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► **To cite this version:**

Eugénie d'Alessandro. Meningitis, From Practitioner to Prescriber. Medical Innovations in Humanitarian Situations The Work of Médecins Sans Frontières, , 2009. hal-01419384

HAL Id: hal-01419384

<https://hal.science/hal-01419384>

Submitted on 20 Dec 2016

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Meningitis

From Practitioner to Prescriber

Eugénie d'Alessandro

Meningococcal cerebrospinal meningitis is caused by a gram-negative diplococcus, *Neisseria meningitidis*, also known as the meningococcus. Although meningococci are present throughout the world, causing sporadic cases and small epidemics, meningococcal disease is a different entity in semi-arid sub-Saharan Africa, where devastating and unpredictable epidemics occur. This phenomenon was first described in the 1960s by Dr. Lapeyssonnie, a French Army general in the medical services. Covering a “band of terrain from the Atlantic to the Red Sea,” the meningitis belt is an endemic–epidemic region. The epidemic risk is particularly high during the dry season. The severe consequences of these outbreaks in terms of morbidity and mortality make the disease a public health priority.

Lapeyssonnie refined the first single-dose treatment for meningococcal meningitis epidemics in the early 1960s. His works on the meningococcus and its sensitivity to antibiotic treatment created the hope that “the discovery of long-acting sulphamides may permit the reduction of medical intervention to a single injection” (Lapeyssonnie, Momenteau, 1961; Lapeyssonnie, Chabbert, Bonnardot, et al., 1961; Lapeyssonnie, Bonnardot, Louis, et al., 1961). In practice, it was indeed difficult to give oral antibiotics three times a day to thousands of patients, some of them in comas, and spread over potentially large distances. This is why the development of a long-acting intramuscular sulphamide, Sultirene, was a signif-

icant step forward in treatment—due to its efficacy and ease of use (Chippaux, 2001).

Sadly, the use of this drug was quickly compromised. Fewer than ten years after its development, the first resistances appeared. By the beginning of the 1970s the sulphamides were no longer sufficiently efficacious, and classical seven- to ten-day treatments were difficult to administer in practice.

Michel Rey, back in France after a long spell in West Africa, where he had been in charge of the Infectious Diseases department at Dakar Hospital, became involved in the research and development of short treatments for meningococcal meningitis. Inspired by Yves Chabbert at the Pasteur Institute (who collaborated with Lapeyssonnie on long-acting sulphamides) and Jacques Acar, Rey launched a new single-dose treatment—oily chloramphenicol by intramuscular injection. Once the dosage form was perfected, Rey and his team tested the treatment in several West African countries. Encouraging initial results were obtained in Dakar and Ouagadougou (Rey et al., 1975). The study was completed by looking at 74 consecutive meningitis cases in Bobo-Dioulasso, treated by single injection of oily chloramphenicol. The results obtained in 1976 led the authors to propose chloramphenicol in oily suspension as an alternative to long-acting sulphamides in epidemics of cerebrospinal meningitis epidemics, and also as initial treatment for endemic and sporadic cases in rural African settings (Rey et al., 1976).

The efficacy of oral and intravenous chloramphenicol in the treatment of meningococcal meningitis had already been studied (Girgis et al., 1972; Whittle et al., 1973). The development of a long-acting intramuscular injection dosage form, however, allowed single-dose treatments. Following the results of this study, oily chloramphenicol was registered in France and produced by Roussel Laboratories.

Epicentre's Contribution to the Prescription of Oily Chloramphenicol and Ceftriaxone in Africa

The first major epidemic outbreak occurred in countries that are part of the so-called "meningitis belt" between 1987 and 1989. Sudan was particularly affected in 1988, followed by Ethiopia in 1989, reporting thirty-two thousand and forty-one thousand cases respectively (WHO, 1998). MSF opened a mission in Sudan in 1988 and proposed oily chloramphenicol for curative care of meningitis cases. The treatment protocol was refused by Sudanese authorities as it did not correspond to national guidelines. MSF teams were thus forced to use ampicillin injections over several days. A doctor from the mission explained that "half the patients left before finishing treatment. It was just impossible. The teams were going out of their minds."

Medical practice and research in English-speaking countries evolved more quickly towards evidence-based medicine than in French-speaking countries. Treatments and therapeutic protocols were studied according to international biomedical criteria and communicated through publication in reputed medical journals.

The single-dose oily chloramphenicol protocol was unheard of in the former British colonies at the time, despite being in everyday use in French-speaking countries. Clinical trials carried out on the molecule did not provide sufficient proof as far as criteria in English-speaking countries were concerned. As far as we know, only four studies can be found in medical literature before 1988, two of which were performed by Rey's team in Saliou, in Senegal, and Ouedraogo, in Burkina Faso (1975, 1976), and published in French journals. The other two were written by one English-speaking group (Wali et al., 1979; Puddicombe, Wali, Greenwood, 1984). Results were comparable: (1) oily chloramphenicol seemed just as efficacious as longer, classical treatments; (2) the single- or two-injection protocols were

significantly advantageous in resource-limited countries; (3) the low cost of treatment also made it more affordable in these countries; (4) theoretical chloramphenicol toxicity appears negligible when compared with the morbidity and mortality of meningococcal disease, particularly during epidemics. In short, this protocol appeared to be a promising first-line treatment option in developing countries. None of these studies provided “scientific approval” according to the standards in English-speaking countries, however. In all four studies, the numbers of patients studied were too low to provide statistically significant results, and only two were published in English.

MSF senior staff members were quickly convinced of the need for progress. They knew from their own experience that chloramphenicol was easier to use and efficacious. According to field doctors, this drug needed to be available for use in all meningococcal meningitis epidemics, including in East Africa. The experience in Sudan demonstrated the need to perform an efficacy study according to international scientific norms.

The study protocol, written by an Epicentre epidemiologist, was applied in two referral hospitals in Niamey and Bamako, in collaboration with Nigerien and Malian health authorities. An unblinded, random controlled trial of 515 patients compared the clinical and biological efficacy of two injections of oily chloramphenicol with the previous standard, which involved eight days of intravenous ampicillin.

Results showed comparable efficacy for the two treatments. Given feasibility and cost criteria, the authors recommended the use of oily chloramphenicol as first-line treatment for bacterial meningitides in peripheral health structures in the Sudan–Sahel region. They also added that better chloramphenicol pharmacokinetics studies were required to optimize treatment efficacy, and, furthermore, that high mortality rates should motivate

further research for new, better, simple-to-use treatments such as ceftriaxone (Varaine, 1990).

The study was published in *The Lancet* in 1991 (Pécoul, Varaine, Keita, et al., 1991). These results scientifically validated the protocol and led to its worldwide transmission. Oily chloramphenicol use quickly became widespread in former British colonies following the publication of this article (it was used in 1991 in Uganda, for example), and became the rule, as shown by national protocols in the Sudan–Sahel region from this time on.

In terms of international health policy, the World Health Organization (WHO) put oily chloramphenicol on its essential drugs list, then subsequently recommended it in its first guide on controlling meningitis epidemics (WHO, 1995). It became the recommended first-line treatment a few years later, in 1997, after the creation of the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG), and still is today.

The drug is not fully accepted by some scientists and officials, however. Its toxicity in oral and intravenous use has been criticized, and the drug was pulled from the European market after a number of cases of bone marrow aplasia in richer countries. This led the original manufacturer, Roussel, to halt production. The International Dispensary Association (IDA) started production after calls from MSF, but transferred production to an Indian pharmacological laboratory following technical production difficulties. This company is still the only oily chloramphenicol manufacturer in the world.

Some countries in the meningitis belt have categorically refused to use the drug, despite WHO recommendations, because it was seen as “a drug for poor countries.” There is often confusion with respect to the benefits of this particular dosage

form and the use of the molecule in general. Over and above occasional refusals to use the drug, lack of knowledge also leads to doubts about its inclusion on the WHO essential drugs list.

Finally, an alternative exists: the third-generation cephalosporin ceftriaxone. During the 1990s, this drug was too expensive for use in resource-limited countries, particularly in such large-scale public health interventions as meningitis epidemics.

MSF's involvement in ceftriaxone use began early, through a randomized double-blind trial in 1991 comparing the efficacy of two injections of either oily chloramphenicol or ceftriaxone in the treatment of bacterial meningitis. The study was carried out in Niamey and Bamako between 1991 and 1995, and the study population included children of two to thirty-five months of age, suffering from purulent bacterial meningitis (all germs). The results suggested that two injections of ceftriaxone were more efficacious in reducing mortality than two doses of oily chloramphenicol. The study authors publicly requested the immediate availability of cheaper generic ceftriaxone for use in resource-limited countries (Varaine et al., 1997). This position was restated at international conferences and expert working groups, such as the Eighth Infectious Diseases Conference in Boston in 1998 (Varaine, Keita, Kaninda, et al., 1998).

The significance of the study results was somewhat limited, however. The study did not question the use of oily chloramphenicol, nor did it examine efficacy during epidemics. The study was not carried out during epidemic periods, and only a third of cases were meningococcal.

In 2002, facing increasing difficulties in the supply of oily chloramphenicol, and with the price of ceftriaxone progressive reduced, MSF and Epicentre decided to proceed with an equivalence study comparing oily chloramphenicol and ceftriaxone.

The way this study was set up in the field is a good example of MSF's specific potential. The aim was to recruit enough patients during an epidemic,¹ which, according to a senior Epicentre staff member, involved "being in the right place at the right time." The four selected countries for the study were Chad, Mali, Niger, and Burkina Faso. Preliminary negotiations to obtain agreements from the health authorities were successful except in Burkina Faso. An epidemic then began in Burkina Faso at the start of winter 2003. The MSF and Epicentre team immediately left for the site, but authorizations were slow to arrive. Senior MSF staff in Paris then asked their team to go to neighboring Niger. A few days later, the epidemic hit the Zinder region and spread to Maradi, where the research team was in place and waiting, supported by regular regional MSF field teams; the study could be started, and 510 meningitis patients were subsequently recruited for the cohort. The results showed no inferiority of ceftriaxone when compared with oily chloramphenicol when both are used as short treatments for meningococcal meningitis. The authors conclude that ceftriaxone is an equivalent alternative to chloramphenicol for epidemic responses (Nathan et al., 2005). The specificity of this study was that it was conducted during an *epidemic*.

The study required a significant amount of technical input from MSF. MSF's logistics potential was a major asset, and the presence of MSF teams across the region and locally, in this case in Maradi, provided material and technical support for research teams. Logistical coordination was another key factor during this intervention, both in material and medical logistics (particularly laboratory services in the case of meningitis epidemics). Furthermore, the absence of institutional administrative and diplomatic red tape allowed for reactivity and flexibility that are not to be found in most state or United Nations bodies. Nor

¹ Reminder: meningitis belt epidemics only last from a few weeks to a couple of months, and over five hundred patients needed to be recruited for the study.

did this autonomy undermine interactions with collaborating partners: effective and efficacious collaboration was built with national institutions, particularly the Medical and Sanitary Research Centre of Niger and Nigerien health authorities.

In 2008, both treatment protocols validated by MSF became international standards for meningococcal meningitis outbreaks in the meningitis belt region. The availability of these two drugs means that sporadic cases and epidemic outbreaks can be treated. Both are of significant clinical benefit in the treatment of meningococcal meningitis.

Vaccines and Vaccination Strategies

The first trials of anti-meningococcal vaccines were held in Sudan in 1915, but all efforts to put them into use were in vain until the 1960s. Gotschlich, Goldschneider, and Artenstein, working for a United States Army research institute, were the first to extract and purify the A and C polysaccharides. Their work demonstrated the immunogenicity of these polysaccharides in man (Gotschlich et al., 1969). A monovalent C polysaccharide vaccine was quickly developed for the United States, where this serogroup predominates. The first trials were performed in 1970 in US Army training centers, where regular outbreaks occurred (Artenstein et al., 1970).

This new technology quickly crossed the Atlantic to French-speaking Africa. In 1970–71, Emil Gotschlich and Charles Mérieux collaborated to produce a vaccine providing protection against the meningococcal serogroup A, directly followed by a study of immune response in cohorts of adults in the United States and children in Dakar (Emil Gotschlich and Michel Rey). The study demonstrated serogroup A vaccine immunogenicity, although the results suggested that this was lesser than that of the C serogroup vaccine. The study also reported that immu-

nogenicity was very poor in infants aged six to thirteen months (Gotschlich, Rey, Triau, Sparks, 1972; Gotschlich, Rey, Etienne, et al., 1972).

The Mérieux Institute launched vaccine production. Lapeyssonnie, working for the WHO in Alexandria, supported the first controlled trials performed in Egypt in 1972 (Wadhan et al., 1973) and in Sudan in 1973 (Erwa et al., 1973). Immediately following these studies, Charles Mérieux and Lapeyssonnie entrusted the vaccine to Pierre Saliou's team at the Biology Department of the Muraz Centre in Bobo-Dioulasso. During the outbreaks in Mali and Upper Volta in 1974, Saliou and his team put into place vaccination campaigns to compensate for sulfamide resistance in African strains of *Neisseria meningitidis*. The campaigns were deemed a success (Saliou, Stoeckel, Lafaye, et al., 1978).

Description of Initial Vaccination Strategies

Epidemic control measures were transformed by the arrival of these new anti-meningococcal vaccines (monovalent A and C and bivalent AC). Lapeyssonnie immediately proposed a guide to their use at the International Seminar on Immunization, in Bamako, 1974 (Lapeyssonnie, 1970; Lapeyssonnie, 1974). Pierre Saliou and Philippe Stoeckel's team then performed several studies defining the main elements of a "circumstantial" vaccination strategy (Saliou et al., 1978; Saliou, Rey, Stoeckel, 1978; Yada et al., 1983).

This strategy is based on epidemiological surveillance at peripheral health centers during the epidemic season. As soon as the first cases are reported, two interventions occur: curative care (treatment of sick patients) to reduce mortality; and the identification of the serogroup involved; with an ensuing circumstantial vaccination campaign targeting the affected population to stop the spread of the epidemic.

Circumstantial vaccination is a reactive approach. Given that the polysaccharide vaccine is only immunogenic from two years of age, its inclusion as a blanket protective measure in expanded programs of immunization was not feasible. A reactive strategy targets children aged eighteen months through to adults aged thirty years in the affected region, starting as quickly as possible once the first cases are confirmed². The most affected area is the first priority, and vaccination coverage progressively extends to neighboring areas in expanding concentric circles. The problem is being sensitive enough to react as quickly as possible, but specific enough not to launch unnecessary campaigns because the human and financial inputs for mass vaccination are often to the detriment of curative care. In other words, the main difficulty resides in the sensitivity and specificity in detection thresholds used.

Several years passed before the first reference study regarding detection thresholds was performed, however. A Centers for Disease Control and Prevention (CDC)³ team at the beginning of the 1990s analyzed data gathered between 1979 and 1984 in the Burkina Faso epidemiological surveillance system. Because vaccination response depends on the rapidity and the reliability of epidemic detection, the authors proposed an evaluation of the usefulness of a weekly incidence rate using retrospective analysis. The results suggest acceptable sensitivity and specificity for a threshold of fifteen cases per one hundred thousand inhabitants per week averaged over two weeks for populations of at least thirty thousand to fifty thousand, and of five cases per one hundred thousand inhabitants per week for zones neighboring epidemic outbreaks. According to the authors, given the rudimentary nature of data collected in Sahel countries'

² Initial studies having shown poor group A vaccine immunogenicity in infants, early recommendations proposed excluding them from vaccination campaigns.

³ The CDC, based in Atlanta, in the USA, is one of the thirteen main US Department of Health and Human Services agencies.

surveillance systems, these measures were acceptable to detect epidemic emergencies. They underlined, however, that further studies were required to examine the appropriateness of these recommended thresholds (Moore et al., 1992).

The CDC team's conclusions quickly became an international standard. In its first *Practical Guidelines for Control of Epidemic Meningococcal Disease*, the WHO cited the study results, which subsequently became official recommendations in epidemic detection and for launching mass vaccination campaigns (WHO, 1995).

Several retrospective analyses of epidemic responses have progressively called into question the thresholds defined by the CDC team, however. Furthermore, worldwide anti-meningococcal vaccine shortages during the 1996 outbreak in Nigeria were decisive in changing the face of vaccination strategies.

MSF Meningitis Vaccination Experience

MSF intervened regularly in meningitis belt countries during the 1980s, where teams were confronted by meningitis epidemics. The organization employed the strategies established by the pioneers of meningitis vaccination in Africa the preceding decade. Circumstantial vaccination campaigns spreading concentrically from outbreak zones were the rule, such as during the Ugandan epidemic in 1982-83.

At the same time, MSF missions were progressively supported by the headquarters' medical department and Epicentre. The first field experiences, considered in the light of improving technical analysis, along with capacity-building from centrally documented experiences, led to questions about internationally accepted practices.

MSF missions involving responses to meningitis epidemics multiplied during the 1990s, mostly in direct collaboration with

national health authorities. Nineteen missions between 1990 and 1999 were formally analyzed by MSF and Epicentre, and these descriptive studies supplied quantitative data about the epidemiology of the disease, as well as the effect of responses put in place by national health authorities and NGOs. In 1993 the first two guidelines were published (Epicentre, Varaine, 1993a,b).

The results of these analyses often suggest a weak effect, if any at all, of vaccination campaigns on overall epidemic progression. For MSF meningitis specialists, it became increasingly apparent that preventive measures to control the disease needed reviewing. Initially, vaccination strategies dating from the 1970s were re-adapted. The “concentric circle” strategy was gradually abandoned in favor of urban agglomeration outbreak vaccination. These kinds of strategies were based on careful compromises between curative and preventive interventions. Simply put, curative care was decentralized with adequate peripheral drug stocks, and vaccination efforts were concentrated on the largest demographic areas hit by the epidemic. Later, for example in 1996, during the outbreaks in which Nigeria was hardest hit, the need to adapt vaccination strategies became apparent.

Meningitis cases began to be reported in North and East Nigeria in December 1995. By the beginning of February, increasing disease incidence was reported to the national health authorities. The Ministry of Health reinforced the vaccination campaign that had already been launched, and organized an evaluation in affected districts. On February 13, 1996, an MSF team arrived in the country for an exploratory mission to work alongside the government team and the accompanying WHO and United Nations Children’s Fund (UNICEF) staff to evaluate the outbreak in the northern and central regions of Nigeria. The mission confirmed a meningitis epidemic outbreak and identified *N. meningitidis* serogroup A as the causal agent. In four

states, 7,400 cases and 1,560 deaths were reported in the first two months of 1996, a specific mortality rate of 20%. MSF decided to establish a mission to support government vaccination activities, curative care, and surveillance-system reinforcement in the three most affected states—a population of fourteen million. The emergency mission grew rapidly and involved the recruitment of several dozen international staff, the participation of all five MSF operational centers, and the emergency supply of several tons of medical equipment. From March to May almost three million people were vaccinated and more than thirty thousand cases treated. A worldwide shortage of vaccine stocks followed.

As the epidemic developed, MSF requested an external evaluation of the intervention by the European Agency for Development and Health (AEDES).⁴ Their conclusions raised the same questions MSF specialists had been asking previously. Prevention strategies put into action were compromised by a surveillance system that provided inadequate data in terms of rapidity and reliability: the mass vaccination campaign's effect was probably weak because it was introduced too late. Although the authors underlined the fact that the results were impressive in terms of the number of people vaccinated and treated, it still appeared painfully obvious that the results obtained were not equal to the significant means employed to achieve them (Farese et al., 1996).

International Health Politics, a New Type of Collaboration Between MSF and the WHO

For the majority of meningitis specialists, including those at the WHO and MSF, the 1996 crisis showed the need to organize a coordinated international response to better confront future epidemics. At the time, WHO reports were asking the same questions about vaccination strategies as those elucidated in MSF–Epicentre studies. The WHO brought together the world's

⁴ The AEDES is “a consulting firm, specialized in the Food, Social and Public Health sector,” and a regular Epicentre collaborator.

major players in meningitis in Geneva, December 1996. Participants included the CDC, UNICEF, the International Cooperation Agency for Preventive Medicine (AMP),⁵ the International Federation of Red Cross and Red Crescent Societies (IFRC), MSF, and various scientific specialists. A funding appeal signed by the WHO, UNICEF, the IFRC, and MSF was subsequently launched. The ICG was created in January 1997. Additional technical partners were added to the core organization (the CDC, the Tropical Medicine Institute of the Military Health Service in Marseille, and the National Public Health Institute in Oslo), as well as vaccine manufacturers.

The first objective of the newly created ICG was to evaluate vaccine needs in meningitis belt countries and compare these with available international resources. Group members immediately entered into discussions with vaccine manufacturers to guarantee minimum stock levels and costs for epidemic responses. After estimating epidemic season needs for 1997, a joint international appeal was launched in February for the \$6.4 million needed by ICG members. The funds obtained paid for stocks of the first bivalent A C combined vaccines reserves produced by the two manufacturers at the time: GlaxoSmithKline (GSK) and Pasteur-Mérieux (later Aventis-Pasteur, then Sanofi Pasteur). Authorization procedures were created to regulate stock distributions. When receiving a request from a Sahel-region country, the four members of the ICG guaranteed a consultative answer within forty-eight hours, and supply depending on epidemic risk criteria and proposed vaccination strategies. The key issues for ICG members were to evaluate vaccination campaign appropriateness and to guarantee rational use of supplied vaccines. In 1997–98, over half of the vaccines supplied to Africa were sourced from the ICG (WHO, 1997).

⁵ The AMP is a non-governmental association created by Charles Mérieux and Jacques Monod in 1972. It aims to constitute a relay between research progress and its application in the field.

Over and above vaccines and injection material, the ICG also secured stocks of oily chloramphenicol as production was regularly threatened. To complete the list of tools required for epidemic response, the ICG proposed diagnostic and epidemiological follow-up material (latex agglutination tests, transport, and culture media). Furthermore, the group recruited new partners, creating a worldwide meningitis network, the “greater ICG” that meets once a year. Discussion topics include the evaluation of epidemic responses over the preceding year, technical and scientific progress, and future response planning.

Redefining Detection Thresholds

Analyses of the interventions in African countries in the 1990s suggested that epidemic detection was inadequate for effective preventive control. MSF tries to systematically evaluate its interventions, and each time the evaluation authors question the effect of vaccination campaigns, as seen in the numerous reports by Epicentre and several articles published in the international medical press (Barrand et al., 1993; Lewis et al., 2001). External audits reach the same conclusions: the efficacy of preventive measures with respect to epidemic curve progress is questioned and the cost-benefit ratio often appears unfavorable (Lengeler et al., 1995; Woods et al., 2000; Veeken et al., 1998). As a key actor supporting countries in mass vaccination campaigns, MSF missions in this domain are regularly criticized.

In 1999 the ICG mandated MSF to report on the progress of field research into epidemic thresholds for meningitis. In June 2000 MSF and Epicentre met in Paris with international research teams and public health actors from affected countries to draft new recommendations for meningitis epidemic detection in Africa. The experts present agreed that the threshold of fifteen cases per one hundred thousand inhabitants a week averaged over two weeks was very specific in confirming a meningitis

epidemic. They nevertheless explained that this indicator has several limits: (1) it is not sufficiently sensitive to detect all epidemics; (2) the delay between crossing the threshold value and the epidemic peak is too short (less than three weeks) to perform a mass vaccination campaign; (3) under-reporting and case-declaration delays in affected countries' surveillance systems reduced threshold sensitivity and significantly contributed to delays in the detection of epidemics. The need to use lower epidemic threshold values to allow sufficient time for mass vaccination campaigns was recognized. To avoid false alerts, however, the recommendations are adjusted according to the context in which they are applied. Contextual elements to be taken into account include recent or ongoing meningitis epidemics in the region, calculated meningitis vaccination coverage, the time of year, population size and density, and surveillance system quality.

These new recommendations define an alert threshold to launch investigations and begin preparations for a meningitis epidemic, and an epidemic threshold, confirming an epidemic and reinforcing control measures. For each threshold, a series of actions are suggested according to epidemic risk and population size and density. Where there have been no recent epidemics, or in areas where vaccination coverage is low, the lowest threshold is recommended. In an epidemic context, attaining alert levels is sufficient to launch a full epidemic response. These new recommendations provide a general framework for meningitis epidemic detection and responses in highly endemic African countries (Epicentre, 2000).

The WHO validated this meeting's recommendations and embraced them as official policy. It then transmitted the new recommendations through international ICG meetings and WHO publications (WHO, 2000).

For MSF meningitis specialists, the June 2000 meeting led to changes in how detection thresholds are perceived. A new notion was born: the idea of geographical control of epidemic spread. If the first outbreak is difficult to recognize in time, adjusted thresholds can serve as quality indicators of epidemic spread to adjacent areas. When actors are alerted of an outbreak, surveillance is reinforced and detection thresholds can then reach acceptable sensitivity. For MSF specialists, this new approach promised to lead to better control of meningitis epidemics in Africa (Lewis, Nathan, Communier, et al., 2001).

The Emergence of the N. Meningitidis W135 Serogroup

A new wave of epidemics occurred in 2001, particularly in Burkina Faso and Niger, and the Pasteur Institute and AMP began a joint exploratory mission. The results showed the highest levels of the W135 serogroup ever recorded in Africa (Taha et al., 2002; Châtelet et al., 2002). The dominant A serogroup vied for the first time in meningitis belt countries with the W135 strain, found in 38% of investigated cases in Burkina Faso and 39% in Niger.

The survey's conclusions immediately raised new questions about the evolving epidemiological landscape and vaccination strategies, even if it was clear that the A serogroup continued to dominate other countries in the region. Before the appearance of W135, vaccination campaigns used bivalent AC vaccines, with stocks guaranteed by the ICG. At that time, only two vaccine manufacturers produced tetravalent ACYW135 polysaccharide vaccine effective against the W135 strain. Given the high cost of this vaccine and limited production capacity, its large-scale public health use in Africa was not feasible. MSF reacted quickly to the new situation, and senior staff members established initially informal contacts with one of the pharmaceutical companies producing the tetravalent vaccine, GSK. Following

these initial discussions, expert meetings were organized involving ICG members and GSK representatives. Two possibilities are discussed: a monovalent W135 vaccine, or a trivalent ACW135 product. The second option was chosen, and GSK agreed to start production on the condition of prepayment for a minimum of six million doses. MSF contributed €2 million, and enlisted other ICG partners. GSK began production, and Belgian government authorities, under pressure from all partners, registered the product in record time. Continuing the same frenetic pace, the WHO, GSK, and the CDC performed a trial in Burkina Faso to validate large-scale use of the product. A few months after the first W135 epidemic in 2001, the new vaccine was available for use in meningitis belt countries and quickly employed. The following year, a new W135 epidemic hit Burkina Faso, and the WHO reported the first large-scale epidemic due to the strain since its arrival in Africa the previous year (Bertherat et al., 2002).

Since 2002, no major W135 epidemic has occurred, and the ICG still has more than half of its initial vaccine stocks (around 2.5 million were used out of the 6 million doses delivered). The epidemiological history of potential strains (including W135) does suggest, however, that new large-scale epidemics may soon occur (Traoré et al., 2006). Strain variations underline the importance of regular serogroup surveillance by field actors sending samples to reference laboratories in Oslo and Marseille.

The WHO and MSF have transformed meningitis control policy through the mediation of the ICG, an innovative public health–intervention action group of a type that has since gained widespread acceptance. It has been a model for yellow fever control (the Yellow Fever ICG) and for the fight against drug-resistant tuberculosis (the Green Light Committee).

The sequence of practices developed by MSF in meningitis epidemic responses is one example amongst others of the specific nature of the institution's evolution. With the exception of the first chloramphenicol trial in 1989, MSF intervened throughout the 1980s and 1990s first and foremost as a field practitioner. MSF's efforts were focused on curative care for affected populations in collaboration with local health authorities. Solid scientific evidence was produced based on field experience, which MSF used in another sphere of action, that of international health policy. The WHO and MSF worked together, in a new kind of collaboration, and defined new meningitis control strategies. As such, MSF became a recommender of new international health policy alongside the WHO.

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