, the temperature on the site was around $35\,^{\circ}\mathrm{C}$–$40\,^{\circ}\mathrm{C}$. Despite this disappointment, the safety and the immunogenicity of the vaccine had been confirmed during the trial.[102] Nonetheless, it was only some years later (after 1975) that scientists understood that the recovery of freeze-dried vaccines in solution required maintaining them at a constant temperature below $-20\,^{\circ}\mathrm{C}$.[103] Failure to do so, even in freeze-dried form, led to the degradation of the polysaccharides.

The Lagos trial ended in disappointment. It could not continue anyway. The epidemic season of CSMa ran from September to May in the meningitis belt of Africa, so the protagonists would have to wait until the next year to perform a new trial. As early as May 1971, a new batch of the meningococcal A polysaccharide vaccine was in preparation at the Institut Mérieux.[104] While the Lyon institute had performed the initial tests on the vaccine on the other batches, Gotschlich usually performed the physicochemical tests on the purity of the polysaccharides. Now, Gotschlich asked Donikian to take over these analyses.[105] This would allow the Institut Mérieux to fully control the vaccine production chain. Moreover, it would limit the amount of time the vaccine spent in transit, which could otherwise damage the vaccine. Indeed, sending a package of vaccine and maintaining a temperature of $-20\,^{\circ}\mathrm{C}$ was relatively difficult. The vaccines sent by the Institut Mérieux could have been affected by a temperature change – affecting its heat-sensitivity – and consequently, Gotschlich's analyses would have been distorted. While the Institut Mérieux settled the last details of the production of the new vaccine batch, the WHO again looked for a country to accept a vaccine trial. An opportunity appeared in September 1971 at the XII^{e} Congrès International de Standardisation Biologique (Twelfth International Congress of Biological Standardisation) held in Annecy.[106] During this meeting, a special session devoted to the meningococcal vaccine brought together many actors involved in the vaccine's development: the Institut Mérieux, the WHO, Pharo, the Rockefeller Institute, the Centre Muraz and the United States Naval Medical Research Units (NAMRU). During this event, and in agreement with the health authorities of the

[100] Archives of the Institut Mérieux, box D11, D11_11, 3_18/05/70.
[101] Archives of the Institut Mérieux, box D11, D11_12, 1_23/05/70.
[102] Archives of the IMTSSA, box 2013 ZK 005-227, 'XIIè Congrès International de Standardisation Biologique, 20 au 24 septembre 1971, Annecy-France – Rapport de mission par le docteur Jean Étienne Médecin-Chef de la Sous-Section Méningite, Centre Muraz, Bobo-Dioulasso' (1971), 4.
[103] René Triau and Micha Roumiantzeff, 'La vaccination anti-méningococcique', *Médecine et Maladies Infectieuses*, 14, 1 (1984), 87–8.
[104] Archives of the Institut Mérieux, box D11, D11_15, 1_18/05/71.
[105] Archives of the Institut Mérieux, box D11, D11_15, 3_14/06/71.
[106] Archives of the IMTSSA, *op. cit.* (note 102).

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country and the participants of the session, it was decided that the next vaccine trial would be carried out in Egypt.

Before the vaccine trial in Egypt, vials of the batch V6 – in production since May 1971 – had been sent to Rey in Dakar to evaluate its immunogenicity. The serum of the vaccinated had been sent to Gotschlich in New York, who performed the physicochemical tests for the last time. Donikian had agreed to take over the physicochemical tests of the vaccine. After having greatly contributed to the vaccine's development, Gotschlich would now be able to devote himself to other work. As for previous batches, everything was good regarding safety, sterility and immunogenicity for the meningococcal A polysaccharide vaccine. The vaccine trial was organised by the WHO and the NAMRU between December 1971 and February 1972. The organisation was facilitated by the establishment of a NAMRU team in Cairo, which had conducted the negotiations with Egypt. Experiments were performed in three cities, Alexandria, Cairo and Giza, during the meningitis 'winter season'.[107] In total, 124 349 children between the ages of six and fifteen were vaccinated: the vaccine was administered to 62 295 children while 62 054 received the tetanus toxoid, and a control group of 1 403 508 children received neither the vaccine nor the tetanus toxoid.[108] In line with the elements highlighted before, the vaccine was transported and stored at a temperature of $-20\,^{\circ}\mathrm{C}$. On site and before its use, tests were performed to check its degradation rates in polysaccharides: the initial molecular weight of 170 000 Da remained unchanged. This value, well above the value of the 100 000 Da necessary for the antigenic power of the vaccine, guaranteed its immunogenicity. After the trial, no case of CSMa was reported in the vaccinated cohort, while 181 cases were reported in the control group and eight cases in the group which had received the tetanus toxoid. The vaccine's safety, already known, was confirmed again: there were no generalised side effects, and the local reactions were considered benign and temporary. The value of the results obtained was statistically significant and proved the efficacy of the meningococcal A polysaccharide vaccine version V6 produced by the Institut Mérieux. Ten years after the WHO launched a research programme concerning vaccination against CSMa, and after having faced many difficulties, the Institut Mérieux and its collaborators succeeded in developing an effective meningococcal A vaccine.

The success of the actors involved in the development of the vaccine did not stop there. Indeed, another opportunity to check again the efficacy of the vaccine presented itself to them. A new trial was planned in Khartoum, Sudan, for the spring of 1973. Sudan, which had refused to organise a trial a few years before, was now convinced of the merits of this undertaking.[109] It is a safe bet that the success of the Egyptian trial greatly contributed to this decision. Ironically, this decision was again conditioned by a change of Minister of Health in the country – as had been the case previously for the rejection of the trial – but this time with a favourable outcome for the vaccine's proponents.[110] Planning a trial one year in advance was obviously necessary to establish another stockpile of vaccine, and to organise the logistics in the field. For this trial, the Institut Mérieux produced a

[107] Archives of the WHO, box C11-181-16, 'CTS Agreement with the High Institute of Public Health, Alexandria, in respect of field study of meningococcal-polysaccharide A vaccine' (1972).
[108] M.H. Wahdan, F. Rizk, A.M. El-Akkad, A.A. El Ghoroury, R. Hablas, N.I. Girgis, A. Amer, W. Boctar, J.E. Sippel, Emil C. Gotschlich, René Triau, W.R. Sanborn and B. Cvjetanović, 'A Controlled Field Trial of a Serogroup A Meningococcal Polysaccharide Vaccine', *Bulletin of the World Health Organization*, 48, 6 (1973), 667–73.
[109] Archives of the WHO, *op. cit.* (note 62).
[110] Archives of the WHO, *op. cit.* (note 62).

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new batch (V7), the first batch where the production chain was entirely controlled by the Lyon pharmaceutical company. Even the immunogenicity tests, which had hitherto been completed by Rey in Dakar, were now made by the Institut Mérieux. The vaccine trial was carried out in April 1973, but contrary to the Egyptian trial, the Sudanese trial was supported by the country's health authorities without caveat. Sudan was ready to accept a foreign vaccine trial, but apparently under certain conditions. The WHO contributed by sending a consultant to provide assistance and by a small financial payment.[111] Upon arrival in Khartoum, the vaccine was stored at $-20\,^{\circ}\mathrm{C}$ for seven days, a period that was considered not to damage the vaccine. However, before the beginning of the trial, and as a precaution, analyses were performed to check the molecular weight stability of the vaccine.[112] During the trial 21 640 people were inoculated, 10 891 with the vaccine and 10 749 with the tetanus toxoid. Children up to fifteen years old, especially between six and ten years old, formed the majority of the vaccinated participants in this trial (70 per cent). After the trial, no case of CSMa was reported in the group of vaccinated subjects while ten cases were reported in the group which had received the tetanus toxoid.[113] The value of these results was statistically significant and proved once again the efficacy of the meningococcal A polysaccharide vaccine produced by the Institut Mérieux in partnership with the WHO, Gotschlich and Pharo.

In October 1973 the WHO organised a round table on the immunoprophylaxis of the CSMa at the Mas d'Artigny in Saint-Paul de Vence in France.[114] This meeting brought together the main protagonists involved in the development of the meningococcal A vaccine over the previous years: Charles Mérieux, René Triau and Robert Donikian of the Institut Mérieux, Bychenko Cvjetanović of the WHO, Léon Lapeyssonnie and Vandekerkove from Pharo, Emil C. Gotschlich of the Rockefeller Institute, Jean Étienne from the Centre Muraz, Michel Rey a collaborator of the WHO in Dakar, and representatives of the NAMRU. This event was the occasion to discuss the positive results obtained during the trials in Egypt and Sudan. Cvjetanović opened the meeting with these words:

> Doctor Mérieux, My General [Lapeyssonnie], My Dear Colleagues, I am happy to be here with you, because this time, after ten years of collaboration and several failures in our projects, we have finally arrived at results which are very encouraging. We have a vaccine that meets the pressing needs of many developing countries, especially in Africa. So we have completed part of the program. But we still have a lot of things to do.

Reflections and Perspectives

In the end, the development of the CSMa vaccine was a winning bet for the Institut Mérieux. It was a risk. Developing this vaccine presented a number of drawbacks for pharmaceutical laboratories, as presented in the introduction. But the outcome was certainly not as Mérieux and its collaborators would have imagined. Although the vaccine

[111] Archives of the WHO, box C11-446-2SUD, 'Grant of $1000 to the government of Sudan in relation with field study of meningococcal polysaccharide A vaccine' (1974).
[112] Archives of the IMTSSA, box 2013 ZK 005-549, 'Letter to W.R. Sanborn from Léon Lapeyssonnie', 8 February 1973.
[113] H.H. Erwa, M.A. Haseeb, A.A. Idris, Léon Lapeyssonnie, W.R. Sanborn and J.E. Sippel, 'A Serogroup A Meningococcal polysaccharide Vaccine: Studies in the Sudan to Combat Cerebrospinal Meningitis Caused by *Neisseria meningitidis* Group A', *Bulletin of the World Health Organization*, 49, 3 (1973), 303–4.
[114] Archives of the IMTSSA, box 2013 ZK 005-538, 'Table ronde sur l'immunoprophylaxie de la méningite cérébro-spinale – Le Mas d'Artigny 06570 Saint-Paul de Vence (France) – Vendredi 12 Octobre 1973' (1973).

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was developed for Africa,[115] it was massively used for a vaccination campaign in Brazil in 1974–75. During this event, 90 million Brazilians were vaccinated in less than a year, stopping the epidemic in the country, and establishing an international reputation for the Institut Mérieux.[116] This winning bet is all the more surprising because just a few years later the meningococcal A polysaccharide vaccine was replaced by a protein conjugate vaccine considered to be better.[117] Indeed, the polysaccharides hardly activate the T-cells, leading to a poor immunological memory response and relatively short-lived levels of protective antibodies. The duration of immunity rarely exceeded three years. So, this vaccine was good enough to control localised outbreaks in the meningitis belt. The chemical conjugation to carrier proteins (tetanus or diphtheria toxoid) converted the polysaccharides into T-dependent antigens, offering a better duration of immunity.[118] The meningococcal A polysaccharide vaccine had a lifetime of less than twenty years, a shorter lifespan than other vaccines produced at the same time, such as the polio vaccine or the MMR vaccine. Subsequently, other meningococcal polysaccharide vaccines were introduced against meningococci W-135 or Y; for example, a quadrivalent A, C, W-135 and Y polysaccharide vaccine was licenced in the United States of America from 1981.[119] As with the meningococcal A polysaccharide vaccine, these meningococcal polysaccharide vaccines were gradually replaced by protein conjugate vaccines, because they provided a short-lived protection against meningococci (rarely more than three years). In 2010, The Meningitis Vaccine Project developed an affordable group A conjugate vaccine (MenAfriVac). More than 250 million people have been vaccinated across the meningitis belt and Meningitis A appears to have been controlled in immunised regions. However, *Neisseria meningitidis* is composed of six subgroups that threaten sub-Saharan Africa (A, W-135, Y, X, C and, potentially, B). With the temporary disappearance of meningococcus A, these other meningococci have gained virulence and triggered serious epidemics for which vaccines were not available.[120] Finally, controlling MenA alone is not enough to control meningitis epidemics in Africa: all meningococci must be controlled.

In this study, we have focused on the social factors of vaccine development and production. These social factors include various collaborations, informal discussions, the circulation of products and materials, formal meetings, trials and setbacks. These social factors are essential to understanding the complex reality of the development, production and use of a vaccine. As Stuart Blume suggests:

> Jenner's discovery, and the work of the pioneering bacteriologists ... Laid the foundations for modern vaccinology: the development and production of more and better vaccines. Looking back, it is relatively easy to construct a narrative of progress – scientific, technological and medical – from all that happened since. This is how the history of science and technology is generally presented, so it seems familiar. But it is not the only narrative that can be drawn from the history of vaccines and vaccination ... There is a simple reason why the 'scientific' story, the story of progress, is so much more familiar than these. A history that shows increasingly

[115] At that time, the CSMa was almost exclusively in Africa.
[116] M. Machado, 'L'épidémie de méningite cérébro-spinale au Brésil', *Médecine et Hygiène*, 34 (1976), 483–5; Charles Mérieux, 'Une aventure des temps modernes: la lutte contre l'épidémie de méningite au Brésil', *Informations Chimie*, 157 (1976), 173–7.
[117] A vaccine that uses a carrier protein to enhance the efficacy of the antigen.
[118] Caroline Vipond, Rory Care and Ian M. Feavers, 'History of Meningococcal Vaccines and their Serological Correlates of Protection', *Vaccine*, 30 (2012), B11.
[119] Lionel K.K. Tan, Georges M. Carlone and Ray Borrow, 'Advances in the Development of Vaccines Against *Neisseria meningitidis*', *The New England Journal of Medicine*, 362, 16 (2010), 1512.
[120] Graham, *op. cit.* (note 19), 422–3.

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sophisticated tools being crafted to vanquish one terrible disease after another is a story that offers comfort and holds hope.[121]

The explanatory narrative constructed around this history of CSMa is definitively not a history that 'offers comfort and holds hope'. The explanatory narrative constructed around this history is complex and reveals the uncertainties and difficulties in the history of the development, production and use of a vaccine. A vaccine cannot be produced without a producer. A vaccine cannot be tested without a 'field' for a trial. The organisation of a trial requires negotiations, exchanges and partnerships. It is essential to find the right collaborator, the right place and the right technique. Although often recounted in terms of a success story, vaccine development is rarely as straightforward, as these narratives suggest. The development of an effective vaccine is often punctuated by setbacks, by a waste of time and money and by doubts. The development of an effective vaccine is often upset by apparently insignificant events that can spoil a vaccine trial in preparation for over a year. But above all, the development of an effective vaccine is often a risky bet to take for the people, laboratories and organisations involved.

In the twenty-first century, developed countries are no longer ravaged by the scourges of previous centuries. Diseases such as diphtheria and tetanus in the nineteenth century or polio in the twentieth century are now controlled by vaccines. Cases may reappear in developed countries from time to time when the vaccine coverage for a disease decreases, as for example diphtheria in Spain and Belgium in 2015 and 2016,[122] but for poor or undeveloped countries these uncontrolled diseases continue to wreak havoc. Vaccines are available, but too often inaccessible financially for the governments of these countries. There is another unfortunate situation: diseases for which no vaccine exists at present, but which could be developed. The pharmaceutical industry is not ready to finance such developments if there is no upstream likelihood of a return on investment or the certainty of creating a lucrative market. Contemporary vaccines are developed with expensive, advanced technology: in return, companies expect to see a return on their investment. Despite the reintroduction of public–private partnerships, the involvement of new actors, such as the Bill and Melinda Gates Foundation for example,[123] or new schemes, such as the Advance Market Commitment,[124] such initiatives are still rare. So, the question is: will the pharmaceutical industry develop vaccines without prior financial guarantees?

As seen in this study, in the early 1960s, the Institut Mérieux – with essential collaborators – took the risk of developing a vaccine to fight a disease which affected almost exclusively Africa. As presented in the introduction, this story is inscribed in a specific period described by Stuart Blume as a 'Golden Age' of vaccine development and production, where in particular the relationships between public- and private-sector institutions were typically rooted in a common commitment to public health, whether or not allied with the need to make a profit. It may be part of the answer, but it does not explain everything. It was another era, itself inscribed in a particular context with a different world political aspect. Most historians are wary at drawing lessons, let alone obvious ones, in the past; things are never the same again, therefore these considerations are to be taken with great caution. So, another question is: in the twenty-first century, will a pharmaceutical

[121] Blume, *op. cit.* (note 15), 30–3.
[122] Dora Vargha and Jeremy A. Greene, 'Grey-Market Medicines: Diphtheria Antitoxin and the Decay of Biomedical Infrastructure', *The Lancet*, 389, 10080 (2017), 1690.
[123] Blume, *op. cit.* (note 15), 203.
[124] *Ibid.*, 106.

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company take the risk of developing a much-needed vaccine without strong guarantees in return?

This article does not pretend to give a simple answer. Studying similar vaccine development histories could perhaps provide the first elements of a more general reflection on the notion of risk and risk management related to the development of new vaccines, but today we are surely at a pivotal moment in the history of vaccines. We are entering the last phase of the Polio Eradication and Endgame Strategic Plan 2013–2018.[125] For the first time, a malaria candidate vaccine (RTS,S GlaxoSmithKline) has reached a phase 3 trial.[126] We are confronted more than ever with the danger of emerging infectious diseases (EID), which requires an international and quick response supported by considerable means. These EID could plunge the world back into a world which resembled that of the previous centuries, ravaged by scourges. In this case, the notion of risk will maybe have to be reassessed for the development of vaccines.

[125] Global Polio Eradication Initiative (GPEI), http://polioeradication.org, accessed 5 May 2019.
[126] Blume, *op. cit.* (note 15), 108.

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