A predictable comeback: the second pandemic of infections caused by *Neisseria meningitidis* serogroup A subgroup III in Africa, 1995

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Between 14 January and 4 April 1995 we isolated and characterized 44 meningococcal strains in Cameroon, Chad, Niger, and Burkina Faso; among these was the strain A:4:P1.9/clone III-1, which was involved in the second meningitis pandemic. This isolate was found in the clonal form in Niger and strains of the ET-37 complex were also found in the other three study countries, but apparently did not cause epidemics. One strain (Y:2a:P1.2,5 (ET-37 complex)) was isolated in January 1995 and another (A:4:P1.9) in March 1995 in Garoua (Cameroon). Eight strains were isolated in Moundou (Chad) between January and April 1995: the A:4:P1.9/clone III-1 (1 strain); members of the ET-37 complex (Y:2a:P1.2,5 (4 strains), Y:NT:P1.2,5 (1 strain), and Y:2a:-(1 strain)); and serogroup X (1 strain). In Niger, 31 strains were isolated between February and April 1995 from different regions. All were A:4:P1.9/clone III-1; between November 1994 and April 1995 there were 23814 cases of meningitis reported of which 2227 resulted in death. Three strains were isolated in Burkina Faso in April 1995: two were Y:2a:P1.2,5 (ET-37 complex) and one was A:4:P1.9/clone III-1.

Thus in 1995 the epidemic and invasive strain (A:4:P1.9/clone III-1) responsible for the second pandemic was present in the four countries (Cameroon, Chad, Niger and Burkino Faso) that make up the area frequently affected by such epidemics and where cases are generally reported during the dry season.

Introduction

The second pandemic of *Neisseria meningitidis* infections (*1*) involved a strain of antigenic formula A:4:P1.9, which was characterized as clone III-1 by multilocus enzyme electrophoresis (MEE). The pandemic began in China in 1983 and spread to Nepal and to the north of India. About 7000 cases occurred in August 1987 during pilgrimages to Mecca and Medina (*2*). Spread continued to various countries, mostly by pilgrims who carried the strain home. The spread was halted within a few weeks in those countries with good health infrastructures, e.g., the USA (*3*), England (*4*), and France (*5*). However, in other countries, particularly those in Africa, the epidemic spread (*6*) and cases were still being identified in 1995. The A:4:P1.9 strain has caused epidemics not only in those areas often associated with meningitis (the meningitis belt (*7*)) but also in zones well removed from such areas.

The 4:P1.9 strain was first isolated in 1988 and 1989 in East and Central Africa, particularly in Chad (*2*), Ethiopia (*8*), and Kenya (*9*). Subsequently, this strain has been found in the meningitis belt: Niger, in 1991; Sudan, in 1993; Chad, in 1993–94; and Mali, in 1993–94.

In some countries in East and Central Africa, e.g., Cameroon and the Central African Republic, there are two very different climatic zones. The northern zones of these two countries consist of arid savanna, where epidemics of meningitis are frequent in the dry season; the southern zones consist of wooded savanna, where epidemics are less frequent, although there was an epidemic of meningitis in the west of the Central African Republic in 1992 (*10*). There is an apparent association between climatic changes and the onset of meningitis infections, but the reasons for this are not clear. Cartwright described three major risk factors for the development of meningococcal infection: a pathogenic organism, a susceptible host, the influence of extrinsic environmental factors, or perhaps most frequently a combination of all three (*11*).

In 1993–94 the invasive, epidemic, pathogenic clone III-1 was reported in Niger, Chad, and Cameroon. The populations of these countries are large, and there is therefore a subpopulation of sen-

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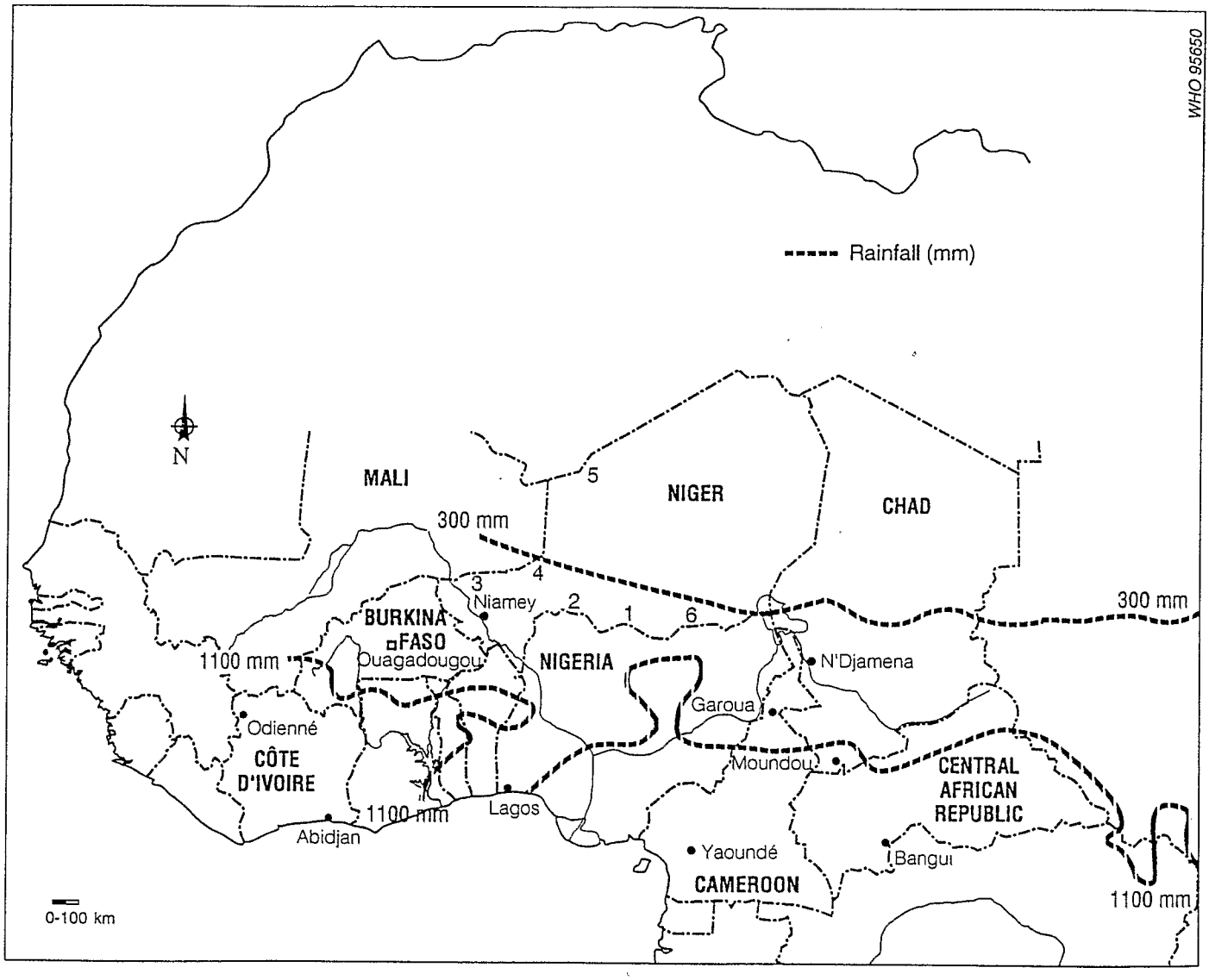
Fig. 1. **Distribution of isolates of *Neisseria meningitidis* A:4:P1.9/clone III-1 and ET-37 complex strains in Cameroon (Garoua), Chad (Moundou), Niger, and Burkina Faso, January–April 1995.** In Niger, the progression of the epidemic clone is illustrated by the following numbers on the map: 1 (Maradi); 2 (Dogon Douchi); 3 (Niamey); 4 (Tillabéry); 5 (Agadez); and 6 (Zinder).



sitive individuals (*6*); an epidemic of meningitis becomes probable if the weather becomes dry and cool.

We report the characteristics of 44 strains that were isolated in Cameroon, Chad, Niger, and Burkina Faso during the 1993–94 epidemic. The cases of meningitis could be divided into two groups: those caused by the strain A:4:P1.9/clone III-1, and the rest. In Niger, strain A:4:P1.9/clone III-1 was the most frequently isolated, where it was responsible for 5815 cases, of which 605 had died by the first week of March 1995 (*12*). Subsequently, the epidemic has continued. Mortality has varied from 6.6% to 18.3% according to the area and time of year.

In this article we report the distribution of strains of the clone III-1 at the end of 1994 and the beginning of 1995 when the climatic conditions favoured the appearance of cases of meningitis. We also report on the presence of other meningococcal strains, for example, nine strains of serogroup Y and one of serogroup X.

Methods

Bacterial strains

Clinical isolates. Strains were isolated on "chocolate agar" and identified bacteriologically at Centre

Pasteur, Garoua, Cameroon; Moundou Hospital, Chad; the Niamey Meningitis and Schistosomiasis Research Centre (CERMES) Niger; and the Yalgado Ouedraogo Hospital, Burkina Faso. In some cases, the serogroup was also determined in the laboratory where the strains were isolated. Cultures of all strains (18–24-hours old) were used to inoculate the transport medium described by Vandekerkove et al. (*13*), incubated overnight at 37 °C, and sent in secure packaging (Sanofi Diagnostics Pasteur, Paris, France) to the Neisseria Unit, Institut Pasteur, Paris, France.

Reference strains

Strains LNP 6818, LNP 6796, and LNP 12412 were used as references to determine variations in the allelic profile in the ET-37 complex.

Bacterial identification

After transportation, strains were reisolated both on gonococcal–meningococcal agar (G medium) (Sanofi Diagnostics Pasteur, Paris, France) and selective G medium containing 3 µg/ml vancomycin, 7.4 µg/ml colimycin, and 2 µg/ml fungizone (*14*), as appropriate.

Strains were identified by analysis of morphological, culture, and bacteriological characteristics, as described previously (*14*).

Antibacterial sensitivity

The sensitivity to each of the following antibacterials was determined using a standard diffusion technique on G medium (*14*): amoxicillin, amoxicillin + clavulanic acid, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, erythromycin, pefloxacin, penicillin G, rifampicin, spiramycin, and sulfonamides (sulfadiazine).

Serogrouping

Rabbit sera prepared in the laboratory were used for slide seroagglutination tests, as previously described (*14*). In cases where there was no clear agglutination, the method described by Vedros was used (*15*).

Serotyping and subtyping

The whole cell enzyme-linked immunosorbent assay (ELISA) technique described by Poolman & Abdillahi was used (*16*).

Multilocus enzyme electrophoresis

The techniques described by Selander (*17*) and Caugant (*18*) were used for MEE. Analysis was carried out for 13 enzymes: malic enzyme (ME), glucose-6-phosphate dehydrogenase (G6P), peptidase (PEP), isocitrate dehydrogenase (IDH), aconitate hydratase (ACO), two glutamate dehydrogenases (GD1 and GD2), alcohol dehydrogenase (ADH), fumarase (FUM), alkaline phosphatase (ALK), two indophenol oxidases (IP1 and IP2) and adenylate kinase (ADK). The clinical isolates were classified by comparing their electrophoretic profiles with the profiles of the reference clone III-1 and of ET-37 complex.

Strain storage

All strains were stored both lyophilized and frozen at −80 °C, as described previously (*14*). The strains concerned are shown in Tables 1 and 2.

Results

Epidemiological and clinical findings

The first strain of *N. meningitidis* was isolated in Garoua (northern Cameroon) on 14 January 1995. However, up to April 1995 only 11 cases of meningitis had been reported in Cameroon. Meningococci were only successfully isolated from two of these cases: one serogroup Y and one serogroup A. In 1995 three groups of strains were received from Chad: two in January and six in March.

Few epidemiological data are available for Chad, but it appears that there have been few cases of meningococcal meningitis in either N'Djamena or Moundou. Five groups of strains were received from CERMES (Niger) between February and April 1995. The National Health Information System Directorate (Public Health Ministry, Niger) reported 23814 cases of meningitis and 2227 deaths up to 11 April 1995. The proportions of the national total of cases reported in various towns in the south of the country and the corresponding morbidity levels were as follows: Diffa (0.02%; 2.5 per 100000); Zinder (17%; 225 per 100000); Maradi (24%; 320 per 100000); Dosso (16%; 300 per 100000); Niamey (9%; 375 per 100000); and Tillabery (8%; 110 per 100000). The comparable data for two towns in the north were as follows: Agadez (0.2%; 20 per 100000) and Tahoua (26%; 380 per 100000).

The first strains from Burkina Faso were sent at the beginning of April 1995. Five provinces were affected: Kénédougou, Sissili, Komitenga, Sèna and

Boulgou. By the end of March 1995 there were 1000 cases and 250 deaths.

Bacteriological findings

Bacteriological identification. All the strains collected were Gram-negative diplococci that were positive for oxidase, catalase, and the acidification of glucose and maltose, and negative for fructose, sucrose, mannitol and lactose; and they expressed a gamma-glutamyltransferase. Consequently, they were identified as *N. meningitidis*.

Antibacterial sensitivity

All the strains were sensitive to all the antibacterials tested other than the sulfonamides, to which they were all resistant.

Serotyping

All the strains of serogroup A were serotype 4 and subtype P1.9 (Table 1), including all the strains isolated in Niger. The three serogroup Y strains were Y:2a:P1.2,5; Y:NT:P1.2,5; and Y:2a:- (Table 1).

Table 1: **Description of the 44 *Neisseria meningitidis* strains isolated in Cameroon, Chad, Niger and Burkina Faso from 14 January to 4 April 1995**

Country (town)	Isolation date	LNP No.[a]	Age	Sex	Antigenic formula	Clone
Cameroon (Garoua)	14/01/95	13230	6 months	M	Y:2a:P1.2,5	ET-37
	01/03/95	13534	9 years	M	A:4:P1.9	III-1
Chad (Moundou)	14/01/95	13265	10 years	M	Y:2a:P1.2,5	ET-37
	14/01/95	13266	4 years	F	Y:2a:P1.2,5	ET-37
	11/03/95	13405	7 years	M	A:4:P1.9	III-1
	13/03/95	13406	11 years	F	Y:2a:P1.2,5	ET-37
	16/03/95	13407	2 years	M	X:NT:P1.5	—
	20/03/95	13453	2 months	M	Y:2a:P1.2,5	ET-37
	23/03/95	13454	10 years	M	Y:NT:P1.2,5	ET-37
	30/03/95	13474	11 years	M	Y:2a:-	ET-37
Niger (Niamey)	13/02/95	13325	5 years	F	A:4:P1.9	III-1
	16/02/95	13326	—	F	A:4:P1.9	III-1
	16/02/95	13327	6 years	F	A:4:P1.9	III-1
	17/02/95	13328	6 years	M	A:4:P1.9	III-1
	19/02/95	13329	15 years	M	A:4:P1.9	III-1
	25/02/95	13353	7 years	F	A:4:P1.9	III-1
	25/02/95	13354	4 years	F	A:4:P1.9	III-1
	25/02/95	13355	8 years	M	A:4:P1.9	III-1
	25/02/95	13356	6 years	F	A:4:P1.9	III-1
	25/02/95	13357	20 years	F	A:4:P1.9	III-1
	26/02/95	13358	18 years	F	A:4:P1.9	III-1
	26/02/95	13359	2 years	F	A:4:P1.9	III-1
	26/02/95	13360	12 years	M	A:4:P1.9	III-1
	26/02/95	13361	Child	M	A:4:P1.9	III-1
	26/02/95	13362	Child	M	A:4:P1.9	III-1
	26/02/95	13363	3 years	F	A:4:P1.9	III-1
	01/03/95	13383	7 years	F	A:4:P1.9	III-1
	03/03/95	13384	—	—	A:4:P1.9	III-1
	03/03/95	13385	8 months	M	A:4:P1.9	III-1
	04/03/95	13386	2 years	F	A:4:P1.9	III-1
	04/03/95	13387	5 years	F	A:4:P1.9	III-1
	06/03/95	13388	15 years	M	A:4:P1.9	III-1
	07/03/95	13389	15 years	M	A:4:P1.9	III-1
	07/03/95	13390	—	—	A:4:P1.9	III-1
	12/03/95	13421	8 months	M	A:4:P1.9	III-1
	16/03/95	13422	12 years	M	A:4:P1.9	III-1
	16/03/95	13423	13 years	F	A:4:P1.9	III-1
	17/03/95	13424	15 years	F	A:4:P1.9	III-1
	27/03/95	13465	10 months	—	A:4:P1.9	III-1
	27/03/95	13467	6 years	—	A:4:P1.9	III-1
	29/03/95	13463	7 months	—	A:4:P1.9	III-1
Burkina Faso	04/04/95	13460	13 years	M	Y:2a:P1.2,5	ET-37
	04/04/95	13459	20 months	M	Y:2a:P1.2,5	ET-37
	04/04/95	13457	10 years	F	A:4:P1.9	III-1

[a] LNP = Laboratoire des *Neisseria*, Institut Pasteur, Paris, France.

Table 2: **Allelic profiles of 44 meningococcal isolates in Cameroon, Chad, Niger, and Burkina Faso (January–April 1995)**

	No. of isolates	Allele at indicated enzyme locus:[a]												
		ME	G6P	PEP	IDH	ACO	GD1	GD2	ADH	FUM	ALK	IP1	IP2	ADK
Clinical isolates: clone III-1														
Cameroon	1	1	4	5	6	4	1	3	2	1	8	2	3	2
Chad	1													
Niger	31													
Burkina Faso	1													
Clinical isolates: ET-37 complex														
Cameroon	1	4	3	4	5	2	1	4	1	1	8	2	3	2
Chad	6													
Burkina Faso	2													
Control strains: ET-37 complex														
	12412	4	3	4	5	2	1	4	1	1	8	2	3	2
	6818	4	3	4	5	2	1	4	1	1	8	2	3	2
	6796	4	3	4	5	2	1	4	1	1	8	2	3	2
Chad, 1994	12538	4	3	4	5	2	1	4	1	1	8	2	3	2
	12451	4	3	4	5	2	1	4	1	1	8	2	3	2
Other profile														
Chad	1	1	4	4	8	4	1	4	2	1	3	2	3	2

[a] ME = malic enzyme; G6P = glucose 6-phosphate dehydrogenase; PEP = peptidase P; IDH = isocitrate dehydrogenase; ACO = aconitate hydratase; GD1 and GD2 = glutamate dehydrogenases; ADH = alcohol dehydrogenase; FUM = fumarase; ALK = alkaline phosphatase; IP1 and IP2 = two indophenol oxidases; and ADK = adenylate kinase.

Multilocus enzyme electrophoresis

The MEE profiles are described in Table 2. All the strains isolated in Niger (n = 31) were clone III-1. This clone was also isolated on one instance each in Cameroon (Garoua), Chad (Moundou), and Burkina Faso (Ouagadougou). The other Y:2a:P1.2,5 strains (one from Cameroon, four from Chad, and two from Burkina Faso) and the strains Y:NT:P1.2,5 and Y:2a:- all belonged to the ET-37 complex.

Discussion

The 44 strains isolated in the four study countries had different antigenic formulae and MEE profiles.

The 31 strains isolated in Niger were apparently identical (A:4:P1.9/clone III-1, resistant to sulfonamides), as assessed by the methods used in the study. By definition, a clone is a group of bacteria descended from a single ancestral cell, all the members of which have numerous identical properties (*1*). There may be differences in some of the less stable characters between individuals of the clone; strains of the clone III isolated before the Mecca epidemic, for example, expressed variably the Opa protein 5h, whereas those isolated after this epidemic expressed variably the protein 5i (*19*). Thus, the description of a population as single or subdivided depends both on the power of the epidemiological markers and their genetic variability. More profound variations can also occur, as observed in 1992 in the Central African Republic with the re-emergence of an A:4:P1.7/clone IV-1 strain responsible for a previous epidemic.

The clonal structure of *N. meningitis* serogroup A was first described by Olyhoek et al. (*20*). There have subsequently been numerous studies of the epidemics caused by this serogroup and its clonal variations. For example, Wang et al. reported 290 strains that could be classified into nine groups (84 different patterns in total) by MEE (*21*). One of these nine groups is the clone III that we have reported in the present study. These strains originated in China, where they are now rare.

The subgroup III was first found in the eastern, then the central regions of the area of Africa covered by our study. Finally, the strain appeared in the west, north, and south. This pattern of spread is similar to that which we reported in 1994 in 12 African countries (*22*).

Our findings therefore indicate that the second meningitis pandemic has returned to the following African countries: Burkina Faso, Cameroon, Chad, and Niger. However, a severe epidemic has only developed in Niger. A large-scale vaccination campaign has been launched to prevent its spread: in developing countries, vaccination is the best approach to combating epidemics (*23*, *24*).

Because the climatic conditions were favourable, the reappearance of the strain A:4:P1.9/clone III-1 at the end of 1994 resulted in the return of the second pandemic. However, this second pandemic does not appear to extend beyond the meningitis belt and, except in Niger, is less severe than previous pandemics: the numbers of cases in Garoua (Cameroon), Moundou (Chad), and Ouagadougou (Burkina Faso) are relatively low.

Serogroup Y strains were first characterized only recently: the strains are both members of the ET-37 complex (first described in 1993 by Wang et al. (*25*)) and are virulent. Over the last 10 years, 20% of the meningococcal disease in Norway has been due to serogroup C strains (*26*). These strains are all similar and belong to a single clone (ET-37 complex). Caugant has reported that the meningitis epidemics in the U. S. army in the 1960s and in Brazil and South Africa in the 1970s were due to serogroup C strains (*26*), and that these strains display substantial variability (*27*).

The association of serogroup Y and with the antigenic formula 2a:P1.5,2 has been described previously (*26*).

N. meningitidis serogroup A (antigenic formula 4:P1.9/clone III-1) is currently causing a major epidemic in Niger. Strains of the ET-37 complex have also recently been found in northern Cameroon (Garoua), Chad (Moundou), and Burkina Faso (Ouagadougou). Since the 1980s, the intervals between epidemic outbreaks of meningitis have become both shorter and more irregular (*28*). These epidemics reach their peak after several weeks, but can last many months in the absence of mass vaccination. The kinetics of the levels of anti-capsular polyoside and anti-outer membrane pro-tein anti-bodies can affect the progress of the epidemic (*6*). Climatic conditions also contribute to its severity, spread being favoured by the dry season or period of relative dryness. Strain A:4:P1.9/clone III.1 is strongly implicated in this epidemic, but is not the only strain involved.

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Résumé

Un retour prévisible: la deuxième pandémie d'infections à *Neisseria meningitidis* sérogroupe A sous-groupe III en Afrique (1995)

Entre le 14 janvier et le 4 avril 1995, nous avons étudié 44 souches de méningocoques isolées dans quatre pays africains, et déterminé leurs caractéristiques. Il s'agissait de la souche responsable de la deuxième pandémie (souche A:4:P1.9/clone III-1) qui a émergé d'une façon prévisible, et s'est présentée sous une forme clonale au Niger, et des souches assimilables au complexe ET-37 par leur profil en électrophorèse enzymatique multilocus, mais qui n'ont apparemment pas causé d'épidémie. Une souche Y:2a:P1.2,5 (complexe ET-37) a été isolée en janvier et une souche A:4:P1.9 en mars à Garoua (Cameroun). Huit souches ont été isolées à Moundou (Tchad) entre janvier et avril 1995: une souche A:4:P1.9/clone III-1, six souches appartenant au complexe ET-37 (quatre Y:2a:P1.2,5, une Y:NT:P1.2,5 et une Y:2a:-), et une souche de sérogroupe X. Au Niger, 31 souches ont été isolées entre février et avril 1995 dans différentes régions. Il s'agissait dans tous les cas de souches A:4:P1.9/clone III-1. Dans ce dernier pays, entre novembre 1994 et avril 1995, on a dénombré 23 814 cas et 2 217 décès. Trois souches ont été isolées au Burkina Faso en avril 1995 : deux souches Y:2a:P1.2,5 (ET-37) et une souche A:4:P1.9/clone III-1.

Ainsi en 1995, la souche épidémiogène et invasive responsable de la deuxième pandémie était présente dans quatre pays (Tchad, Niger, Cameroun et Burkina Faso) qui sont des pays fréquemment affectés par de telles épidémies durant la saison sèche.

References

1. **Achtman M.** Molecular epidemiology of epidemic bacterial meningitidis. *Review of medical microbiology*, 1990, 1: 29–38.
2. **Moore PS et al.** Intercontinental spread of an epidemic group A *Neisseria meningitidis* strain. *Lancet*, 1989, **2**: 260–262.
3. **Moore PS et al.** Group A meningococcal carriage in travelers returning from Saudi Arabia. *Journal of the American Medical Association*, 1988, **260**: 2686–2689.
4. **Jones DM, Sutcliffe EM.** Group A meningococcal disease in England associated with the Haj. *Journal of infection*, 1990, **21**: 21–25.
5. **Riou JY et al.** Characterization of *Neisseria*

meningitidis serogroup A strains from an outbreak in France by serotype, serosubtype, multilocus enzyme genotype and outer membrane protein pattern. *European journal of clinical microbiology and infectious diseases*, 1991, **10**: 405–409.

6. **Moore PS.** Meningococcal meningitis in sub-Saharan Africa: a model for the epidemic process. *Clinical infectious diseases*, 1992, **14**: 515–525.
7. **Lapeyssonnie L.** La méningite cérébrospinale en Afrique. *Bulletin of the World Health Organization*, 1963, **28** (suppl): 3–114.
8. **Haimanot RT et al.** Characteristics of serogroup A *Neisseria meningitidis* responsible for an epidemic in Ethiopia, 1988–89. *Scandinavian journal of infectious diseases*, 1990, **22**: 171–174.
9. **Pinner RW et al.** Epidemic meningococcal disease in Nairobi, Kenya, 1989. *Journal of infectious diseases*, 1992, **166**: 359–364.
10. **Guibourdenche M et al.** Characteristics of serogroup A *Neisseria meningitidis* strains isolated in the Central African Republic in February 1992. *European journal of clinical microbiology and infectious diseases*, 1994, **13**: 174–177.
11. **Cartwright K.** Meningococcal carriage and disease. In: Cartwright K., ed. *Meningococcal disease*. Chichester, John Wiley & Sons, 1995: 115–146.
12. Cerebrospinal meningitis. *Weekly epidemiological record*, 1995, **70**(12): 85–86.
13. **Vandekerkove M et al.** Milieu de transport pour méningocoques. *Annales de l'Institut Pasteur*, 1967, **113**: 260–263.
14. **Riou JY, Guibourdenche M.** *Laboratory methods*: Neisseria *and* Branhamella. Paris, Edition Institut Pasteur, 1993: 307.
15. **Vedros NA.** Serology of the meninococcus. In: Bergan T, Norris IR, eds. *Methods in microbiology*. London, Academic Press, 1978: 291–314.
16. **Poolman JT, Abdillahi H.** Outer membrane protein serosubtyping of *Neisseria meningitidis*. *European journal of clinical microbiology and infectious diseases*, 1988, **7**: 291–292.
17. **Selander RK et al.** Methods of multilocus enzyme electrophoresis for bacterial population genetics and systematic. *Applied environmental microbiology*, 1986, **51**: 873–884.
18. **Caugant DA et al.** Genetic relationships and clonal population structure of serotype 2 strains of *Neisseria meningitidis*. *Infection and immunity*, 1987, **55**: 1503–1513.
19. **Morelli G et al.** Immunogenecity and evolutionary variability of epitopes within IgA1 protease from serogroup A *Neisseria meningitidis*. *Molecular microbiology*, 1994, **11**: 175–187.
20. **Olyhoek TB, Crowe BA, Achtman M.** Clonal population structure of *Neisseria meningitidis* serogroup A isolated from epidemics and pandemics between 1915 and 1983. *Reviews of infectious diseases*, 1987, **9**: 665–692.
21. **Wang JF et al.** Clonal and antigenic analysis of serogroup A *Neisseria meningitidis* with particular reference to epidemiological features of epidemic meningitis in the People's Republic of China. *Infection and immunity*, 1992, **60**: 5267–5282.
22. **Riou JY et al.** Continued spread of meningococcal disease caused by serogroup A *Neisseria meningitidis* strains of subgroup III in Africa (1989–1994). In: Evans JS et al., eds. *Proceedings of the Ninth International Pathogenic* Neisseria *Conference, 26–30 September, Winchester, England*. Potters Bar, Herts, England, NIBSC, 1994: 322–323.
23. **Greenwood BM, Wali SS.** Control of meningococcal infection in the African meningitis belt by selective vaccination. *Lancet*, 1980, **1**: 729–732.
24. **Harrison LH.** The worldwide prevention of meningococcal infection. Still an elusive goal. *Journal of the American Medical Association*, 1995, **273**: 419–421.
25. **Wang J et al.** Antigenic and epidemiological properties of the ET-37 complex of *Neisseria meningitidis*. *Journal of infectious diseases*, 1993, **167**: 1320–1329.
26. **Caugant DA.** Epidemiologie moléculaire de *Neisseria meningitidis*. L'analyse des clones. *Annales de l'Institut Pasteur, actualités*, 1994, **5**: 130–137.
27. **Ashton FE.** Emergence of a virulent clone of *Neisseria meningitidis* serotype 2a that is associated with meningococcal disease in Canada. *Journal of clinical microbiology*, 1991, **29**: 2489–2493.
28. Meningococcal meningitis. *Weekly epidemiological record*, 1995, **70** (15): 105–107.

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