Association of meningococcal serogroups with the course of disease in the Netherlands, 1959–83

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To study the association of meningococcal serogroups with the course of disease, we reviewed the case histories of 1221 patients. The meningococci from these patients constituted a sample from isolates collected and serogrouped systematically in the Netherlands since 1959. Of these 1221 isolates, 64% were serogroup B. The overall case fatality rate was 5.1%, and the rate was lowest for patients with serogroup A infections (2.3%) and highest for serogroup W135 (18%) (P < 0.01). The occurrence of septicaemia without meningitis (case fatality rate 15.3%) was similarly distributed among the serogroups (A, 4.0%; W135, 30%). Sequelae occurred in 7.9% of patients (loss of hearing, 3.2%) and were remarkably prevalent after disease due to minor serogroups (X and Y: 4 out of 12). In a log-linear analysis, both age and serogroup were significantly associated with case fatality rate and with the occurrence of septicaemia and sequelae. It is argued that these data are representative, despite the problems inherent in a retrospective investigation. The course and outcome of meningococcal disease appear to be related to the Neisseria meningitidis *serogroup and to host factors.*

Neisseria meningitidis, a frequent cause of meningitis, can be subdivided into 12 serogroups (A, B, C, 29E, H, I, K, L, W135, X, Y, Z), based on the heterogeneity of the capsular polysaccharides (*1*). Isolates from patients with meningococcal disease belong almost exclusively to five of these serogroups (A, B, C, and, less frequently, W135 and Y) (*2–5*), while the other groups are mostly isolated from carriers. Besides this difference in case-to-carrier ratio, other epidemiological differences among the various serogroups, e.g., in geographical and age distribution, in the cyclical changes in the prevalence of groups and in sulfonamide resistance, have been well documented (*3, 5–8*).

A few studies have described the relationship between the course of meningococcal disease and serogroup. For example, in the USA and Nigeria, groups B and C are more frequently associated with myocarditis, septicaemia, and mortality than is group A (*9, 10*). Some investigators have reported that group W135 is associated more frequently with septicaemia than the other groups (*2, 11–13*). In addition, W135 has been associated with hypogammaglobulinaemia and immunosuppression (*11, 14*).

In the Netherlands, the case fatality rate for meningococcal disease over the period 1974–78 was higher for group W135 than for the other groups (*12*). In contrast, in Scotland, the rate for 1972–82 was similar for groups A and C and lower for groups B and W135 (*13*).

Here, we describe the association of serogroups of *N. meningitidis* with the outcome, complications, and age distribution of meningococcal disease for 1221 patients in the Netherlands over the period 1959–83.

MATERIALS AND METHODS

Strains of Neisseria meningitidis

Since 1959, strains of *N. meningitidis* isolated from patients with meningitis and/or septicaemia have been submitted to the Netherlands Reference Laboratory for Bacterial Meningitis by bacteriological laboratories throughout the country (*15*). In the

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1960s, the number of submissions amounted on average to 59% of the statutorily notified number of cases of meningococcal disease, but from 1972 onwards this has increased to about 120% (5, 8). Serogrouping was performed by agglutination and by microprecipitation. The epidemiological features of this strain collection have been described previously (5). Samples of cerebrospinal fluid were examined for meningococcal polysaccharide antigens (16).

Data on patients

We examined the medical histories of 1221 patients represented in this collection by a strain of N. meningitidis isolated from cerebrospinal fluid and/or blood (n=1198) or by a sample of cerebrospinal fluid containing meningococcal polysaccharide (n=23). Medical records were requested from 45 hospitals in six regions throughout the Netherlands, chosen because they are evenly spread geographically and because the regional laboratories had been submitting strains regularly to the reference laboratory. In three regions (16 hospitals), the period studied was 1959–81 (758 records obtained), while for the other three we requested records for 1970–81 (274 records obtained). Finally, in 1983 we asked all Dutch hospitals to supply copies of discharge letters for patients with meningococcal disease. The serogroup distribution of the strains isolated from the patients whose histories we examined was similar to that for all strains submitted to the reference laboratory between 1959 and 1983 (15), over which period the Dutch population increased from 11.3 million to 14.3 million.

Definitions and methods

For the purpose of the study, meningitis was defined as the presence of culture- or antigen-positive cerebrospinal fluid, and septicaemia as the presence of a positive blood culture and/or shock and/or haemorrhagic skin lesions. As focal neurological signs were included: abnormality of a cranial nerve, forced deviation of head and/or eyes, dysphasia, ataxia, nystagmus, paralysis, and reflex abnormality. The following factors were considered as predisposing to meningococcal disease: malignancy, immunosuppression, diabetes mellitus, chronic or recurrent respiratory infection, alcohol abuse, absence of the spleen, and severe head injury or cerebrospinal fluid leak.

Computerized data processing was carried out using the "Statistical Package for the Social Sciences"[a] and the "Biomedical Computer Programs",[b] while a χ^2-test of significance was performed (with Yates's correction for 2×2 tables). A log-linear model was used to analyse whether age was a confounding factor (17). For this purpose, the age groups were <1, 1–9, 10–49 and ≥50 years while serogroups W135, X, Y, Z, and non-groupable strains were pooled. A constant (0.5) was added to each cell of a table before the analysis.

[a] From SPSS, Chicago, IL, USA.
[b] From BMDP Statistical Software, Los Angeles, CA, USA.

Table 1. Outcome of meningococcal disease in the Netherlands from 1959 to 1983, according to Neisseria meningitidis serogroup

| Serogroup | No. of cases | Outcome | |
		Fatal	With sequelae
A	176 (14.4)[a]	4 (2.3)[b]	17 (9.9)[c]
B	784 (64.2)	40 (5.1)	54 (7.3)
C	209 (17.1)	10 (4.8)	13 (6.5)
W135	33 (2.7)	6 (18)	2 (7)
Others	19 (1.6)	2 (11)	5 (29)
X	4	1	1
Y	10	1	3
Z	1	0	0
Non-groupable	4	0	1
Total	1221 (100.0)	62 (5.1)[d]	91 (7.9)[e]

[a] Figures in parentheses in this column are percentages of total number of cases.

[b] Figures in parentheses in this column are percentages per serogroup.

[c] Figures in parentheses in this column are percentages of surviving patients.

[d] Comparison of case fatality rates: all serogroups ($\chi^2 = 15.8$; degrees of freedom = 4; $P = 0.003$; serogroup A versus all other serogroups ($\chi^2 = 2.7$; degrees of freedom = 1; $P > 0.09$); without serogroup A ($\chi^2 = 11.5$; degrees of freedom = 3; $P = 0.009$).

[e] Comparison of proportions of patients with sequelae: all serogroups ($\chi^2 = 12.8$; degrees of freedom = 4; $P = 0.013$); without "others" ($\chi^2 = 1.7$; degrees of freedom = 3; $P > 0.6$).

RESULTS

Serogroup and outcome

Table 1 shows the distribution of the 1221 patients by serogroup and disease outcome. Meningococcal serogroup B was isolated from almost 65% of the patients. The case fatality rate was 5.1%; for serogroup A, the rate was 2.3%, which was lower, but not significantly so, than the rate for the other groups combined (5.6%; $P > 0.09$). The case fatality rate for group W135 was 18%, significantly higher than that for groups B, C, and "others" ($P = 0.009$). Sequelae occurred in 7.9% of surviving patients and the differences between the serogroups were significant ($P = 0.013$), mainly because of the high proportion of

Table 2. Distribution of sequelae, according to *Neisseria meningitidis* serogroup

| Serogroup | No. of survivors | Sequelae[a] | | | | |
		Loss of hearing	Motor disturbance[b]	Epilepsy	Hydrocephalus	Other[c]
A	172	9 (5)[d]	5 (3)	2 (1)	1 (1)	3 (2)
B	744	14 (2)[e]	23 (3)	5 (1)	9 (1)	13 (2)
C	199	8 (4)	4 (2)	0	1 (0)	2 (1)
W135	27	2 (7)	0	0	0	0
Others	17	4 (24)	1 (6)	0	0	1 (6)
Total	1159	37 (3.2)	33 (2.8)	7 (0.6)	11 (0.9)	19 (1.6)

[a] Some patients had more than one sequela.
[b] Developmental disturbance and/or paralysis.
[c] Including speech disorders, severe skin necrosis, and contracture after arthritis.
[d] Figures in parentheses are percentages per serogroup.
[e] Significantly less than loss of hearing due to all other groups combined: $\chi^2 = 10.4$; degrees of freedom = 1; $P = 0.001$.

those with sequelae in the "other" serogroups: five out of 17 survivors, four of whom suffered from loss of hearing (Table 2). This was the most frequently occurring sequela, but serogroup B was associated significantly less with loss of hearing than all other groups combined (1.9% versus 5.5%, respectively; $P = 0.001$).

Adjustments for period of study, sex, and age

Of the 1221 cases, 398 (32.6%) occurred over the period 1959–70, and 823 (67.4%) over the period 1971–81 plus 1983. The proportion of group B strains decreased from 77.6% in the former period to 57.7% in the latter. Increases occurred for group A (9.0% to 17.0%), C (12.1% to 19.6%) and group W135 (0% to 4.0%) (5). Furthermore, the case fatality rate increased slightly (4.3% to 5.5%) as did the proportion of patients with sequelae (7.3% to 8.1%), but both increases were non-significant. Except for serogroup W135, the group-specific proportions did not differ significantly over the two periods.

The ratio of males to females was 1.15 (651:568; sex not specified for two patients). The serogroup-specific ratios (ranging from 1.04 for group C to 1.73 for group A) were not significantly different. For males, the case fatality rate was 4.6% and for females 5.6%, but the difference was also not significant. Patients aged less than 1 year formed 21% of the study sample (256 out of 1221) and 33.8% (413) were aged between 1 year and 4 years. The age distributions for the various serogroups differed (Fig. 1). Interestingly, the proportion of patients with group B

strains (the highest in every age group) decreased with age, in contrast to that of the other serogroups.

The case fatality rate increased from 3.5% in the first year of life to 17.8% for those aged ≥50 years (Table 3; $\chi^2 = 34.2$; degrees of freedom = 3; $P < 0.001$). Only in the third, fourth, and ninth decades of life was the rate lower than in the immediately foregoing decade (Fig. 2). Table 3 shows also that, with the exception of group A, the age-specific case fatality rates for each serogroup increased with age. A log-linear analysis of the association between serogroup, age, and case fatality
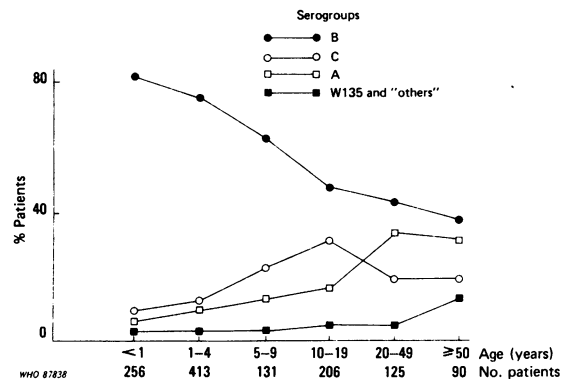

Fig. 1. Distribution of *Neisseria meningitidis* serogroup according to age group (points indicate the percentage per age group).

Table 3. Effect of age and *Neisseria meningitidis* serogroup on case fatality rate and sequelae

Age (years)	All patients			No. per serogroup					Case fatality rate per serogroup (%)					% Sequelae per serogroup[a]				
	No. of patients	Case fatality rate (%)	Proportion with sequelae (%)[a]	A	B	C	W135	Others	A	B	C	W135	Others	A	B	C	W135	Others
<1	256	3.5	10.5	15	209	23	7	2	7	3.8	0	0	0	7	10.9	9	0	50
1–9	544	3.5	5.9	58	391	81	9	5	2	4.1	3	0	0	11	5.3	4	0	40
10–49	331	5.4	7.7	75	151	88	9	8	0	7.3	7	11	0	8	6.4	7	25	13
≥50	90	17.8	13.5	28	33	17	8	4	7	15.2	12	63	50	15	10.7	13	0	50
Total	1221	5.1	7.9	176	784	209	33	19	2.3	5.1	4.8	18	11	9.9	7.3	6.5	7	29

[a] Expressed as a percentage of surviving patients.

rate indicated that age was a confounding factor ($P<0.001$); nevertheless, the differences in case fatality rates between the various serogroups remained significant ($P=0.01$).

Sequelae were frequent in babies and those aged ≥50 years (Table 3, Fig. 2). A log-linear analysis (serogroups A, B, C, W135, "others", and age groups <1, 1–49, and ≥50 years) showed that both serogroup and age had a significant effect on the occurrence of sequelae ($P=0.02$ and 0.01, respectively). The above-mentioned difference in prevalence of loss of hearing between group B and the other serogroups occurred for all age groups.

Association of predisposing factors and complications with serogroup, age, and outcome

Table 4 shows the distribution of serogroups and case fatality rate according to factors predisposing to meningococcal disease. The occurrence of these factors was not significantly different between the serogroups. Overall, and for patients with disease due to serogroup A and the "other" serogroups, the case fatality rate was significantly higher for those with a predisposing factor. A log-linear analysis established that predisposing factors and age were both associated with mortality ($P=0.004$ and 0.001, respectively).

The proportion of patients with septicaemia varied between the serogroups (Fig. 3): group A had significantly more cases of meningitis without septicaemia than the other groups combined (62% versus 45%, respectively; $P<0.001$), while group W135 had more septicaemia without meningitis than any other group (A: 4.0%; B: 7.0%; C: 10.0%; W135: 30%; "others" 26%; $P<0.001$). A log-linear analysis indicated that serogroup and age were both significantly associated with the distribution over these three clinical pictures.

The case fatality rate for meningitis without septicaemia was 1.4% (8 out of 583), for meningitis with septicaemia 7.2% (39 out of 540), and for septicaemia without meningitis 15.3% (15 out of 98). To further analyse the influence of serogroup and
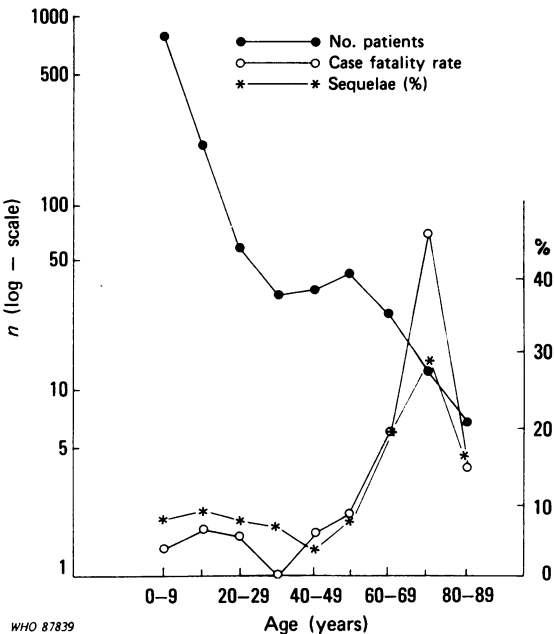
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Fig. 2. Relationship of age distribution with case fatality rate and the occurrence of sequelae (shown are the percentages of sequelae for surviving patients).

Table 4. Distribution of predisposing factors and case fatality rate, according to Neisseria meningitidis serogroup

Serogroup	No. of patients	No. with predisposing factors	Case fatality rate[a] when predisposing factors:	
			Absent	Present
A	176	15 (9)[b]	0.6	20.0[c]
B	784	66 (8)	4.6	10.6
C	209	21 (10)	4.8	4.8
W135	33	5 (15)	14	40
Others	19	2 (11)	0	100[c]
Total	1221	109 (8.9)[d]	4.2[e]	13.8[e]

[a] Expressed as a percentage per serogroup.

[b] Figures in parentheses are percentages per serogroup.

[c] Case fatality rate was significantly higher when predisposing factors were present: $P < 0.02$ by Fisher's exact test.

[d] Comparisons between groups: $x^2 = 2.2$; degrees of freedom = 4; $P > 0.5$.

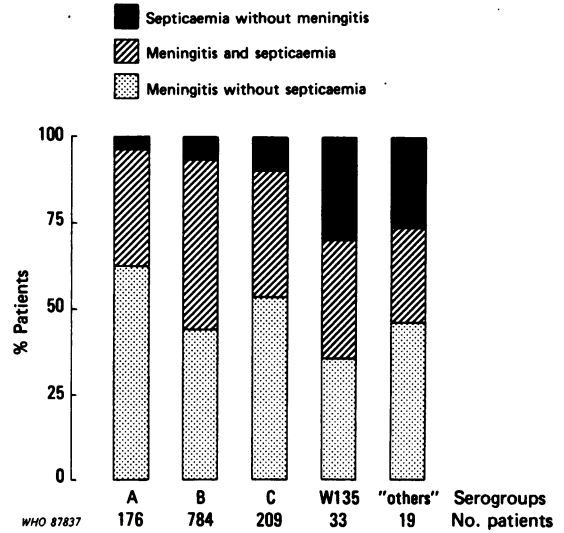[e] Comparison of case fatality rates: $x^2 = 16.8$; degrees of freedom = 1; $P < 0.001$.

Fig. 3. Distinction between meningitis and septicaemia by Neisseria meningitidis serogroup.

septicaemia on case fatality rate, we divided the sample population into two groups: patients with meningitis but no septicaemia ($n = 583$; case fatality rate, 1.4%) and all other patients ($n = 638$; case fatality rate, 8.5%; Table 5). For all serogroups the rate was higher for cases of septicaemia than for meningitis, even after adjustment for age; the difference in rates was greatest for serogroups W135 and "others" (Table 5).

Focal neurological signs occurred significantly less frequently in patients with group B disease than in those with disease due to groups A and C (13% versus

Table 5. Distribution of septicaemia and case fatality rate and of complications of the central nervous system during the hospital stay, according to Neisseria meningitidis serogroup

Serogroup	No. of patients	No. with septicaemia	Case fatality rate[a] when septicaemia:		No. with complications:	
			Absent	Present	Focal signs	Convulsions
A	176	67 (38)[b]	0.9	4.5	31 (18)[b]	17 (10)[b]
B	784	442 (56)	1.2	8.1	101 (13)[c]	95 (12)
C	209	98 (47)	2.7	7.1	38 (18)	22 (11)
W135	33	21 (64)	0	29	9 (27)	1 (3)
Others	19	10 (53)	0	20	5 (26)	2 (11)
Total	1221	638 (52.3)	1.4	8.5[d]	184 (15.1)[e]	137 (11.2)

[a] Expressed as a percentage per serogroup.

[b] Figures in parentheses are percentages per serogroup.

[c] Comparison between group B and groups A + C combined: $x^2 = 4.9$; degrees of freedom = 1; $P = 0.03$.

[d] Comparison of groups W135 and "others" combined, with groups A, B, C: $x^2 = 13.7$; degrees of freedom = 3; $P = 0.003$.

[e] Comparison between all groups: $x^2 = 11.1$; degrees of freedom = 4; $P = 0.025$.

18%, respectively; $P=0.03$; Table 5). Convulsions were equally distributed over the serogroups. In patients with these complications, sequelae (17.7%) and fatal outcome (11.2%) were more frequent than in uncomplicated cases, even after adjustment for age using a log-linear model.

DISCUSSION

In the study, we examined the medical records of patients with bacteriologically confirmed meningococcal disease and studied the influence of the pathogen on its course, looking for differences between the serogroups. A few similar studies have been carried out (10, 12, 13), but, as far as we know, this is the first to include information on the predisposing factors, neurological complications, and sequelae of more than 1000 patients.

In retrospective investigations the incompleteness of the collected data may be a cause for concern. Especially the computed case fatality rates might be liable to errors, and studies based on hospital admissions may miss patients with fulminating disease who died before admission (18). However, there is no reason to suppose that the data not available to us, e.g., death before admission or sequela not recorded, would have a different distribution over the serogroups than those we obtained. Thus, the reported rates may be slightly lower than the real rates, but are unlikely to be erroneously distributed over the serogroups. Indeed, the case fatality rate found was lower (5.1%) than that for other countries: 8.6% on average in Scandinavia (1970–79) (19), 9.5% in Scotland (1972–82) (13), 6.1% in Belgium (1975–79, patients < 15 years) (18), and 9–20% in the USA (2, 4, 20).

Clear differences existed between the case fatality rates of the different serogroups. In agreement with the findings of other workers (9, 10), we found that group A disease ran a less fulminating course than disease due to the other serogroups, but this contrasts with the situation in Scotland (13). In the Netherlands, the case fatality rate was highest for group W135 disease.

Although age appeared to be a confounding factor in the association between serogroups and case fatality rate, the differences in the latter among the groups were also found using a log-linear analysis that involved serogroup, age, and case fatality rate together. The distribution of cases of septicaemia without meningitis over the serogroups was similar: group W135 and the minor serogroups produced this clinical picture relatively often, which is in agreement with results reported previously (2, 11, 13, 14).

Loss of hearing was the most frequent sequela (3.2%); other workers have reported 2% to 11% for this sequela (21–23). Disease caused by less common serogroups, such as X and Y, resulted in loss of hearing in about 20% of patients. Group B was associated with loss of hearing and with focal neurological signs significantly less often than the other serogroups. A recent follow-up study of 60 children who had had meningococcal meningitis, mainly due to group B, revealed no differences in neurological disturbances between cases and controls (22). Although the genesis of neurological sequelae of meningitis has not yet been elucidated, these data might indicate that group B disease causes less cerebrospinal fluid inflammation than that due to the other serogroups. This could arise because the immune system reacts less to the capsular polysaccharide of serogroup B N. meningitidis, which is immunochemically identical to a fetal brain glycopeptide (24).

Generally, serogroups W135, X, and Y were more frequently associated with a poorer outcome than groups A, B and C (29% versus 12%, respectively). The invasiveness of less common groups, such as W135, X, and Y, has been reported to depend on predisposing factors in the patient (11, 14). Our data do not confirm this, perhaps as a consequence of incomplete recording or of unknown risk factors. However, we did find an association between predisposing factors and case fatality rate in disease due to minor serogroups, as well as such an association for group A disease.

Why the clinical picture and case fatality rate differ among the serogroups is not clear. Since the capsular polysaccharide of N. meningitidis plays a role against phagocytosis and killing by complement and raises the level of serogroup-specific antibodies in the host, the efficacy of these mechanisms may differ among the serogroups. Also important in this respect is the serotyping of N. meningitidis, which is based on differences in outer membrane proteins and lipopolysaccharides (25). There is a relation between serogroups and certain serotypes; for example, types 2b and 15 are found mainly within group B and type 2a within the groups C and W135 (5, 26). Serogroup B type 15 is the epidemic strain in Norway, where the case fatality rate is about 10% at present (27–28). Thus, serotypes might partly account for differences between serogroups. In group B meningococcal disease, we found serotype 2b to be associated with a significantly higher case fatality rate than other serotypes (29).

Clear differences therefore exist among meningococcal serogroups, emphasizing the importance of carrying out surveillance of the various groups and types and of further investigating the defence mechanisms and immunological disturbances produced in the host.

ACKNOWLEDGEMENTS

RÉSUMÉ

ASSOCIATION ENTRE LES SÉROGROUPES DE MÉNINGOCOQUES ET L'ÉVOLUTION DE LA MALADIE AUX PAYS-BAS, 1959-1983

Afin d'étudier l'association entre les sérogroupes de méningocoques et l'évolution de la maladie, nous avons passé en revue les antécédents de 1221 malades. Les méningocoques de ces malades constituaient un échantillon des isolements ayant fait l'objet d'un recueil et d'un groupage systématiques aux Pays-Bas depuis 1959. Sur les 1221 isolements examinés, 64% appartenaient au sérogroupe B, 17% au sérogroupe C, 14% au sérogroupe A, 3% au sérogroupe W135 et 2% à d'autres sérogroupes (X, Y, Z et "non groupables").

Le taux de létalité global était de 5,1%, mais si l'on examine chaque groupe en particulier, on constate qu'il a été le plus faible dans le groupe A (2,3%), moyen dans les groupes B et C (environ 5%) et le plus élevé dans le groupe W135 (18%; $P=0,003$). De la même façon, l'apparition d'une septicémie sans méningite se répartissait comme suit: groupe A, 4%; groupe B, 7%; groupe C, 10%; groupe W135, 30%; ($P<0,001$). Le taux de létalité chez les malades présentant ce tableau clinique était de 15,3%, mais pour ceux atteints de méningite sans septicémie il n'était que de 1,4%. Afin d'analyser de manière plus approfondie l'influence respective du sérogroupe et de la septicémie sur le taux de létalité, nous avons divisé la population à l'étude en deux groupes: les malades atteints de méningite sans septicémie ($n=583$; taux de létalité=1,4%) et tous les autres malades ($n=638$; taux de létalité=8,5%). Pour l'ensemble des sérogroupes, le taux de létalité était plus élevé chez les sujets atteints de septicémie que dans les cas de méningite seule; cette différence était encore plus nette pour le groupe W135 et les "autres" groupes. Parmi les malades atteints de septicémie, la différence entre le taux de létalité dû au groupe W135 plus les "autres" groupes et celui dû à l'ensemble des groupes A, B et C était significative (26% contre 7,6%; $P=0,003$); 7.9% des malades ayant survécu ont présenté des séquelles (perte de l'audition,

3,2%), avec une prévalence remarquable chez les sujets dont la maladie avait été provoquée par des sérogroupes mineurs (X et Y: 4 cas sur 12). La perte de l'audition était significativement moins fréquente chez les sujets atteints par le sérogroupe B que pour l'ensemble des autres cas (1,9% contre 5,5%; $P=0,001$).

La répartition par âges et par sérogroupes n'était pas la même: la proportion de souches du groupe B (très élevée dans toutes les classes d'âge) montrait une diminution avec l'âge, contrairement à celle des autres groupes. Le taux de létalité passait de 3,5% au cours de la première année de la vie à 17,8% chez les personnes âgées de 50 ans et plus, tandis que les séquelles étaient fréquentes aussi bien parmi les sujets âgés de moins d'un an (11%) que chez ceux de 50 ans et plus (14%). L'analyse log-linéaire des données indique que l'âge comme le sérogroupe sont associés de manière significative au taux de létalité et à l'apparition d'une septicémie et de séquelles.

On a relevé des facteurs prédisposant à une méningococcie dans 9% des cas, avec une distribution allant de 8% (groupe B) à 15% (groupe W135; $P>0,5$). Le taux de létalité était significativement plus élevé lorsqu'on pouvait relever la présence d'un facteur prédisposant (14% contre 4%).

On ne comprend pas bien pourquoi le tableau clinique et le taux de létalité diffèrent selon le sérogroupe. Le polysaccharide capsulaire spécifique de groupe protège *Neisseria meningitidis* de la phagocytose et de l'action du complément; l'efficacité de ces mécanismes pourrait varier selon les sérogroupes. Les sérotypes pourraient aussi expliquer en partie les différences entre sérogroupes. Les résultats de cette étude indiquent que l'évolution et l'issue d'une méningococcie semblent liées au sérogroupe bactérien et à des facteurs tenant à l'hôte.

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