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MAJOR ARTICLE

Meningococcal Meningitis: Unprecedented Incidence of Serogroup X–Related Cases in 2006 in Niger

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Background. In Niger, epidemic meningococcal meningitis is primarily caused by *Neisseria meningitidis* (Nm) serogroup A. However, since 2002, Nm serogroup W135 has been considered to be a major threat that has not yet been realized, and an unprecedented incidence of Nm serogroup X (NmX) meningitis was observed in 2006.

Methods. Meningitis surveillance in Niger is performed on the basis of reporting of clinically suspected cases. Cerebrospinal fluid specimens are sent to the reference laboratory in Niamey, Niger. Culture, latex agglutination, and polymerase chain reaction are used whenever appropriate. Since 2004, after the addition of a polymerase chain reaction–based nonculture assay that was developed to genogroup isolates of NmX, polymerase chain reaction testing allows for the identification of Nm serogroup A, Nm serogroup B, Nm serogroup C, NmX, Nm serogroup Y, and Nm serogroup W135.

Results. From January to June 2006, a total of 4185 cases of meningitis were reported, and 2905 cerebrospinal fluid specimens were laboratory tested. NmX meningitis represented 51% of 1139 confirmed cases of meningococcal meningitis, but in southwestern Niger, it represented 90%. In the agglomeration of Niamey, the reported cumulative incidence of meningitis was 73 cases per 100,000 population and the cumulative incidence of confirmed NmX meningitis was 27.5 cases per 100,000 population (74.6 cases per 100,000 population in children aged 5–9 years). NmX isolates had the same phenotype (X:NT:P1.5), and all belonged to the same sequence type (ST-181) as the NmX isolates that were circulating in Niamey in the 1990s. Nm serogroup W135 represented only 2.1% of identified meningococci.

Conclusions. This is, to our knowledge, the first report of such a high incidence of NmX meningitis, although an unusually high incidence of NmX meningitis was also observed in the 1990s in Niamey. The increasing incidence of NmX meningitis is worrisome, because no vaccine has been developed against this serogroup. Countries in the African meningitis belt must prepare to face this potential new challenge.

The African meningitis belt is characterized by periodic large epidemics of meningococcal meningitis that occur on a background of high incidence of endemic cases during interepidemic years. Most cases occur during the dry season, from January to April. In this area, until recently, most large epidemics of meningococcal meningitis were caused by *Neisseria meningitidis* (Nm) serogroup A (NmA) [1, 2]. Nm serogroup C isolates were more rarely involved [3, 4]. Small outbreaks caused by Nm serogroup X (NmX) were reported in Niamey, Niger, in 1990 [5, 6] and from 1995 to 2000 [7], and in Ghana in 2000 [8]. In 2002, the first epidemic ever identified in Africa as being caused by Nm serogroup W135 occurred in Burkina Faso [9, 10], and the risk of a rapid spread of the epidemic within the meningitis belt was considered to be high. Four years later, this threat has not yet been realized, but in Niger, an important increase in the incidence of NmX meningitis has been observed. In this context of a changing epidemiology of epidemic meningococcal meningitis, we describe the new epidemiological features of the 2006 meningitis epidemic season in Niger. Because the only available vaccines to control meningococcal meningitis outbreaks in the African meningitis belt are the bivalent

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NmA–Nm serogroup C and the trivalent NmA–Nm serogroup C–Nm serogroup W polysaccharide vaccines [11], the current situation in Niger may be an indication of critical forthcoming meningitis seasons because of the absence of a vaccine that targets NmX.

METHODS

Data collection. In Niger, reporting of cases of meningitis is performed on the basis of the standard clinical definition of acute bacterial meningitis [12]. Laboratory confirmation of meningitis is not required to report a case. Quantitative morbidity and mortality data on meningitis are collected weekly within the national reporting network. Meningitis is considered to be epidemic in a district when the incidence exceeds 10 presumed cases per 100,000 inhabitants per week (the so-called "epidemic threshold") and when a laboratory confirmation of meningitis has been obtained for several cases. Health professionals are required to complete an epidemiological questionnaire form intended to document the biological specimens sent to the Centre de Recherche Médicale et Sanitaire, the national reference laboratory, in Niamey. The completeness and quality of individual records vary.

Laboratory methods. In November 2002, the microbiological surveillance of acute bacterial meningitis in Niger was considerably enhanced by the inclusion of the PCR assay for etiological diagnosis of meningitis to the national framework of the surveillance system. Most health facilities, and even district hospitals, do not perform a basic examination of CSF specimens. Health care staff who work outside of Niamey were asked to keep frozen all or part of every CSF sample that was collected from patients with suspected cases of meningitis. CSF specimens that were sent to the Centre de Recherche Médicale et Sanitaire were neither exhaustive nor randomized, but depended on the willingness of clinical staff members.

Since 2002, a PCR assay has been used for the diagnosis of the 3 main etiologies of acute bacterial meningitis in Niger: Nm, *Streptococcus pneumoniae,* and *Haemophilus influenzae b,* as described elsewhere [13, 14]. An aliquot of each CSF sample or each Trans-Isolate medium [15] supernatant is freeze-thawed, boiled for 5 min and centrifuged at 10,000 *g* for 10 min. A multiplex single-tube PCR assay is performed on 10 μL of the supernatant (crude extract) to amplify the *crgA* gene of Nm [16], the *lytA* gene of *S. pneumoniae* [17], and the *bexA* gene of *H. influenzae* [18]. For genogrouping of Nm-positive specimens, a second PCR is performed to amplify the *siaD* gene for Nm serotypes B, C, Y, and W135, and the open reading frame 2 of the *mynB* gene for NmA [16].

In 2004, a PCR protocol developed by the *Neisseria* unit of Institut Pasteur (Paris) to detect NmX was introduced and added to our array of nonculture genogrouping PCR assays for Nm serogroups A, B, C, Y, and W135. For the NmX PCR protocol, 2 primers were designed in the serogroup X capsule biosynthesis *(xcbA)* gene, 1 of the *xcbABC* cluster of 3 genes that are unique to NmX and were confirmed to be essential for NmX capsule expression [19]. These 2 primers are primer X-10 5′-ACAGCCCATAAAACACCCGTATCATC-3′ and primer X-11 5′-GTGATTGGAATCTTGCAATATCGGT-3′, and they specifically amplify a 202–base pair DNA fragment. No amplification was obtained from any isolates of a collection of isolates from the other serogroups.

When CSF specimens were suitable for culture (i.e., they had been transported under adequate conditions and delivered to the laboratory within 5–6 h of collection), classical bacteriological testing methods were also used—essentially, this applied to specimens collected in Niamey. Specimens that had been inoculated into bottles of Trans-Isolate medium were also suitable for culture, provided that they were not contaminated. For financial reasons, the use of latex agglutination tests was not systematic.

A relevant selection of Nm isolates that had been collected during the meningitis epidemic season were sent to the World Health Organization's Collaborating Centre for Reference and Research on Meningococci (Le Pharo, Marseilles, France) for serogroup confirmation, serotyping, and further determination, including multilocus sequence typing [20]. Multilocus sequence typing directly identifies alleles from the nucleotide sequences of internal fragments of 7 housekeeping genes and can characterize each strain by its sequence type (ST). Closely related STs are grouped in ST complexes according to their similarities to a central ST.

Data analysis. For statistical analysis, Pearson's χ^2 test, Fisher's exact test, and the Kruskal-Wallis ANOVA test were used, whenever appropriate. A P value <.05 was considered to be statistically significant.

RESULTS

The 2006 meningitis season in Niger was characterized by a late start, around the fifth week of the year, followed by a reporting of epidemics (incidence, >10 cases per 100,000 population per week) in 5 of the 42 health districts. From 1 January 2006 to 30 June 2006, a total of 4185 presumed cases of meningitis were reported to the national surveillance system, and the reference laboratory received 2905 CSF specimens. Results obtained using culture and nonculture methods (i.e., PCR-based testing and latex agglutination testing) revealed that 54.5% of CSF samples were negative. Among the CSF specimens that tested positive, Nm, *S. pneumoniae,* and *H. influenzae* represented 86.2%, 8.9%, and 3.3% of identified etiologies, respectively. Among 1139 confirmed meningococcal etiologies that were recovered, the most frequent were serogroup X (51%) and serogroup A (45%). Nm serogroup W135 accounted for 2.1% of isolates, and Nm serogroup Y accounted for 0.1%,

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Table 1. Cross-tabulation of results obtained with PCR and with culture for the identification of *Neisseria meningitidis* serogroup A (NmA) and serogroup X (NmX) in CSF specimens.

	No. of PCR results				
Culture	Nm-ind	NmA positive	NmX positive	*N. meningitidis* negative	Total
Not performed	0	359[a]	294[a]	5	658
Contaminated	0	15[a]	18[a]	0	33
Sterile	0	68[a]	107[a]	1	176
NmA	1[b]	57[c]	0	6[b]	64
NmX	0	0	135[c]	24[b]	159
Indeterminate	0	0	3[a]	0	3
Total	1	499	557	36	1093

NOTE. Nm ind, Nm serogroup not identified.
[a] Diagnoses made by PCR only.
[b] Diagnoses made by culture only.
[c] Diagnoses made by PCR and culture.

whereas a nonidentified serogroup represented 1.8% of Nm isolates. The contribution of PCR to a serogroup identification was proportionally higher for NmA than for NmX, because most patients with NmA meningitis were from areas that were located far from the testing laboratory, and their CSF specimens were not suitable for culture. In total, 442 cases of NmA (87.5%) and 422 cases of NmX (72.6%) were identified by PCR only (table 1). Six NmA cases were identified by latex agglutination testing only.

Both NmX and NmA were involved in meningitis outbreaks, each being associated with particular space and time characteristics. The incidence of cases of NmA infection increased first and peaked during the ninth week of the year before decreasing after the implementation of a mass immunization campaign with a NmA–Nm serogroup C polysaccharide vaccine (figure 1). NmA was, by far, the predominant serogroup identified from samples obtained in the epidemic districts of the region of Maradi, Niger (figure 2), where it represented 92.7% of 437 identified meningococcal isolates. On the other hand, the incidence of cases of NmX infection began increasing significantly around weeks 9–10 of the year, to peak at the 16th week. NmX was greatly predominant in the southwest region of Niger, including in Niamey, where the epidemic threshold was crossed at the 15th week of the year. In Niamey, NmX infection was involved in 96.4% of 251 laboratory-confirmed cases of meningococcal meningitis. From confirmed cases and for an estimated population of 882,000, the overall incidence of NmX meningitis cases in Niamey was 27.5 cases per 100,000 population during the 2006 meningitis season, whereas the incidence of confirmed cases of NmA infection was 0.3 cases per 100,000 population. The age-specific incidences of confirmed cases of NmX meningitis in Niamey were 62.8 cases per 100,000 population among the 1–4-year age group, 74.6 cases per 100,000 population among the 5–9-year age group, and 41.5 cases per 100,000 population among the 10–14-year age group.

Patients with NmX meningitis were significantly younger than those who were affected by NmA (mean age, 7.9 years and 9.2 years, respectively; $P < .001$), and the proportion of patients who had NmX meningitis who were children aged <5 years was 27.7%, compared with 22.2% of patients who had NmA meningitis who were children aged <5 years. The sex distribution of patients was not different between NmA and NmX, with male patients being significantly more frequently affected than female patients: 58.5% of individuals who had NmA meningitis were male patients and 61.6% of individuals who had NmX meningitis were male patients.

The clinical pictures did not differ significantly among cases of NmX and NmA meningitis, except for consciousness impairment (46.8% and 35.7% for NmX and NmA meningitis, respectively; $P < .04$) and convulsions (39.2% and 28% for NmX and NmA meningitis, respectively; $P < .02$). Information about patient outcome was reported for 361 patients with NmX meningitis and 374 patients with NmA meningitis. The case-fatality rate for NmX meningitis (12.2%) was significantly higher than it was for NmA meningitis (5.1%; $P < .001$). The largest difference in case-fatality rate, although not statistically significant, was observed in the 1–4-year age group (17.6% and 7.3% for NmX and NmA meningitis, respectively).

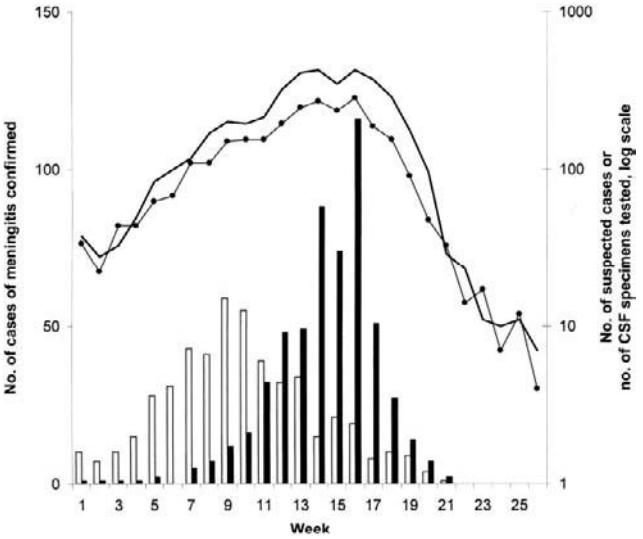

Figure 1. Weekly numbers of notifications of suspected cases of acute bacterial meningitis, of CSF specimens collection for testing, and of identifications of cases of *Neisseria meningitidis* serogroup A (NmA) and serogroup X (NmX) meningitis in Niger, during the 2006 meningitis season (weeks 1–26 of the year). *Continuous line,* number of suspected cases of acute bacterial meningitis notified (corresponding to the right y-axis label); *dotted line,* number of CSF specimens tested (corresponding to the right y-axis label); *white bar,* number of cases of identified NmA meningitis (corresponding to the left y-axis label); *black bar,* number of identified cases of NmX meningitis (corresponding to the left y-axis label).

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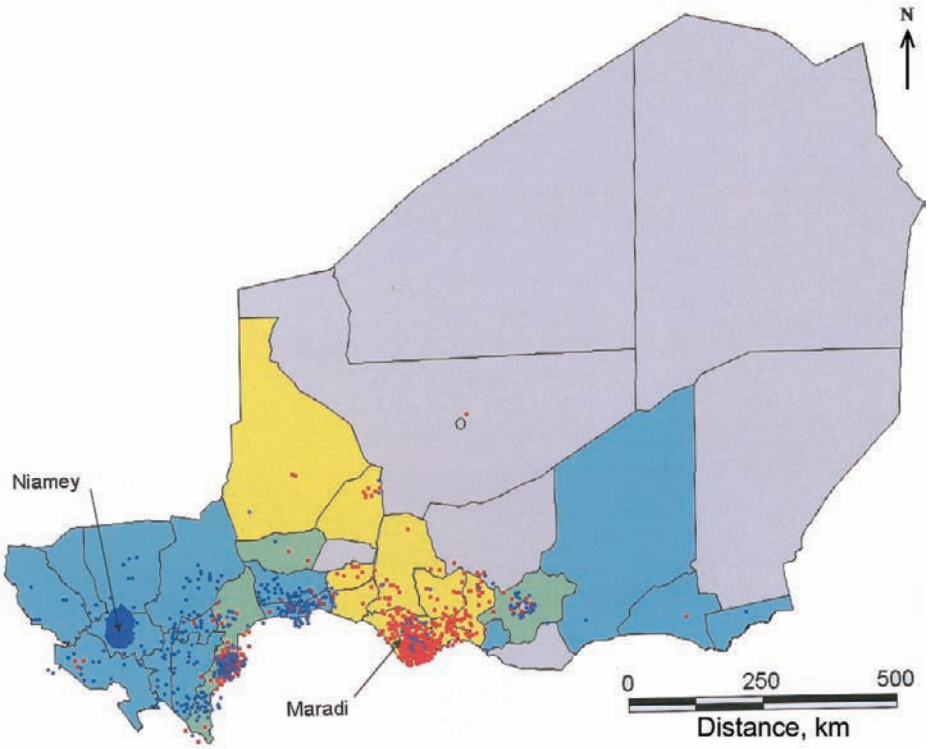

Figure 2. Geographic distribution of confirmed cases of *Neisseria meningitidis* serogroup A (NmA) and serogroup X (NmX) meningitis in Niger, during the period January–June 2006. *Yellow,* districts with a ratio of cases of NmA meningitis:cases of NmX meningitis >2; *green,* districts with a ratio of cases of NmA meningitis:cases of NmX meningitis ⩽2 and ⩾0.5; *blue,* districts with a ratio of cases of NmA meningitis:cases of NmX meningitis <0.5; *red dots,* cases of NmA meningitis; *blue dots,* cases of NmX meningitis.

In 2006, a total of 158 isolates of NmX and 63 of NmA were obtained, of which 39 NmX and 59 NmA isolates were tested for susceptibility to antibiotics commonly used for the treatment of meningococcal meningitis. All tested isolates were determined to be susceptible to ampicillin, ceftriaxone, and chloramphenicol, the latter being the drug recommended for use in an epidemic context by the Nigerien health authorities.

Eighteen isolates of NmX recovered from patients who developed meningitis during the 2006 season were further documented by the World Health Organization's Collaborating Centre for Reference and Research on Meningococci. All were nontypeable; 2 were nonsubtypeable and 16 were determined to be subtype P1.5. Sixteen of 18 isolates that were tested using multilocus sequence typing were determined to be ST-181 and 2 were ST-5789—2 STs not related to any known hypervirulent clonal complex.

DISCUSSION

To our knowledge, we report the largest series of laboratory-confirmed cases of NmX meningitis occuring in a single epidemic meningitis season. In 2005, the incidence of meningococcal meningitis was exceptionally low in Niger; one could have considered this situation to be the bottom of an epidemic cycle, as described by Lapeyssonnie [2]. The 2006 meningitis season started according to the same cycle pattern until the onset of an epidemic in February in the Maradi region. As usual, it was caused by NmA. An epidemic of NmX meningitis occurred ~1 month later, around Niamey. In this region, in contrast to what was observed in 1990 and again from 1995 to 2000 [6, 7], the incidence of cases of NmX meningitis in 2006 was exceptionally high and was associated with a very low incidence of cases of NmA meningitis. In 1997, the year with the highest incidence of cases of NmX meningitis during the period 1995–2000, the overall incidence of cases of NmX meningitis in Niamey was 15.1 cases per 100,000 inhabitants, compared with 30.5 cases per 100,000 inhabitants for cases of NmA meningitis [7]. Obviously, the overall incidence of 27.5 cases per 100,000 inhabitants (74.6 cases per 100,000 persons in the group aged 5–9 years) that we calculated from confirmed cases of NmX meningitis during the 2006 meningitis season underestimates the true incidence, because CSF specimens were not available for all the notified suspected cases. This original situation observed in 2006 was heralded because, as early as 2005, the unusually large proportion of cases of NmX meningitis drew the attention of the surveillance system, although it occurred in a context of very low incidence of meningococcal meningitis

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(figure 3). In the other countries of the African meningitis belt that reported Nm serotype identification during the 2006 meningitis season, the incidence of Nm of serotypes other than A and W135 were rare: 0 of 240 total Nm isolates in Burkina Faso, 4 of 84 in Benin, 1 of 35 in Mali, and 0 of 39 in Chad were identified as belonging to serotypes other than A and W135 [21].

The lower mean age of patients with NmX meningitis, compared with that of patients with NmA meningitis, was not observed in the 1990s in Niamey [7]; however, at that time, the series of observations was smaller. Although most cases of NmX and NmA meningitis occurred in distinct areas, this would not explain the difference in age among cases of meningitis due to the 2 serogroups, because the age distribution of the population was homogeneous between regions. The case-fatality rate that was observed in 2006 for cases of NmA meningitis was comparable with that observed during the period 2003–2005: ~6% (P.B.'s and H.B.M.'s unpublished data). The 2-fold higher case-fatality rate for cases of NmX meningitis confirmed previous observations that had been made in Niger of shorter case series. Because the NmX and NmA strains had the same susceptibility patterns, the higher case-fatality rate for NmX meningitis cannot be explained by drug susceptibility. The higher frequency of impaired consciousness and convulsions and the significantly lower age of patients who had NmX meningitis might contribute to explain the difference in case-fatality rates. Further studies will be performed to collect more-complete clinical observations.

During other epidemics of meningitis in the African meningitis belt that have been caused by uncommon Nm serogroups, the possible role of previous mass vaccination against NmA facilitating the emergence and epidemic spread of other serogroups had been suggested [22–24]; however, until now, this hypothesis was not supported by convincing arguments. In 2006, the highest incidence of cases of NmX meningitis was observed in southwestern Niger, where, because of the absence of any recent epidemic of meningitis, the last immunization campaign dated back to 2001. For these reasons, this part of the country was estimated to be the most at-risk region to experience an epidemic of NmA meningitis. Surprisingly, cases of NmA meningitis in this area have been very few.

Thorough characterization of strains of Nm is essential for the epidemiological monitoring of meningococci. In addition to serogrouping, Nm strains are differentiated on the basis of the immunological specificities of their class 1 outer-membrane protein (serosubtype), class 2 or 3 outer-membrane protein (serotype), and lipopolysaccharide (immunotype). The differentiation of these phenotypic characteristics is, however, not sufficient for epidemiologic purposes, because closely related strains can be further differentiated by their genetic character-

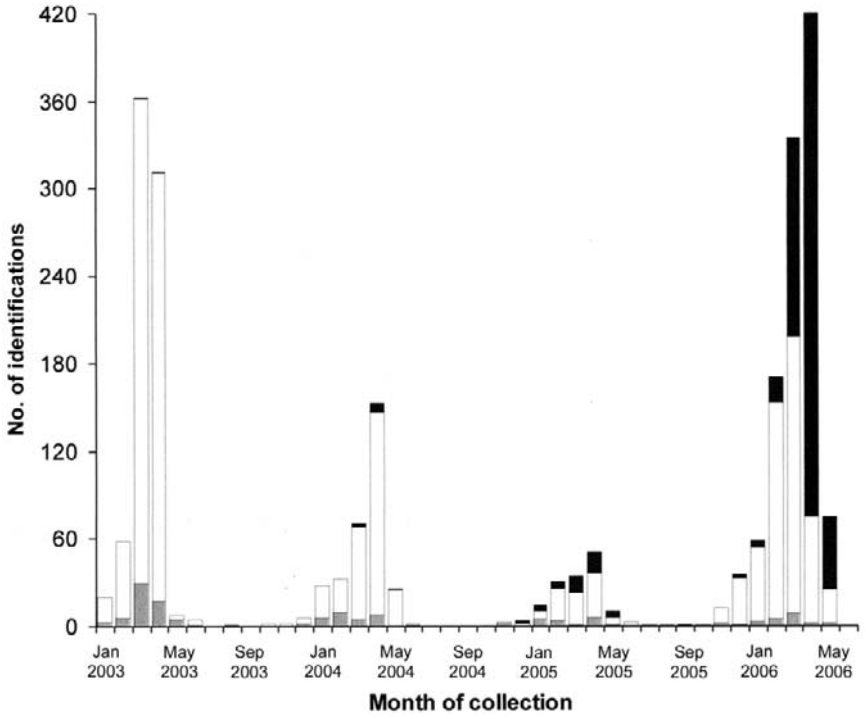

Figure 3. Evolution of the monthly distribution of identification of cases of *Neisseria meningitidis* serogroup A (NmA), serogroup X (NmX), and serogroup W135 (NmW135) meningitis in Niger, during the period 2003–2006. *White bars,* number of identified cases of NmA meningitis; *black bars,* number of identified cases of NmX meningitis; *gray bars,* number of identified cases of NmW135 meningitis.

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istics. Multilocus sequence typing provides unambiguous results and permits high-level discriminations between isolates. Because only housekeeping genes are involved, long-term epidemiological projections are possible; this technique is used to track clonal complexes that are circulating worldwide. When associated with epidemiological data, this technique should aid in the understanding of the responsibilities of STs and ST complexes in endemic cases and in outbreaks in Africa, the proposing of hypotheses on what might happen in the future, and preparing adapted responses. Epidemics show the emergence of isolates with the same serogroup, serotype, serosubtype, and ST. In the last few years in the African meningitis belt, most of the strains of Nm that were isolated from patients with meningitis could be classified into 2 ST complexes: serogroup A meningococci belonging to the ST-5 complex and serogroup W135 meningococci belonging to the ST-11 complex. A few other STs were also found among Nm serogroups W135, X, B, C, and Y [25]. In 2006 in Niger, epidemics of NmA meningitis were caused by ST-7 strains belonging to the ST-5 complex, whereas the epidemic of NmX meningitis was caused by the emergence of X:NT:P1.5 strains belonging to ST-181. The clonality of the strains responsible for the outbreak of NmX meningitis was assumed, because most of the isolates had the same group, type, subtype, and ST. Although other phenotypic markers, such as immunotype, may differ, it is important to note that the strain X:NT:P1.5 is well known in Niger, where it was already responsible for cases of meningitis in the 1990s and for a small epidemic in Niamey in 1997 [7]. Strains of NmX have already been isolated in Africa for 40 years; they have been responsible for sporadic cases of meningitis in Senegal (in 1981), Niger (in 1982), Chad (in 1995), and Burkina Faso (in 2003). NmX ST-181 was also circulating in Mali in the 1970s among pharyngeal carriers. Closely related isolates (ST-751; differing only in 2 loci) were identified by multilocus sequence typing from carriers and patients in Ghana during the period 1998–2000 26].

Until now, it was believed that NmX ST-181 had considerably lower virulence than usual epidemic strains of NmA [22]. This hypothesis must be considered cautiously, because the rate of incidence of NmX meningitis that was observed in Niamey, although lower than that observed during severe epidemics of NmA meningitis, was the highest ever observed for cases of NmX meningitis. Such a level of incidence is frequently observed in many local epidemics of NmA meningitis. Before the Hajj-related epidemic (in 2000 and 2001) and the Burkina Faso epidemic (in 2002), Nm serogroup W135 was not forecasted to be of public-health importance, particularly in the African meningitis belt. The forthcoming meningitis seasons will be of the highest interest to further assess the virulence of NmX ST-181.

The epidemiological characteristics of meningococcal meningitis seem to be unpredictable. The large meningitis epidemic caused by Nm serogroup W135 belonging to the hypervirulent colonal complex ST-11 in Burkina Faso was not followed by an extension of the epidemic within the African meningitis belt [27]. The emergence of NmX isolates of a low virulence ST (ST-181) may reflect a subtle balance between circulating isolates, herd immunity, environment, and other yet-unknown factors. The enhanced microbiological surveillance of meningitis that has been implemented since 2002 in the World Health Organization's initiative will probably help to reveal more epidemic situations in the African meningitis belt than may have been identified in the past. However, concerning Niger, it is unlikely that increased incidence of meningitis due to an unusual Nm serogroup for several weeks (as occurred in the southwest of the country in 2006) would not draw attention, even in a remote region. The nationwide reporting system had been in effect for many years, and would have likely detected a marked increase in the number of suspected cases, which would have signalled a field investigation wherein some CSF specimens would have been collected. Any unusual proportion of meningococci not belonging to serogroup A would have been reported, even if the serogroup was not identified. We believe that the situation reported here was, indeed, unprecedented in Niger.

The threat represented by NmX must be considered seriously, because there is no vaccine that protects individuals against this serogroup. Wisdom from experience would insist that there is a great need to develop meningococcal vaccines targeting this serogroup, which can no longer be considered to be a marginal one. Similarly, current serogroup X–specific antisera can be only used with meningococcal cultures; as such, their use is restricted to few laboratories in the African meningitis belt. The implementation of PCR that targets NmX should be promoted in other countries within the African meningitis belt, for use with noncultivable CSF specimens. There is no rapid diagnostic test that allows for the identification of NmX; this type of test would be highly desirable to reinforce the set of rapid diagnostic tools [28] available in basic laboratories in this area.

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