

# Epidemiology of bacterial meningitis in Niamey, Niger, 1981–96

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In the African meningitis belt the importance of endemic meningitis is not as well recognized as that of epidemics of meningococcal meningitis that occur from time to time. Using retrospective surveillance, we identified a total of 7078 cases of laboratory-diagnosed bacterial meningitis in Niamey, Niger, from 1981 to 1996. The majority (57.7%) were caused by *Neisseria meningitidis*, followed by *Streptococcus pneumoniae* (13.2%) and *Haemophilus influenzae* b (Hib) (9.5%). The mean annual incidence of bacterial meningitis was 101 per 100 000 population (70 per 100 000 during 11 non-epidemic years) and the average annual mortality rate was 17 deaths per 100 000. Over a 7-year period (including one major epidemic year) for which data were available, *S. pneumoniae* and Hib together caused more meningitis deaths than *N. meningitidis*. Meningitis cases were more common among males and occurred mostly during the dry season. Serogroup A caused 85.6% of meningococcal meningitis cases during the period investigated; three-quarters of these occurred among children aged <15 years, and over 40% among under-5-year-olds. Both incidence and mortality rates were highest among infants aged <1 year. In this age group, Hib was the leading cause of bacterial meningitis, followed by *S. pneumoniae*. The predominant cause of meningitis in persons aged 1–40 years was *N. meningitidis*. Use of the available vaccines against meningitis due to *N. meningitidis*, *S. pneumoniae*, and Hib could prevent substantial endemic illness and deaths in sub-Saharan Africa, and potentially prevent recurrent meningococcal epidemics.

Voir page 506 le résumé en français. En la página 507 figura un resumen en español.

## Introduction

Niamey, the capital of Niger, lies in the centre of the African meningitis belt (1), an area which experiences repeated epidemics of meningococcal meningitis in addition to a substantial number of cases of endemic meningitis. This situation poses a serious public health threat to the region, compared with other parts of the world. The last wave of epidemic meningococcal meningitis in Niger, which began in 1995, affected several countries during the following two years (2, 3). A total of 41 930 meningitis cases and 3639 deaths were reported in Niger in 1995 (4).

Epidemics of meningococcal meningitis in the meningitis belt are relatively well documented, as a result of investigations carried out during control efforts (5–10). In contrast, only a few studies in sub-

Saharan Africa have reported the rates of bacterial meningitis during non-epidemic periods, and characterized the specific agents causing endemic meningitis (11–13). Cerebrospinal fluid (CSF) analyses have been carried out in the Centre de Recherche sur les Méningites et les Schistosomiasés (CERMES) since 1981, and provide retrospective data on the epidemiology of both endemic and epidemic bacterial meningitis in Niamey over a 15-year period. These estimates of the burden of illness and deaths due to bacterial meningitis might suggest priorities in the use of currently available vaccines and help in the evaluation of new vaccines against the three principal etiological agents — *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* b (Hib).

## Materials and methods

### Study population and geographical setting

Most of the 9-million population of Niger, one of the world's poorest countries, live in the southern, agricultural region. The climate is typical of that in the meningitis belt, with a distinct dry season (November to April) during which the Harmattan dust and sand storms occur. The rainy season begins in May or June and lasts until October. Niamey is densely populated (total: 547 743 in 1995), especially during the dry season when people migrate from the rural areas and return to their villages when the rains begin. Resources for health care are limited.



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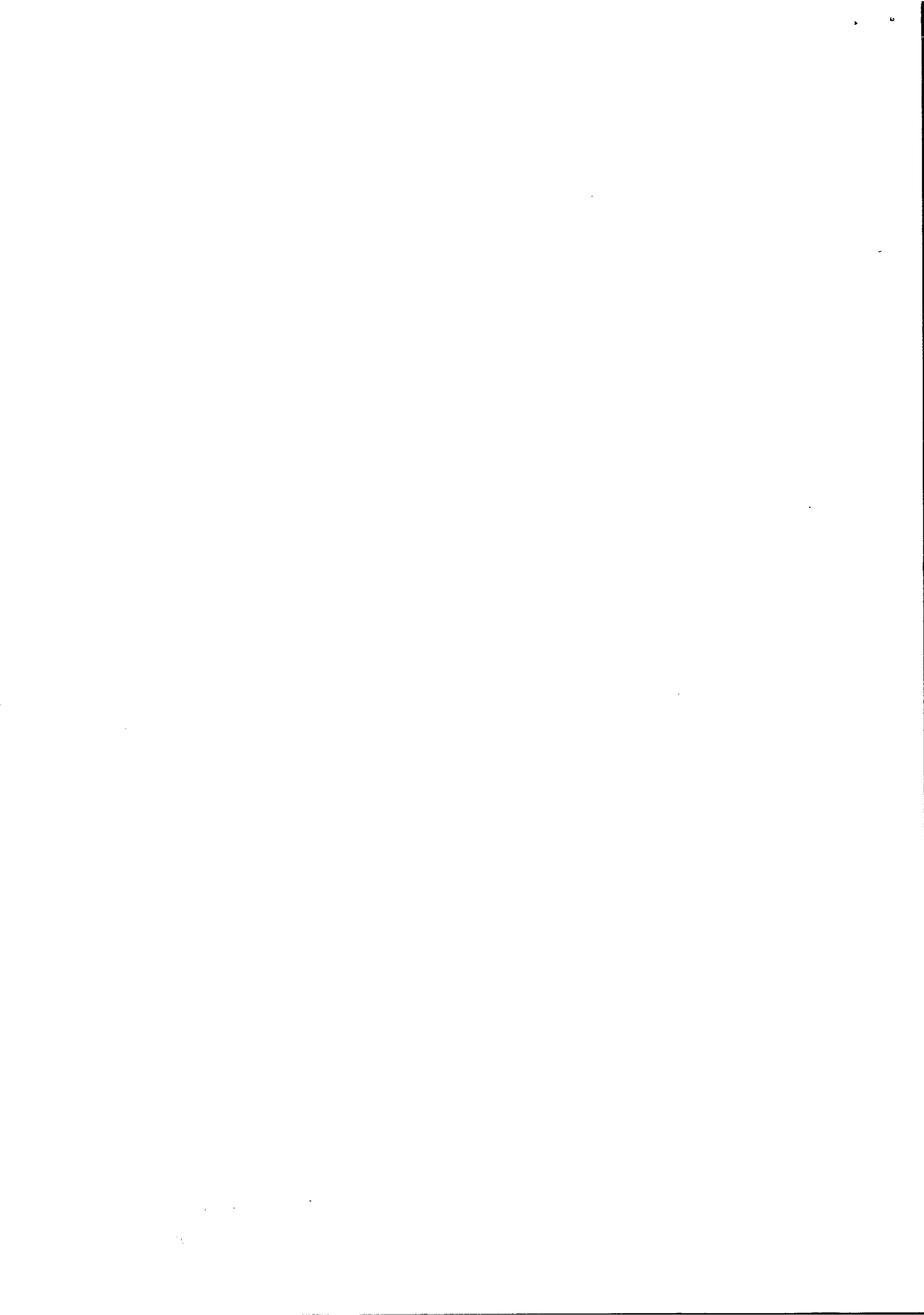
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### Data collection

The bacteriology laboratory of CERMES processes all CSF specimens submitted by the infectious disease service of the National Hospital of Niamey, where all cases of suspected meningitis in Niamey are treated. CSF specimens are obtained only rarely in the other wards of the hospital or at other health centres in Niamey.

Laboratory registers containing the results of CSF analysis served as the initial source of data for this study, which covered all specimens collected from 1 September 1981 to 30 June 1996. For each case, we recorded information on demographic characteristics and CSF analysis (cell count, Gram stain, culture and serology); excluded were CSF specimens that were collected to monitor a patient's response to antibiotic therapy. We also reviewed hospital registers to determine the outcome of the infection and any missing demographic data. Hospital records were available only for the period 1989–96.

### Laboratory methods

Standard methods were used for the analysis of CSF specimens and serogrouping of meningococci (14). Until 1994, latex agglutination testing was routinely conducted on specimens using the Slidex Meningitis Kit-5 (BioMerieux, Marcy-Etoile, France, reference No. 58803), which identifies *H. influenzae* type b, *N. meningitidis* A, B, or C; or *S. pneumoniae*. Counter-immunoelectrophoresis was used rarely. Additional serogrouping of selected isolates of *N. meningitidis* was carried out at the French Army's Pharo Laboratory in Marseilles or the Institut Pasteur in Paris.

Antimicrobial susceptibility was tested at CERMES for some specimens collected between 1985 and 1996 by the disk method using Bio-discs (BioMerieux, reference No. 5400 and 5466) for ampicillin and chloramphenicol. The number of isolates due to each pathogen tested for antimicrobial susceptibility varied substantially over the study period, so that we had limited ability to evaluate trends in antimicrobial resistance among the CSF isolates we examined.

### Case definition

A case of bacterial meningitis occurred when at least one of the following criteria was met:

- isolation from CSF of *N. meningitidis*, *S. pneumoniae*, *H. influenzae*, Enterobacteriaceae, or other pathogens;
- detection in CSF of antigen for *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* b by latex agglutination and/or counter-immunoelectrophoresis;
- presence of Gram-negative rods/cocci or Gram-positive cocci in CSF, by direct examination; or
- detection in the CSF of >100 white blood cells per ml.

### Data analysis

By designating that each year ran from 1 July until 30 June, we were able to group all cases for the same

dry season together; however, data for the first year (1981–82) were available only for 10 months beginning on 1 September. Incidence was calculated per 100 000 population. The chi-squared ( $\chi^2$ ) test was used to compare proportions.

The population of Niamey for each year from 1981 to 1996 was derived from the 1977 census figure (242 973) and the 1988 census (391 876), by applying an annual growth rate of 4.5% for the period 1977–88, and 4.9% (the official growth rate for Niamey) for the years after 1988. To determine the population by age group, we applied the age distribution from the 1988 census to each year's estimated total population. Nonresidents were excluded from the calculations of incidence and mortality rates. Data were analysed with Statview II for Macintosh software.

### National reporting system

Surveillance for reportable diseases in Niger is conducted by the Système National d'Information Sanitaire (SNIS), to which health centres report cases of clinically defined meningitis. We compared the data from the CERMES laboratory records with data reported to the SNIS from 1992 (when SNIS was reinforced) until 1996.

### Epidemic and nonepidemic years

By defining an epidemic year as one in which the total incidence of bacterial meningitis exceeded 140 cases per 100 000 population, we identified three such years (1984–85, 1985–86 and 1994–95) during our 15-year study period. Our data for the analysis of meningococcal meningitis cases between epidemics as well as the incidence of other pathogens cover only 11 nonepidemic years between 1981–82 and 1993–94; reagents for the identification of *H. influenzae* and *S. pneumoniae* and materials for collection of CSF were less available during the 1994–95 epidemic and 1995–96. Our description of the demographic characteristics of meningitis due to *S. pneumoniae*, *H. influenzae*, and other agents covers the entire 15-year period.

## Results

### Overall data

**Etiological agents.** During the study period, 13 802 CSF specimens were analysed, of which 7078 (54.1%) met the case definition. A pathogen was identified by culture and/or serological testing in 5846 (82.6%) cases; culture was positive in 3154 (*N. meningitidis*, 1983; *S. pneumoniae*, 613; *H. influenzae*, 397; other agents, 161). Latex testing identified 2692 additional cases (*N. meningitidis*, 2098; *S. pneumoniae*, 321; *H. influenzae*, 273). A total of 1232 cases were identified by other criteria only, and for further analyses were designated as indeterminate etiology. Of the meningitis specimens that were positive for *H. influenzae*, 95.2% were identified as type b by latex agglutination testing.

**Residence, incidence, case-fatality ratios and mortality rates.** The residence of 5839 (82.5%) of the 7078 patients with bacterial meningitis was known; 87.3% were from Niamey and 12.7% were declared to be nonresident. The distribution of etiological agents causing meningitis among nonresidents was similar to that among residents. The average annual incidence of cases and deaths and the case-fatality ratio due to bacterial meningitis for each agent are shown in Table 1. The annual incidence of all bacterial meningitis due to the three main agents are shown in Fig. 1. The total incidence in Niamey exceeded 140 cases per 100 000 in 1984–85, 1985–86 and 1994–95, which were defined as epidemic years. The 1994–95 meningococcal epidemic caused by serogroup A was the most severe, with an incidence in Niamey of 327 per 100 000.

15-year-olds, the predominance of males was substantially higher (e.g. up to 70% of cases) for cases caused by both *N. meningitidis* and *S. pneumoniae*.

***N. meningitidis* serogroups.** The majority of meningococcal meningitis cases (85.6%) over the 15-year study period were caused by *N. meningitidis* serogroup A, which was the predominant serogroup in 14 years of the study years. Serogroup C caused sporadic cases during most of the study period, but resulted in much more disease during 1990–93, with the rate of serogroup C meningitis in 1991–92 (23 cases per 100 000) exceeding that for serogroup A. A small outbreak of serogroup X meningococcal disease occurred in 1990 (incidence: 6.6 per 100 000). Other serogroups (B, W-135, 29-E) caused sporadic cases only. Nongroupable isolates of *N. meningitidis* caused 5.1% of cases, with polyagglutination identi-

Table 1. Number of cases and mean annual incidence of bacterial meningitis (1981–96), as well as pathogen-specific case-fatality ratios and mean mortality rates (1989–96) in Niamey, Niger

Pathogen	1981 to 1996		1989 to 1996			
	No. of cases	Mean annual incidence <sup>a</sup> (per 100 000)	No. of cases	No. of deaths	Case-fatality ratio <sup>b</sup>	Mean annual mortality rate <sup>a</sup> (per 100 000)
<i>N. meningitidis</i>	4 081 (57.7) <sup>c</sup>	55.3 (3.6–330.4) <sup>d</sup>	2 843	239	11.7	6.0
<i>S. pneumoniae</i>	934 (13.2)	14.2 (2–25.6) <sup>e</sup>	405	179	52.7	4.8
<i>H. influenzae</i>	670 (9.5)	10.5 (0.5–15.9) <sup>e</sup>	306	110	43.3	2.9
Others	161 (2.3)	2.3 (0.7–4.6)	103	40	54.1	1.2
Indeterminate	1 232 (17.4)	18.5 (4.4–57.6)	520	73	17.3	1.9
Total	7 078 (100)	100.8 (27.3–347.6)	4 177	641	20.5	16.8

<sup>a</sup> Nonresidents in Niamey were excluded from the calculation of incidence and mortality rate.

<sup>b</sup> Fatality among cases for which the outcome was known; the outcome was unknown in 25% of cases.

<sup>c</sup> Figures in parentheses are percentages.

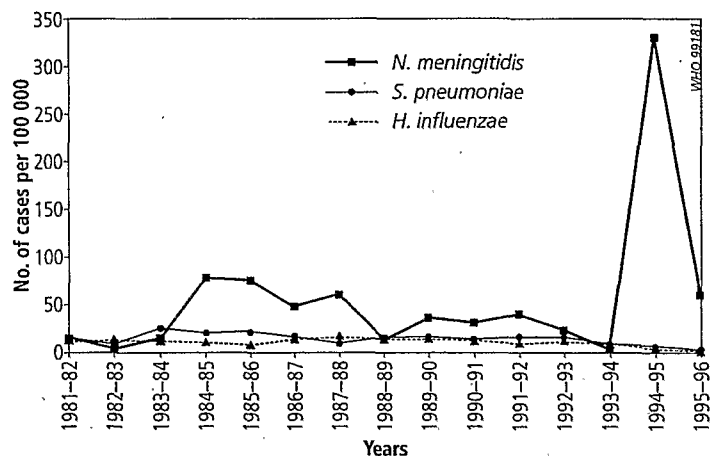
<sup>d</sup> Figures in parentheses are the range.

<sup>e</sup> The supply of reagents for the isolation of these two bacteria was limited during the years 1994–96.

Over the period July 1991 to June 1996, a total of 3418 meningitis cases were diagnosed at the CERMES laboratory, compared with 3563 meningitis cases reported to the mandatory reporting system of the SNIS for Niamey (overall sensitivity of 96%, assuming SNIS data reflect the “gold standard”). The annual numbers of cases reported respectively by CERMES/SNIS for this period were as follows: 1991–92, 469/555; 1992–93, 394/339; 1994–95, 169/169; 1994–95, 1919/1943; and 1995–96, 467/557. Most meningitis cases occurred during the dry season (65.3% from February to April).

**Age and sex of cases.** Information on age was available for 6330 (89.4%) of the cases. Of these, 76.2% were under 15 years of age, and 42.2% were under 5 years of age. Children under 1 year of age represented 22.8% of cases, and 12.2% were over 20 years of age. Meningitis was more common among males than females (Table 2). Overall, for males there was no significant difference between the proportion of meningitis cases caused by specific agents ( $\chi^2$  test = 4.8;  $P = 0.2$ ). However, among over-

Fig. 1. Annual incidence (per 100 000 population) of bacterial meningitis due to *N. meningitidis*, *S. pneumoniae* and *H. influenzae* from 1981 to 1996 in Niamey, Niger



Data for each year represent cases occurring from 1 July to 30 June, except in 1981–82 when cases were identified between 1 September 1981 and 30 June 1982.

Table 2. Number of cases of bacterial meningitis, by sex, for each pathogen, Niamey, Niger, 1981–96

Pathogen	Males	Females	Male : female ratio
	No. <sup>a</sup>	No. <sup>a</sup>	
<i>N. meningitidis</i>	2 441 (60.2) <sup>b</sup>	1 616 (39.8)	1.51
<i>S. pneumoniae</i>	534 (57.5)	395 (42.5)	1.35
<i>H. influenzae</i>	377 (56.5)	290 (43.5)	1.30
Others	93 (58.1)	67 (41.8)	1.38
Indeterminate	743 (60.8)	478 (39.2)	1.55
Total	4 188 (59.5)	2 846 (40.5)	1.47

<sup>a</sup> Cases for which sex was known.

<sup>b</sup> Figures in parentheses are percentages.

fied in 0.7% of strains. Strains from the 1994–95 epidemic were confirmed at the Pasteur Institute in Paris as *N. meningitidis* serosubtype A:4:1.9, identified as belonging to clonal group III-1 (15).

**Meningitis of indeterminate etiology.** No etiology was identified by either culture or serological testing for 1232 of the 7078 meningitis cases (17.4%). Most (941, 76.4%) were diagnosed by cell count alone. By reviewing the epidemiological characteristics of cases without an etiological diagnosis, we attempted to determine whether there was any systematic bias in diagnosing particular agents. The proportion of isolates with indeterminate etiology was relatively stable during the nonepidemic years, ranging from 15.4% in 1993–94 to 28.6% in 1982–83. In contrast, during the two epidemic years (1985–86 and 1994–95) the proportion of indeterminate cases ranged from 33.8% (1985–86) to 2% (1994–95). Most cases of indeterminate etiology occurred during the dry season from December to May, similar to cases with specific etiologies.

We compared the characteristics of identified meningitis cases with indeterminate meningitis cases for the nonepidemic years. The male to female ratio (1.37:1.66;  $\chi^2$  test = 2,  $P = 0.1$ ) was the same for the two groups. The case-fatality ratio was higher for identified meningitis cases (31.3%) than for indeterminate cases (18.7%) ( $\chi^2$  test = 17.5,  $P < 0.01$ ) for years when the evolution was known. The age distribution of cases was different in the two groups ( $\chi^2$  test = 36,  $P < 0.01$ ), with a higher proportion of under-1-year-olds among identified cases (34.7% vs. 25.2%) and the opposite state of affairs for 5–9-year-olds (17.1% vs. 21.2%) and 15–19-year-olds (8.4% vs. 13.1%).

### Nonepidemic years

**Incidence, case-fatality ratio and age-specific etiology.** The average incidence of bacterial meningitis and the case-fatality ratio, according to pathogen and age, during the 11 nonepidemic years are shown in Table 3. Data for all bacterial meningitis over the 1994–95 epidemic year are shown for comparison. During inter-epidemic years, meningococcus ac-

counted for the largest proportion of meningitis cases (37.9%), followed by pneumococcus (20.7%) and *H. influenzae* (16.4%). However, for 5 years, meningococcus was replaced by *S. pneumoniae* and/or *H. influenzae* as the predominant cause of bacterial meningitis. During the inter-epidemic years, pneumococcus was responsible for 38.7% of meningitis deaths, *H. influenzae* for 24.1%, meningococcus for 16.1%, and other bacterial agents for 9.1%. Fig. 2 shows the proportion of inter-epidemic bacterial meningitis attributable to each agent, by age group.

**Seasonality.** The seasonality of bacterial meningitis due to the three major agents during the 11 non-epidemic years is shown in Fig. 3. Meningococcal meningitis peaked in April, pneumococcal meningitis in March, while *H. influenzae* meningitis was fairly stable throughout the year.

**Inter-epidemic meningitis due to *N. meningitidis*.** Information on age was available for 95% of 1331 cases of meningococcal meningitis over the 11 inter-epidemic years. Three-quarters (74.3%) of meningococcal cases occurred in persons under 15 years of age and 25.8% among under-5-year-olds. The incidence of meningococcal meningitis in the inter-epidemic years was similar in all age groups under 20 years (Table 3). Comparison of the age distribution of serogroup A meningococcal meningitis between the 11 nonepidemic years and the three epidemic years showed that the proportion of cases involving under-5-year-olds during epidemic years was higher than that during nonepidemic years (31.3% of 2060 cases vs. 27.3% of 875 cases, respectively;  $\chi^2$  test = 4.6;  $P = 0.03$ ). There was no difference for under-15-year-olds age for the same two periods (73.4% vs. 74.5% of cases, respectively;  $\chi^2$  test = 0.4;  $P = 0.5$ ).

We compared the age distribution and case-fatality ratios for serogroups A and C meningococcal meningitis during the inter-epidemic years for which relevant data were available (1990–93). A similar proportion of cases due to serogroup A and serogroup C occurred among under-15-year-olds (72.9% vs. 71.6%, respectively;  $\chi^2$  test = 0.04;  $P = 0.8$ ); however, serogroup C disease was more common among children aged  $\geq 5$  years (79% of serogroup C vs. 65% of serogroup A;  $\chi^2$  test = 4.9;  $P = 0.04$ ). There was no significant difference in the case-fatality ratios between meningitis cases caused by serogroup A and C of *N. meningitidis*. For cases with a known outcome of infection, 14.7% of those infected with serogroup A and 9.9% with serogroup C resulted in death ( $\chi^2$  test = 2.2;  $P = 0.2$ ).

Resistance to ampicillin (6/811, 0.7%) and chloramphenicol (27/713, 3.8%) was rare among meningococcal isolates between 1985 and 1996 and there was no apparent trend in antimicrobial resistance over time.

### Descriptive information by organism

**Meningitis due to *S. pneumoniae*.** The ages were known for 850 (91%) of the cases of pneumococcal

Table 3. Average annual incidence<sup>a</sup> (per 100 000) and case-fatality ratio (CFR, for cases with known evolution), according to pathogen and age during 11 inter-epidemic years between 1981 and 1994, Niamey, Niger. Data for the epidemic year 1994–95 are shown for comparison.

Pathogen	Age (years)								Total <sup>b</sup>
	<1	1–4	5–9	10–14	15–19	20–29	30–39	≥40	
<b><i>N. meningitidis</i></b>									
Incidence	37.4	32.2	43.3	37.2	30.9	10.9	5.5	3.4	25.8
CFR (%)	19.3	12	9	7.6	5.2	22.9	22.2	41.7	11.6
<b><i>S. pneumoniae</i></b>									
Incidence	149.6	10.4	6.4	6.9	9.0	4.7	3.2	7.9	14.9
CFR (%)	57.7	56.8	15.8	34.8	62.1	58.3	20.0	60.0	52.8
<b><i>H. influenzae</i></b>									
Incidence	210.6	10.6	1.3	0.6	0.3	0	0	0	12.3
CFR (%)	43.6	45.5	44.4	0	0	0	0	0	43.8
<b>Other agents</b>									
Incidence	31.8	3.2	0.7	1.7	1.4	0.2	0.3	0.2	2.6
CFR (%)	36.0	16.0	4.0	5.0	3.0	2.0	1.0	0	67.0
<b>All bacterial meningitis: inter-epidemic years<sup>c</sup></b>									
Incidence	514.8	69.4	68.3	58.2	57.8	20.9	11.7	15.3	70.5
CFR (%)	47.9	29.7	9.7	13.0	19.2	31.9	22.9	44.7	28.8
<b>All bacterial meningitis: 1994–95 epidemic</b>									
Incidence	638.4	489.8	468.8	476.3	475.8	126.0	66.6	31.4	347.6
CFR (%)	29.1	12.8	8.4	10.6	8.1	11.8	19.2	29.4	12.3

<sup>a</sup> Non-residents in Niamey were excluded from calculation of incidence.

<sup>b</sup> Row totals include data for cases with unknown age, as well as those with ages specified.

<sup>c</sup> Includes meningitis of indeterminate etiology.

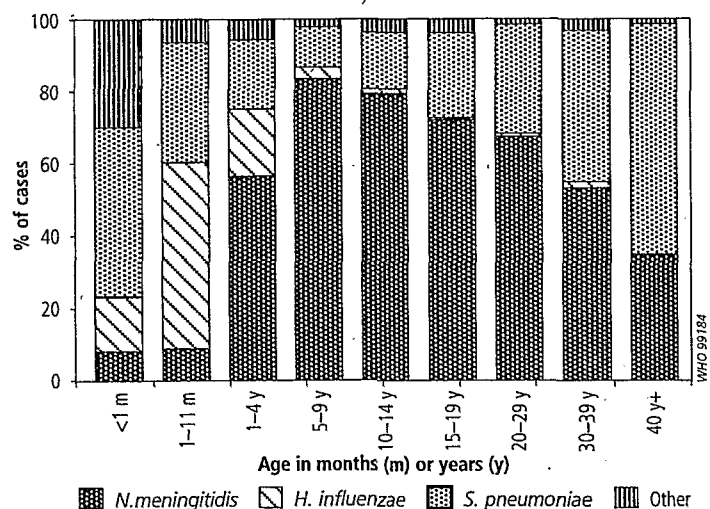
meningitis during the study period. The highest attack rates occurred among under-1-year-olds (Table 3). Those aged <2 years accounted for 53.1% of all pneumococcal meningitis cases and under-1-year-olds for 43.9%, while 25.6% of cases occurred by 6 months of age and 12.5% during the first 3 months. Fig. 4 shows the age distribution of pneumococcal meningitis among under-5-year-olds.

Resistance to ampicillin (7/207, 3.4%) was moderate among pneumococcal isolates, with no temporal trends among the sample available. However, chloramphenicol resistance was identified among 15.6% of pneumococci (42/269), with increased resistance evident after 1990.

**Meningitis due to *H. influenzae*.** The age was known for 631 (94.2%) of the cases of *H. influenzae* meningitis that occurred during the study period. Nearly all (96.8%) occurred among under-5-year-olds, 92.9% among under-2-year-olds, and 84% during the first year of life. Fig. 4 shows the distribution of *H. influenzae* cases among under-5-year-olds. The peak incidence of disease occurred among children aged 5–6 months. The incidence of *H. influenzae* meningitis was over 200 per 100 000 among under-1-year-olds and was negligible in persons aged >5 years (Table 3).

Of 169 isolates of *H. influenzae* tested for susceptibility to ampicillin, 37 (21.9%) were resistant, with a similar proportion (25.2% of 147 strains tested) being resistant to chloramphenicol. Of the

Fig. 2. Proportion of meningitis cases due to specific bacterial agents, by age group, during 11 inter-epidemic years between 1981 and 1994 in Niamey, Niger



131 strains tested with the two antibiotics, 11 (8.4%) were resistant to both. The frequency of ampicillin and chloramphenicol resistance appeared to increase over time. Among the 109 cases of *H. influenzae* meningitis with information on both clinical outcome and antimicrobial susceptibility, there was no significant association between fatality and resistance to

Fig. 3. Month of onset of bacterial meningitis cases occurring during 11 inter-epidemic years between 1981 and 1994 in Niamey, Niger

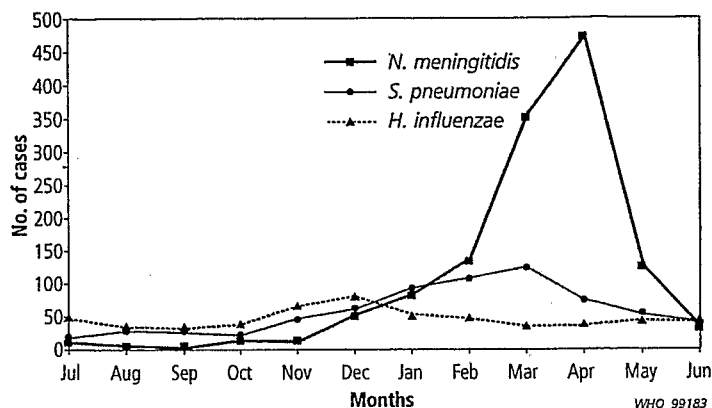
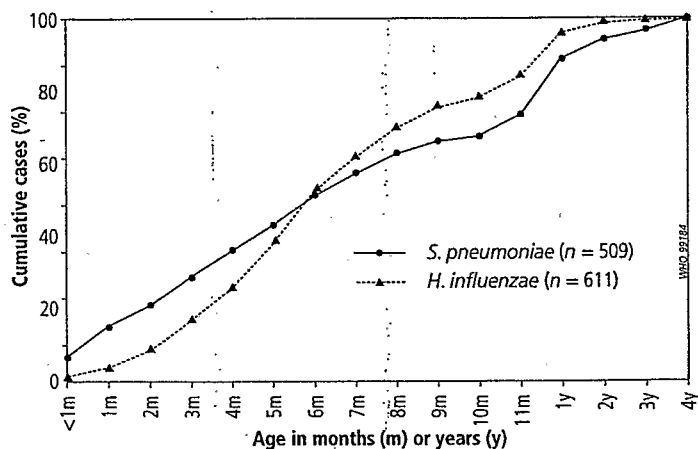


Fig. 4. Cumulative meningitis cases (%) due to *S. pneumoniae* and *H. influenzae* in under-5-year-olds, by age group, from 1981 to 1994 in Niamey, Niger



ampicillin or chloramphenicol ( $\chi^2$  test = 1.9, 0.1, and  $P = 0.2, 0.8$  respectively).

**Other agents causing bacterial meningitis.** Of the 7078 cases of bacterial meningitis, 161 (2.4%) were caused by agents other than *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*. More than half of these (60.2%) were due to Enterobacteriaceae, including 56 caused by *Salmonella* spp.; 32 (19.8%) were caused by staphylococci, while various streptococci, *Pseudomonas* sp., and *Acinetobacter* sp. each caused 12 additional cases. Most cases of meningitis due to Enterobacteriaceae occurred among under-5-year-olds (78.3%). The case-fatality ratio was 54% for the 74 cases caused by other agents for which the outcome was known.

### Neonatal meningitis

There were 101 cases of meningitis identified among neonates (<1 month of age) during the 15-year period. *S. pneumoniae* caused one-third (33.7%) of these cases; other streptococci were identified in 3 instances. Enterobacteriaceae, including *Salmonella*

spp., accounted for 15% of neonatal meningitis, *N. meningitidis* for 11%, and *H. influenzae* for 10%. A total of 9 out of 10 cases of *H. influenzae* meningitis were caused by serotype b. The majority (58%) of cases of neonatal meningitis for which the outcome was known died.

### Discussion

Our retrospective surveillance of diagnostic data over a 15-year period has provided comprehensive information on the specific causes and magnitude of bacterial meningitis in a typical city (Niamey) within the African meningitis belt. Epidemics of meningococcal meningitis, which occur at irregular intervals in Niger and neighbouring countries, represent only a part of the public health burden caused by meningitis within the Sahelian region. In the periods between epidemics the incidence of endemic bacterial meningitis in this area is substantially higher than that observed elsewhere, and is a frequent cause of illness and death among young children. Meningococcus was the leading cause of bacterial meningitis even in the inter-epidemic period in Niamey, although in certain years other agents predominated. Over the period 1989–96, which included one major epidemic of serogroup A meningococcal disease, meningococcus caused 68.1% of cases of bacterial meningitis but only 37.3% of deaths; in contrast, over this period, pneumococcus and *H. influenzae* together caused 17% of cases and 45.1% of deaths.

Our data may be an underestimate of the real burden of bacterial meningitis in Niamey, since they are based on passive case-finding, because only persons who presented to the hospital and underwent lumbar puncture were identified. Some patients with fulminant bacterial meningitis may not reach the hospital and others may not be referred to hospital or may refuse to be admitted because of the cost or for cultural reasons. Certain patients did not undergo lumbar puncture, and poor storage or transport conditions may have spoiled the results of culture in some CSF specimens. Our calculations of incidence were based on population growth estimates applied to the 1988 census, which may be imprecise, and seasonal variations of population are difficult to evaluate. Previous exposure to antibiotics, which is common in Africa, may have interfered with culture of the organism from some patients. Antigen detection tests for bacterial meningitis have different sensitivity. Scarcity of reagents for detecting Hib and *S. pneumoniae* during the last two years of the study period may explain the low incidence of meningitis due to pneumococcus and Hib (after 13 years of remarkable stability) during the 1994–95 epidemic and the following year. We suspect that many pneumococcal and Hib meningitis cases during these 2 years were classified under indeterminate etiology. As we could not identify any other reason to explain this drop in Hib and pneumococcus cases, we

decided to exclude the corresponding data in the evaluation of specific incidence.

Our data for meningitis due to specific agents are minimum estimates because we could not determine the etiology in 17% of bacterial meningitis cases. Comparison of our cases of known and indeterminate etiology suggests that the latter cases were probably due to a mixture of the major identified causes of bacterial meningitis, with meningococcus predominating. The lower case-fatality ratio and higher proportion of cases among age groups >1 year, which were placed in the indeterminate category, support this hypothesis. As far as cases with an identified etiology are concerned, it is unlikely that this was due to our failure to detect a certain agent throughout the study period or to any systematic bias. The agreement between the number of cases reported in recent years by the reinforced *Système National d'Information Sanitaire*, which identifies cases based on clinical diagnosis, and the CERMES bacteriology laboratory data suggest that our data are comprehensive, at least for those meningitis cases that present for medical care.

The annual incidence of all bacterial meningitis in Niamey averaged 101 per 100 000 population, i.e. more than 15 times the rate detected in developed countries (16–18) and 2–3 times the rate detected in Dakar, Senegal, which is located outside the African meningitis belt (11). The rates reported in Niamey are similar to those identified in other areas in the meningitis belt (19). It is particularly striking that the rate of bacterial meningitis (excluding major epidemic years) averaged 70 per 100 000, and that it exceeded 100 per 100 000 in 4 of the 15 years concerned.

Three agents (*N. meningitidis*, *S. pneumoniae* and Hib) caused more than 80% of cases of bacterial meningitis; the majority of remaining cases were of indeterminate etiology. Our estimate of the contribution of these agents to bacterial meningitis is similar to that observed in studies from 12 countries over the last 20 years (5). However, the proportion of meningitis due to each agent differs even between developing countries. A review of meningitis cases in Mali (12), within the meningitis belt, also identified meningococcus as the predominant agent. The predominance of meningococcus probably distinguishes the entire meningitis belt from the pattern observed elsewhere in Africa. In more humid areas, pneumococcal meningitis is more common than meningitis due to *H. influenzae* and meningococcus (11, 13, 20). In industrialized countries, *H. influenzae* was typically the leading cause of bacterial meningitis (16) before routine use of conjugate vaccines.

Bacterial meningitis is a particular problem among children, with over 40% occurring among under-5-year-olds. *H. influenzae* and *S. pneumoniae* were the main causes of meningitis among children under 1 year of age, in both epidemic and inter-epidemic years. The long-term sequelae among meningitis survivors, such as deafness and developmental disabilities, although we did not investigate them in

this study, are particularly frequent for pneumococcal and Hib meningitis in areas where access to adequate treatment is limited.

The higher rate of bacterial meningitis among males has been noted previously in both developing and developed countries (11, 12, 16, 20). These findings may reflect selection bias due to male/female-related care-seeking behaviour, since our data were based on patients who presented at the hospital. However, there may be a real increased risk among males, particularly those aged >15 years, for *N. meningitidis* and *S. pneumoniae*.

Most epidemics of meningococcal disease in Africa over the past 20 years have been caused by serogroup A strains (5). *N. meningitidis* serogroup C also has caused disease in the region, including epidemics in Burkina Faso, Mali, and northern Nigeria in 1979 (5). Our study demonstrated the emergence of serogroup C meningococcal disease in Niger during 1990–93. Following a decline in serogroup C cases, serogroup A disease returned in a major epidemic in 1994–95. The same phenomenon was observed earlier in Bamako, Mali (12). Periodic emergence of serogroup C appears typical of the meningitis belt region, in contrast to the nearly permanent presence of serogroup A strains in this area.

We were unable to estimate the true importance of other meningococcus serogroups among bacterial meningitis cases in Niamey, since only serogroups A and C were systematically identified. An outbreak of more than 60 cases of meningitis due to *N. meningitidis* serogroup X occurred in Niamey between November 1996 and March 1997 (Djibo, S., 1997, unpublished data), similar to that reported during 1990 (21). The presence of this strain is quite unusual and further evaluation of serogroup X strains is planned.

Certain of our findings on inter-epidemic meningococcal meningitis are notable. The age distribution of meningococcal meningitis cases in Niamey extends well beyond early childhood, with relatively stable attack rates among persons under 20 years of age. The shift in the age distribution of cases during epidemics reported by Peltola et al. (22), in which a higher proportion of meningitis cases occurred in older subjects compared with the non-epidemic years, was not observed in Niamey. On the contrary, a higher proportion of cases occurred among under-5-year-olds during epidemic years. Some reports have suggested that serogroup C meningococcus causes more severe disease than serogroup A (23), but in Niamey we found similar mortality rates for serogroup A and serogroup C meningitis cases. There was a slightly greater tendency for serogroup C, rather than serogroup A, to cause disease in older children. In the USA, older children were more likely to acquire serogroup C rather than serogroup B disease (24).

*S. pneumoniae* was the second most common cause of bacterial meningitis. The incidence of pneumococcal meningitis in Niamey (mean: 14.2 per 100 000) is slightly higher than that identified in



other countries of the region (17), but approximately 10 times the incidence of pneumococcal meningitis identified in industrialized countries (16, 18). The seasonal variation observed in Niamey was similar to that described in other parts of West Africa (11, 12). The early onset of this infection in Niamey is characteristic of the epidemiology of pneumococcal infections in developing countries (17). As has been noted previously, pneumococcal meningitis in Niamey was associated with high fatality rates (11, 12, 20, 25).

*H. influenzae* caused substantial illness among under-1-year-olds (incidence, 211 per 100 000 population — a rate similar to that identified in the Gambia (25) and Burkina Faso (26), but much higher than was reported for Dakar, Senegal (11)). The characteristics of *H. influenzae* meningitis in Niamey resembled those described in other developing countries (27), with onset of illness at a young age and a high case-fatality ratio. Serotype b caused over 95% of *H. influenzae* meningitis in Niamey. Little seasonal variation occurred, which is similar to findings elsewhere in the region (11, 25, 26).

Resistance to ampicillin and chloramphenicol was common among *H. influenzae* isolates, but we found no association between resistance and case fatality, perhaps because the mortality rate was so high even among patients whose illness was caused by susceptible isolates. Emergence of ampicillin resistance among *H. influenzae* cases has previously been identified in West Africa (12) and seems to be increasing: 50% of isolates were resistant to ampicillin in a recent study in Malawi (20) and ampicillin resistance was observed in one-third of *H. influenzae* cases in the USA in 1986 (16).

The frequency of chloramphenicol resistance among *H. influenzae* isolates in Niger was similar to that identified in Malawi (20–25%) (20). Antimicrobial resistance among *H. influenzae* cases (and to a lesser extent pneumococci) presents a challenge to the clinical management of meningitis cases in inter-epidemic periods in Niamey. Although our study was focused only on meningitis cases, the burden of Hib disease in Niamey is likely to be much larger than that reported here. In the Gambia, which has rates of Hib meningitis similar to that in Niamey, more than 20% of severe pneumonia was attributable to Hib (28).

Other agents, primarily Enterobacteriaceae, caused bacterial meningitis particularly among neonates, as reported also by Cadoz (17). These pathogens were rare causes of meningitis in our

study, but have been identified more often in certain paediatric settings (20, 29). Although our study included numerous cases of neonatal meningitis, we did not identify an important role for group B streptococci, the leading cause of neonatal meningitis in many industrialized countries (30). In a recent WHO-sponsored multicentre study of serious infections of infants aged <90 days in four developing countries, *S. pneumoniae* was responsible for 17 out of 43 culture-positive cases of meningitis, while group B streptococci caused only one case (K. Mulholland, personal communication, 1998).

Our study provides key elements needed to assess the problem of meningitis in sub-Saharan Africa and can help identify priorities for future efforts to control vaccine-preventable diseases in the region. Pneumococcus and *H. influenzae* meningitis, which attract less attention than meningococcal meningitis, are clearly a major public health problem. Because meningitis is easier than respiratory infections to diagnose precisely, its magnitude has been more readily quantifiable, and it is likely that the benefit of using vaccines for the principal causes of meningitis would greatly exceed that resulting from prevention of the estimated meningitis burden reported here.

The levels of illness and death from meningitis identified during the 15-year period in Niamey suggest the potential value of immunization with either currently available vaccines (e.g. meningococcal polysaccharide vaccines (5), and Hib conjugate vaccines (31)) or those under investigation (meningococcal A/C conjugate vaccines (32) and pneumococcal conjugate vaccines (33)). Unfortunately, demonstration of the burden of disease and the availability of a safe and effective vaccine are not the only factors upon which the decision to introduce a vaccine is based. Economic factors are also critical since decision-makers with scarce or no resources are confronted with competing health priorities. The estimates of illness and death we have reported in this study could be used in cost-benefit analyses to model the economic value of disease prevention. ■

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### Résumé

#### Epidémiologie de la méningite bactérienne, Niamey (Niger), 1981-1996

Bien que les urgences de santé publique que constituent les épidémies de méningite à méningocoques soient relativement courantes en Afrique subsaharienne, l'importance de la méningite endémique dans cette région est moins bien établie. Alors que sont mis au point de nouveaux vaccins contre la méningite bactérienne, la

collecte d'informations sur le nombre des cas de méningite causés par des agents spécifiques aidera à déterminer les priorités des opérations de vaccination.

Nous avons conduit une étude rétrospective, pour la période 1981-1996, des cas de méningite bactérienne diagnostiqués en laboratoire à Niamey, au Niger.

A Niamey (547 743 habitants en 1995), les cas de méningite sont soignés à l'Hôpital national de Niamey, où des ponctions lombaires sont pratiquées systématiquement. Les échantillons de liquide céphalo-rachidien (LCR) ont été examinés au laboratoire du Centre de Recherche sur les Méningites et les Schistosomiasis à Niamey et le diagnostic a été posé sur la base des résultats de colorations de Gram effectuées sur le LCR, de la numération des globules blancs, de la détection d'antigènes et/ou d'isolements de microorganismes pathogènes à partir du LCR.

Au cours de cette période de 15 ans, 7078 cas de méningite bactérienne diagnostiqués en laboratoire ont été recensés. La majorité (57,7%) étaient dus à *Neisseria meningitidis*, suivi par *Streptococcus pneumoniae* (13,2%) et *Haemophilus influenzae* de type b (Hib) (9,5%). L'incidence annuelle de la méningite bactérienne s'est située entre 27,3 et 347,6 (moyenne : 101) pour 100 000 habitants et le taux des décès entre 6,0 et 27 (moyenne : 17) pour 100 000 habitants. Au cours des 11 années où il n'y a pas eu d'épidémie, l'incidence annuelle moyenne de la méningite bactérienne a été de 70 pour 100 000, avec *N. meningitidis* comme principal agent responsable. Pendant toute la période de 15 ans, dont trois années ont été marquées par des épidémies de méningite à méningocoques du sérotype A, l'incidence annuelle moyenne de la méningite a été la suivante pour chaque agent pathogène : *N. meningitidis*, 55 pour 100 000; *S. pneumoniae*, 14 pour 100 000; et *H. influenzae*, 11 pour 100 000. Les taux de létalité ont été les suivants selon les agents considérés : 52,7% pour la méningite à pneumocoques, 43,3% pour

*H. influenzae*, et 11,7% pour la méningite à méningocoques. Les cas ont été plus nombreux chez les sujets de sexe masculin (risque relatif : 1,47) et la plupart sont survenus pendant la saison sèche. Sur une période de 7 ans, dont une année avec une épidémie majeure, pour laquelle ont pu être consultées des données sur l'issue des cas, *N. meningitidis* a été à l'origine de 68,1% de cas de méningite bactérienne et de 37,3% de décès, cependant qu'ensemble, *S. pneumoniae* et *H. influenzae* b (Hib) ont provoqué 17% de cas de morbidité et 45,1% de décès. Au cours de la période de 15 ans, le sérotype A a causé 85,6% des cas de méningite à méningocoques. Les trois quarts des cas de méningite bactérienne se sont produits chez des enfants de moins de 15 ans, et plus de 40% chez des moins de 5 ans. Les taux d'incidence et de mortalité ont été les plus élevés chez les nourrissons de moins d'un an (incidence : 515 pour 100 000 pendant les années entre les épidémies). Dans ce groupe d'âge, la cause première des cas de méningite a été Hib (incidence : 211 pour 100 000), puis *S. pneumoniae* (150 pour 100 000). *N. meningitidis* a été la cause prédominante chez les sujets âgés de 1 à 40 ans.

Ces résultats donnent à penser que l'existence de vaccins contre la méningite à *N. meningitidis*, *S. pneumoniae* et Hib, qui pourraient être administrés dans le cadre du Programme élargi de Vaccination, permettrait de prévenir une morbidité endémique importante et de nombreux décès dus à la méningite en Afrique subsaharienne, et sans doute empêcher des épidémies récurrentes dues à *N. meningitidis*.

## Resumen

### Epidemiología de las meningitis bacterianas en Niame (Níger), 1981-1996

Aunque las epidemias de meningitis meningocócica constituyen emergencias de salud pública habituales en el África subsahariana, en esta región se presta menos atención a las meningitis endémicas. Con la aparición de nuevas vacunas de prevención de las meningitis bacterianas, toda información sobre la magnitud de las meningitis causadas por agentes específicos ayudará a determinar las prioridades de inmunización.

Llevamos a cabo un estudio retrospectivo de los casos de meningitis bacteriana diagnosticados en laboratorio en Niamey (Níger) durante el periodo de 1981 a 1996. En Niamey (547 743 habitantes en 1995) las personas con meningitis son atendidas en el Hospital Nacional de la ciudad, donde las punciones lumbares son una intervención habitual. Los análisis de laboratorio de las muestras de líquido cefalorraquídeo (LCR) se realizaron en el Centre de Recherche sur les Méningites et les Schistosomiasis de Niamey, y el diagnóstico se basó en los resultados del análisis del LCR y de la tinción con Gram, el recuento de leucocitos, la detección de antígenos y/o el aislamiento de un agente patógeno en el LCR.

En el periodo de 15 años considerado se identificaron 7078 casos de meningitis bacteriana diagnosticados en laboratorio; la mayoría (57,7%)

habían sido causados por *Neisseria meningitidis*, seguida de *Streptococcus pneumoniae* (13,2%) y *Haemophilus influenzae* tipo b (Hib) (9,5%). La incidencia anual de meningitis bacteriana osciló entre 27,3 y 347,6 (media: 101) por 100 000 habitantes; y las defunciones por esa causa se situaron entre 6,0 y 27 (media: 17) por 100 000 habitantes. Durante 11 años interepidémicos la incidencia anual media de meningitis bacteriana fue de 70 por 100 000 habitantes, con *N. meningitidis* como causa principal. Durante los 15 años estudiados, incluidos tres años de meningitis epidémica por meningococos del serogrupo A, la incidencia anual media de meningitis por agentes específicos fue la siguiente: *N. meningitidis*, 55 por 100 000; *S. pneumoniae*, 14 por 100 000; y *H. influenzae*, 11 por 100 000. Las tasas de letalidad por meningitis fueron las siguientes: 52,7% para la meningitis neumocócica, 43,3% para *H. influenzae*, y 11,7% para la meningitis meningocócica. Los casos de meningitis fueron, más comunes entre los hombres (riesgo relativo: 1,47) y la mayoría se produjeron durante la estación seca. A lo largo de un periodo de 7 años sobre los que había datos respecto a los resultados, incluido un año en que hubo una gran epidemia, *N. meningitidis* causó el 68,1% de los casos de meningitis bacteriana y el 37,3% de las

defunciones, mientras que *S. pneumoniae* y *H. influenzae* tipo b (Hib), considerados conjuntamente, causaron el 17% de los casos y el 45,1% de las defunciones por meningitis. El serogrupo A causó el 85,6% de los casos de meningitis meningocócica durante los 15 años considerados. Las tres cuartas partes de los casos de meningitis bacteriana se dieron en menores de 15 años, y más del 40% en menores de 5 años. Tanto la incidencia como las tasas de mortalidad fueron máximas entre los lactantes de menos de un año (incidencia: 515 por 100 000 durante los años interepidémicos). En este grupo de edad el Hib fue la causa principal de meningitis

(incidencia: 211 por 100 000), seguido de *S. pneumoniae* (150 por 100 000). *N. meningitidis* fue la causa predominante de meningitis en las personas de 1 a 40 años.

Los resultados indican que la disponibilidad de vacunas contra las meningitis causadas por *N. meningitidis*, *S. pneumoniae* y Hib, susceptibles de integración en el Programa Ampliado de Inmunización, permitiría prevenir gran parte de la morbilidad y mortalidad endémicas por meningitis en el África subsahariana y brindaría la posibilidad de prevenir las epidemias recurrentes por *N. meningitidis*.

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