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Surveillance of meningococcal infections and other forms of purulent meningitis: a 4-year study in the USSR*

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The laboratory examination, by microscopic or bacteriological methods and by counterimmunoelectrophoresis, of CSF and blood from 2653 patients with purulent bacterial meningitis, including those with clinically diagnosed meningococcal infection, was carried out between June 1980 and June 1984. The results showed three main etiological agents: meningococci (79.9%), pneumococci (10.8%) and Haemophilus influenzae *type b (5.25%). Out of 488* Neisseria meningitidis *strains isolated from the CSF or blood, 58.2% belonged to serogroup A, 17.2% to serogroup B, and 14% to serogroup C; infection due to the B serogroup reached nearly 59% among children in 1984. Serotypes were determined in 131 out of 151 strains of* Streptococcus pneumoniae *and the most frequent were types 1, 19 and 3; type 34, which was isolated from 4 patients, is not a component of the pneumococcal vaccine. The age groups at high risk were children under 5 years old (for meningococcal infection), adults and babies in the first year (pneumococcal meningitis), and children under 3 years, especially between 6 months and 2 years old (*H. influenzae *type b infection).*

A notable feature of the increase in meningococcal infections in many countries during the 1960s and 1970s was their multiple etiology. Thus, in addition to epidemics due to *Neisseria meningitidis* of the A serogroup, less intensive outbreaks provoked by organisms of the C serogroup were recorded, as well as rises in infection due to the B serogroup meningococci, especially in European countries (*6, 10, 15*). Some authors have proposed that other agents might be responsible for a substantial number of meningitis cases (*1, 3, 9*). It appears therefore that the health care services in the affected countries should take immediate preventive measures against purulent meningitis, including meningococcal infections, especially when the epidemiological situation is grave.

The present study describes:

— the main etiological agents of purulent bacterial meningitis, based on hospital data from the USSR;

— the groups at highest risk in relation to the etiology;

— the serogroups and serotypes of the agents isolated from infected patients.

MATERIALS AND METHODS

Samples of cerebrospinal fluid (CSF) and blood were taken for laboratory examination from patients who were clinically diagnosed as having a meningococcal infection or some other form of purulent bacterial meningitis, or were suspected to have such a diagnosis. These patients were admitted from the city of Moscow or the Moscow region to the 2nd Infection Clinic in the period between June 1980 and June 1984. Of the total of 2653 patients, 1544 were under and 1109 were over 14 years old. Newborn patients with meningitis were admitted to a special hospital for infants; in our study these cases were rare. The above numbers of cases presenting with meningococcal infection and purulent bacterial meningitis do not give the total incidence of these infections in Moscow, since some patients (especially with purulent bacterial meningitis) could have been admitted to other hospitals.

The CSF and blood samples were examined by established microscopic or bacteriological methods and by counterimmunoelectrophoresis (CIE). In the

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cultures, three types of agar media were used: 20% serum medium, 5% blood medium, and chocolate agar, and the colonies were identified by routine methods. The following antisera were used: meningococcal, produced by the Stavropol Institute for Vaccines and Sera; pneumococcal, produced by the Statens Seruminstitut, Copenhagen, Denmark, and from experimental pneumococcal antisera made in 1983 by the Metchnikov Central Institute for Vaccines and Sera (Moscow); and antiserum to *Haemophilus influenzae* type b (provided by Dr J. Robbins, Bureau of Biologics, Food and Drug Administration, Bethesda, MD, USA).

The sensitivity of the isolated cultures to antibiotics was established by the disc method, using commercial discs with pre-set antibiotic concentrations and a standard nutrient medium AGV (supplied by the Dagestan Institute for nutrient media). Depending on the diameter of the zone of bacterial growth inhibition round the disc, the bacteria were differentiated as sensitive, highly sensitive, or resistant to the antibiotic.

RESULTS

Because the study was focused on the hospital admitted patients or suspected patients with meningococcal infection, this etiology prevailed over the others—the diagnosis being confirmed in 1401 out of 1956 cases (71.6%) (840 children and 561 adults) (Table 1). In the remainder, we failed to isolate meningococci or to discover their antigens in the CSF or blood, the diagnosis having been made clinically.

Out of 697 patients with a clinical diagnosis of purulent bacterial meningitis, a pneumococcal etiology was confirmed in 190 (27.3%) and *H. influenzae* type b in 92 (13.2%). In 70 cases (10%), staphylococci, streptococci, Gram-negative rods, *Candida* and other organisms were confirmed, but we failed to determine the etiology in 345 of these patients with a clinical picture of meningitis (Table 1).

Thus, out of 1753 cases with laboratory confirmation, 79.9% were due to *N. meningitidis*, 10.8% to *S. pneumoniae*, 5.25% to *H. influenzae* type b, and

Table 1. Distribution of meningitis patients according to disease etiology and age (under or over 14 years)

Diagnosis and etiology	Number of patients[a]		
	Under 14 years	Over 14 years	Total
N. meningitidis	840/1197 (70.2)[b]	561/759 (73.9)	1401/1956 (71.6)
Purulent meningitis:	161/347 (46.4)	191/350 (54.6)	352/697 (50.5)
Str. pneumonia	42	148	190
H. influenzae type b	85	7	92
Candida	15	1	16
Streptococci	5	5	10
Staphylococci	8	14	22
Gram-negative rods	—	11	11
Escherichia coli	1	2	3
Salmonella "c"	2	—	2
Ps. aeruginosa	2	1	3
Proteus	1	—	1
Klebsiella	—	1	1
Haemophilus	—	1	1
Totals	1001/1544 (64.8)	752/1109 (67.8)	1753/2653 (66.1)

[a] Where there are two figures, the numerator indicates the number of patients with laboratory confirmation of the diagnosis; the denominator gives the number of patients with a clinical diagnosis whose CSF and blood were examined at the laboratory.

[b] Figures in parentheses are percentages.

Table 2. Age distribution of patients with purulent meningitis according to the three main etiological agents

Etiology	Age group (years) <1	1–2	3–4	5–6	7–13	14–19	20–49	≥50	Total
N. meningitidis	435	409	157	78	114	261	350	152	1956
Total		1001 (51.2)[a]			453 (23.2)		502 (25.7)		
Str. pneumoniae	19	9	6	1	9	9	85	52	190
Total		34 (17.9)			19 (10)		137 (72.1)		
H. influenzae type b	34	40	4	3	5	1	4	1	92
Total		78 (84.8)			9 (9.8)		5 (5.4)		

[a] Figures in parentheses are percentages.

3.99% to other organisms. Our data confirm the results of others on the etiology of purulent bacterial meningitis (*1*, *9*, *12*, *14*).

Table 2 shows the distribution of patients with purulent meningitis by age and the 3 main etiological agents. Over half the patients with meningococcal infection were children under 5 years, 43.1% being under 3 years. The proportions of patients aged between 5 and 20 years and over 20 years were roughly equal.

About 18% of the patients with pneumococcal meningitis were children under 5 years, 10% being under 1 year (Table 2). The majority of these patients were over 20 years (72.1%), 27.4% being over 50 years old. In the *H. influenzae* type b group, 84.8% were children under 5 years old. Since the *H. influenzae* polysaccharide vaccine is effective in infants up to the age of 18 months, the following detailed age-specific incidence data may be noted: under 3 months (2 children), between 3 and 6 months (6), between 6 and 12 months (26), between 1 year and 18 months (19), between 18 months and 2 years (15), and between 2 and 3 years (6). The most affected age group was between 6 months and 2 years.

Among the other etiological agents, *Candida* was detected in the CSF of 15 children aged under 2 months and in one adult over 50 years. These patients had been transferred from other hospitals and this organism must have become associated as a secondary infection. Other agents were identified both in the children and in the one adult.

Considering the marked group-specific protection given by the meningococcal capsulated polysaccharide vaccine (*4*, *5*), we investigated the meningococcal serogroups responsible for the infection in our patients by two methods: isolated cultures were tested

Table 3. Percentage distribution of patients with meningococcal infection according to serogroup (after AR)[a] and meningococcal antigens (after CIE)[a] between June 1980 and June 1984

Patients	No. of cases studied[b]	Percentage belonging to serogroups A	B	C	Y	Other	PAG[a]	NAG or AAG[a]
Under 14 years old	553 (192)[c]	42.8	21.8	21.1	3.0	2.2	5.9	2.9
Over 14 years old	601 (296)	69.4	14.1	9.5	1.6	0.8	2.6	1.8
Total	1154 (488)	56.6	17.8	15.0	2.3	1.5	4.2	2.3

[a] AR = agglutination reaction; CIE = counterimmunoelectrophoresis; PAG = polyagglutinable; NAG = not agglutinable; AAG = autoagglutinable.

[b] Includes all cases obtained by AR (488) and by CIE (666).

[c] Figures in parentheses are the numbers of cases obtained by bacterial agglutination only.

by the agglutination reaction (AR), and antigens found in the CSF were tested by counterimmunoelectrophoresis. The latter method gave 1.4 times more positive samples than the number by AR cultures: 666 and 488, respectively (Table 3). Out of the 488 cultures, 284 (58.2%) were related to the A serogroup, 370 of the 666 CIE-positive samples (55.6%) showing antigens of this serogroup. In a considerable number of adult cases this serogroup was predominant (68.2% by AR and 70.5% by CIE), with fewer cases in children (42.7% and 42.9%, respectively). On the other hand, the B and C serogroup meningococci and their antigens were more often detected in patients aged under 14 years. Other serogroups were also encountered, as shown in Table 3.

Table 4 shows the changes in the distribution of patients according to meningococcal serogroups during the four years of the study. Some differences may be noted. Thus, the proportion of children under 14 years in the meningococcal A serogroup (AR-proven) dropped from 51.9% in 1980 to 37% in 1984 (CIE-proven: from 66.6% in 1980 to 30.5% in 1984). While serogroup C meningococcal infections were initially in the second place, they were found in 1984 only occasionally. At the same time, in 1983 the B serogroup meningococci increased, these infections among the children reaching nearly 59% in 1984. Among adults (>14 years old), the predominant causative organism was *N. meningitidis* of serogroup A.

The sensitivity to antibiotics was studied in 107 strains of *N. meningitidis*: 106 were sensitive or highly sensitive to benzathine benzylpenicillin (10 μg), 103 to ampicillin (10 μg) and erythromycin (15 μg), and 101 to oxacillin (10 μg). All strains were highly sensitive to chloramphenicol (30 μg) and tetracycline (30 μg).

In the surveillance of purulent bacterial meningitis cases, the determination of pneumococcal serotypes from these patients is very important and this serotyping was commenced in 1981, according to WHO recommendations. After the pneumococci were isolated from the CSF or blood, thus confirming their role in the etiology, they were differentiated and identified. Specimens were also sent to the regional WHO collaborating centre (Dr J. Henrichsen, Staatens Seruminstitut, Copenhagen) for a parallel study. Out of 190 such patients with a pneumococcal etiology,

Table 4. Distribution of patients diagnosed by AR and CIE according to the meningococcal serogroups or their antigens, by year and age group[a]

	No. of patients diagnosed by AR in each serogroup:[a]				No. of patients diagnosed by CIE in each serogroup:[a]			
Year and age group	A	B	C	Total[b]	A	B	C	Total[b]
1980 (June–December):								
Children	14	0	6	27	18	0	3	27
Adults	28	0	8	38	25	1	3	29
1981:								
Children	20	1	15	44	36	4	31	75
Adults	32	1	4	44	40	1	7	56
1982:								
Children	20	1	14	42	34	1	14	55
Adults	58	2	4	72	60	0	2	65
1983:								
Children	11	12	4	33	35	14	29	99
Adults	51	12	7	80	55	14	15	86
1984 (January–June):								
Children	17	27	1	46	32	61	10	105
Adults	33	23	5	62	35	31	2	69

[a] AR = agglutination reaction; CIE = counterimmunoelectrophoresis.
[b] The totals include small numbers of patients in other serogroups than A, B and C.

Table 5. Serotypes of pneumococci isolated from meningitis patients during the period 1981–84

Serotypes	Age of patients (years) Under 14	Over 14	Total	No. of strains isolated CSF	Blood	Total
1	4	18	22	22	7	29
2	1	5	6	6	1	7
3	—	9	9	10	4	14
4	—	3	3	2	3	5
5	1	5	6	5	1	6
6	2	7	9	9	3	12
7	1	—	1	1	—	1
9	—	1	1	1	1	2
10	—	1	1	1	—	1
12	5	3	8	8	—	8
13	—	1	1	1	—	1
14	1	1	2	3	—	3
15	—	2	2	2	1	3
18	1	5	6	6	—	6
19	3	9	12	10	5	15
20	—	3	3	4	—	4
21	1	—	1	1	—	1
23	1	1	2	2	—	2
25	—	2	2	2	—	2
27	1	—	1	1	—	1
29	—	1	1	1	—	1
34	1	3	4	4	—	4
35	—	2	2	2	—	2
42	1	—	1	1	—	1
Total	24	82	106	105	26	131

the diagnosis was confirmed bacteriologically in 163 (85.8%), and microscopically in 27 (14.2%). The pneumococci were serotyped in 106 patients: in 4 cases the agent was isolated in the rough form and 13 cases were not agglutinable; and there was one case each that was polyagglutinable, or agglutinable only with "omniserum" or with pool C, while in 37 patients we failed to study the serotypes of pneumococci.

In Table 5 are presented the results of typing of pneumococci isolated from patients between 1981 and 1984. Of these patients, 24 were children under 14 years old and 82 were adults. A total of 131 strains were studied, 105 isolated from CSF and 26 from blood. In 22 patients the pneumococci were isolated from both blood and CSF, in 4 patients from blood only. The typing showed that the pneumococci were related to 24 known types. The frequency of the isolated types was as follows (in decreasing order): 1, 19, 3, 6, 12, 2, 5, 18 which together accounted for 73.3% of the total typed. Type 12 was more often isolated in children. In addition to the results presented in Table 5, we studied 5 strains, 2 of which had been isolated from the CSF of children in the city of Minsk; these were types 5 and 34. The three remaining strains had been obtained from some other Moscow clinics and belonged to types 1 (2 cases) and 3.

The serotypes of pneumococci isolated from the CSF and blood simultaneously or obtained for repeated laboratory examinations were also investigated. In 22 out of 34 patients the agents belonged to the same type. In the others the serological features of the pneumococci differed. Of those that had been isolated from the blood, 6 strains were not agglutinable, 3 strains were in the rough form, and in 2 cases different serotypes were isolated. The results of repeated pneumococcal isolations from the CSF of one 46-year-old patient with a prolonged course of illness are interesting because three serotypes were identified: 3, 14, and 19 (twice). The sensitivity to antibiotics of 15 pneumococcal strains was examined at the time of isolation. All of them were found to be sensitive to benzathine benzylpenicillin, rifampicin, chloramphenicol, oxacillin, and meticillin, i.e., they were sensitive to all the antibiotics used in treating meningitis cases of this etiology.

H. influenzae type b was the causative organism of purulent bacterial meningitis in 92 patients: in 56 (60.9%) the organism was isolated in culture and in 36 (39.1%) the etiology was confirmed by microscopy and CIE. The high yield of the latter method may be noted because it made possible the identification of non-viable bacteria and their antigens. In all 92 cases, for instance, the CIE results were positive and in agreement with bacteriological data (56 cases) and with microscopy (23 cases). Besides, in 23 out of 25 negative samples on microscopy, the specific antigen was found by the CIE test and in the 2 remaining cases the culture was grown. The sensitivity to antibiotics was tested in 19 strains only: 10 were sensitive or highly sensitive to chloramphenicol (30 μg) and 13 were sensitive to tetracycline (30 μg), i.e., they were sensitive to the antibiotics used for treating meningitis of this etiology. Five strains were found to be sensitive to benzathine benzylpenicillin.

DISCUSSION

Acute bacterial meningitis, which is mainly due to meningococcal infection, poses a serious problem for the health services in many countries (*7, 15*). Determination of the main etiological agents responsible (including their type and group specificity) and the age groups at maximum risk is very important both for epidemiological surveillance and for the development of vaccines with an optimum antigen composition. The results of our study of pathological material from 2653 patients with purulent bacterial meningitis showed that meningococci, pneumococci and *H. influenzae* type b were responsible for 96.2%

of laboratory confirmed diagnoses. The predominance of meningococci (79.9%) in the etiology was not due to an epidemic situation, which is supported by the age distribution pattern of these patients. According to Mäkelä et al. (*8*), 50% of the patients with meningococcal illness in a non-epidemic period were children aged under 5 years. In our results of similar patients, 51.2% were under 5 years, 23.2% were between 5 and 20 years, and 25.7% were over 20 years old. Thus, the age group with maximum risk was the 0–5-year-old group.

The serogroup of the isolated meningococci appeared to vary with the age of the patients. In adults, serogroup A was predominant, although the rate fell from 76.5–80.5% in 1980–81 to 54% in 1984. This means that in a serious epidemic situation the use of meningococcal A polysaccharide vaccine must be focused on adults. In patients aged under 14 years the A serogroup was isolated in less than half of the cultures studied (e.g., in 1984, 37%). Other meningococcal serogroups, however, were isolated from patients in this age group (e.g., in 1981–82, 30–38% in C serogroup; in 1984, up to 59% in B serogroup). This means that application of the A serogroup vaccine alone in this age group cannot be sufficiently protective, compared with the A+C vaccine. The increase in the number of infections caused by the B serogroup meningococcus supports the need for development of a specific vaccine against this agent.

It is known that a pneumococcal vaccine will be satisfactory if it contains at least 80% of the pneumococcal serotypes that are frequently isolated from patients. This calls for a study to establish the serotypes of pneumococci that are responsible for disease during the surveillance study of patients with purulent bacterial meningitis. In the present study, standard methods were followed and for the first time in the USSR the serotypes of pneumococci isolated from the CSF and blood of patients are reported (see Results section). Of the 24 known serotypes of pneumococci, 16 are represented in the vaccine preparation (*13*). Serotypes 8, 11, 17 and 22, which are included in the vaccine, were not encountered in our study, while types 7 and 9 were isolated only once and type 34, which is not represented in the vaccine, was found in Moscow (4 cases) and in patients in Minsk. Thus, depending on the prevalent pneumococcal serotypes in any area, the composition of the vaccine preparation has to be modified. This view was also expressed by Denis et al. (*2*).

H. influenzae type b was responsible for 92 cases in our study, this organism having unexpectedly been separated from the CSF of 7 adult patients. Taking into consideration the prolonged course of meningitis due to this etiology, the identification of specific antigens in the samples of pathological material is important.

The epidemiological surveillance of purulent bacterial meningitis cases should take into account the possible resistance of the bacteria to antibiotics (*11*). Our results showed a high sensitivity among the pneumococci and meningococci to the antibiotics normally used in the treatment of meningitis of this etiology, while only 19 strains of *H. influenzae* type b could be tested in this way. These investigations are continuing.

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RÉSUMÉ

SURVEILLANCE DES INFECTIONS À MÉNINGOCOQUES ET D'AUTRES FORMES DE MÉNINGITES PURULENTES: UNE ÉTUDE DE 4 ANS EN URSS

De juin 1980 à juin 1984, on a procédé à l'examen de laboratoire — au microscope ou par des méthodes bactériologiques, et par électrosynérèse — du LCR et du sang de 2653 malades atteints de méningite purulente, le diagnostic clinique d'infection à méningocoques ayant déjà été posé pour un certain nombre d'entre eux. Les résultats ont révélé trois principaux agents étiologiques: méningocoques (79,9%), pneumocoques (10,8%) et *Haemophilus influenzae* type b (5,25%). Sur 488 souches de *Neisseria meningitidis* isolées du LCR ou du sang, 58,2% appar-

tenaient au sérogroupe A, 17,2% au sérogroupe B et 14% au sérogroupe C; en 1984, la proportion des infections dues au sérogroupe B atteignait près de 59% chez les enfants.

Le sérotype a été déterminé pour 131 des 151 souches de *Streptococcus pneumoniae*; les types les plus fréquents étaient le type 1, le type 19 et le type 3; le type 34, isolé chez quatre sujets, n'entre pas dans la composition du vaccin antipneumococcique.

Les groupes d'âge les plus exposés étaient les enfants de moins de 5 ans (pour les infections à méningocoques), les adultes et les enfants de moins d'un an (pour les infections à pneumocoques), et les enfants de moins de 3 ans, plus particulièrement ceux âgés de 6 mois à 2 ans (pour les infections à *H. influenzae* type b).

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