

Communicable Disease Report

Meningococcal infections in England and Wales: 1993

D M Jones, E B Kaczmarek

Summary

One thousand two hundred and ninety-seven meningococcal isolates of clinical significance were submitted for examination to the PHLS Meningococcal Reference Unit in 1993; almost the same total as in 1992. Changes in the number of isolates from individual regions ranged from falls of 25% to increases of 42%. The incidence of meningococcal disease rose late in 1993, apparently affected by the epidemic of influenza. The number of statutory notifications reported to the Office of Population Censuses and Surveys was – for the first time – markedly higher than the number of laboratory diagnosed cases. Serodiagnosis was used to confirm an increased number of clinically suspected cases in 1993.

Introduction

The Meningococcal Reference Unit (MRU) examines isolates of *Neisseria meningitidis* submitted by microbiologists from NHS, PHLS, armed forces, and private laboratories throughout England and Wales. The epidemiological features of invasive meningococcal infection presented in this report are based on laboratory results from the MRU and information sent with the isolates to the unit during 1993. Data on organisms from non-invasive infections and people without symptoms are not included.

Epidemiological data

In 1993, isolates from 1297 cases of invasive infection were received at MRU from laboratories in England and Wales, compared with 1301 received in 1992¹. Early treatment with antibiotics results in fewer cases in which the aetiology is confirmed by culture and a more frequent use of serological methods of diagnosis. Figure 1 includes for the first time cases that were diagnosed serologically, of which there were 56 in 1992 and 71 in 1993. The total of 1368 cases confirmed by culture or serology in 1993 represents a rate of 2.8/100 000/year of invasive meningococcal infections ascertained by laboratories. The provisional number of notifications to the Office of Population Censuses and Surveys (OPCS) for 1993 was 1455, an increase of 126 on the number in 1992 (due mainly to an increase in notifications of septicaemia). One hundred and sixty-six deaths from meningococcal infection were notified in 1993; almost the same as the total for 1992. The PHLS Communicable Disease Surveillance Centre (CDSC) received reports of 870 infections diagnosed in laboratories in 1993.

The 1993/94 meningococcal season began early, associated with widespread influenza in the community², and increased the total for 1993. Figure 2 shows the proportion of meningococcal isolates received during November and December in each of the past eight years. The association between influenza and meningococcal disease in England and Wales in November and December was seen in 1989³ as well as 1993.

Thirty-seven per cent of isolates were from cases of septicaemia, 43% from cases of meningitis, and the remainder were from cases with features of both. The proportion of cases of septicaemia increased from 27% in 1992, and this is reflected in the statutory notifications to OPCS.

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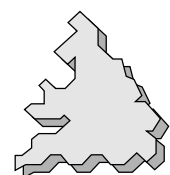


Figure 1 Meningococcal isolates received by the Meningococcal Reference Unit, and serodiagnoses, 1984-1993

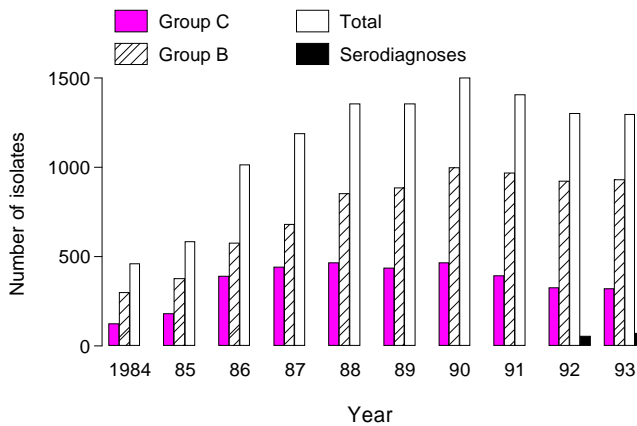
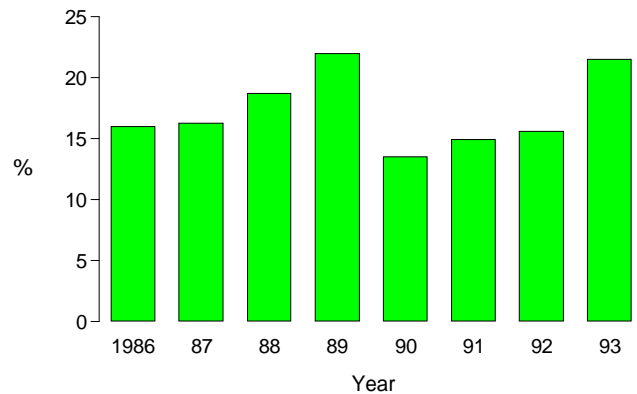


Figure 2 Proportion of the annual total of meningococcal isolates submitted to the Meningococcal Reference Unit during November and December, 1986-1993



Temporal distribution

The temporal distribution of isolates received in 1993 showed a fall of 27% in January and February compared with 1992, but a rise of 37% in November and December (figure 3). This degree of variation from one year to the next is usually only seen when there is a substantial change in the annual incidence of the disease.

Age distribution

The age of 1231 cases (95%) in 1993 was supplied (figure 4). Of these, 674 cases (55%) were children less than 5 years of age. Infant cases (under 1 year) made up 55% of cases under 5 compared with 46% in 1992. There were 206 cases (17%) aged 25 and over compared with 165 (13%) in 1992. During the influenza epidemic in November and December, cases aged 25 or over accounted for 21% (55/262) of the cases whose ages were known, compared with 13% to 14% in the same months of the preceding three years.

Regional distribution

The regional distribution of isolates is shown in table 1. The rates in 1993 were more than 10% higher than those in 1992 in the North West Thames, Oxford, and South Western regions, and Wales; the most marked falls were seen in Northern, Yorkshire, and East Anglia regions. An audit of

the sources of strains sent to MRU in the past three years has not indicated any districts that have systematically failed to submit strains.

Laboratory data

Serogroups

The serogroups identified in 1993 are shown in figure 5. The relative proportions of group B and group C isolates were unchanged and, as in 1992, 4% of infections were due to organisms from other groups.

Serotypes and subtypes

The types and subtypes of group B meningococci received in 1993 are shown in table 2 and are broadly similar to 1992¹. Strains that were type 4 or not typable (nt), subtype P1.4 increased from 134 in 1992 to 202 in 1993. Most strains that were subtyped as P1.4 but failed to give a typing reaction probably did so because the type 4 monoclonal antibody lacked sensitivity. Similarly, many of the B nt P1.15 strains were actually B 4 P1.15. These strains belong to the ET5 complex and probably behave like B 15 P1.16 strains. The number of 2b P1.10 strains was half the total for 1992, as was the total of type 2b strains. Isolates of type 15 P1.16 fell by 14% from the 1992 total but still represent 14% of all group B infections.

Figure 3 Temporal distribution of meningococcal isolates, 1992-1993

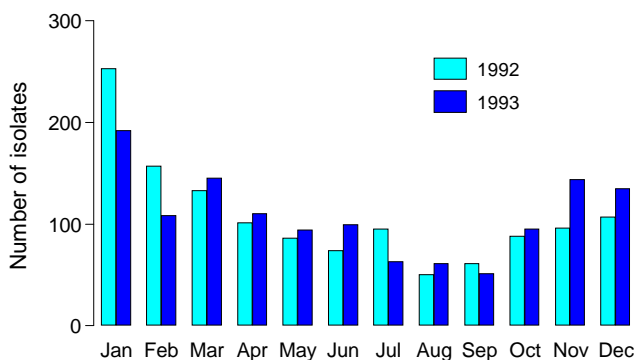


Figure 4 Age distribution of meningococcal isolates, 1993

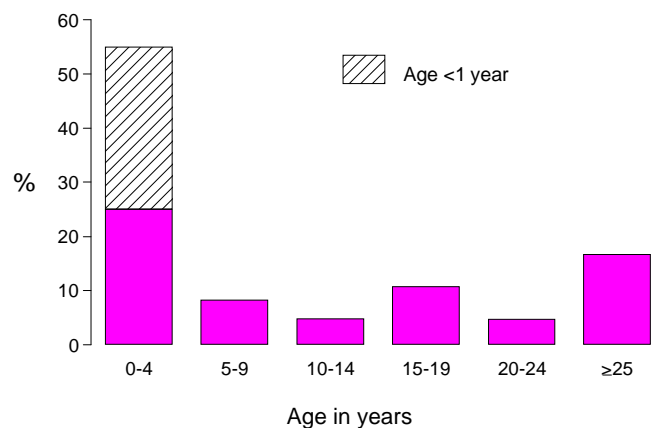


Table 1 Distribution of isolates by region of reporting laboratory

Region	1992				1993				Percentage change in total isolates
	Group B	Group C	Total	Rate/10 ⁵ population	Group B	Group C	Total	Rate/10 ⁵ population	
England									
Northern	82	35	120	3.9	68	18	91	2.9	-24%
Yorkshire	80	26	108	3.0	73	19	97	2.7	-10%
Trent	86	21	113	2.5	84	32	122	2.6	8%
E Anglia	34	23	60	3.2	29	15	45	2.3	-25%
NW Thames	33	16	49	1.4	32	24	59	1.7	20%
NE Thames	42	22	71	1.9	46	24	75	2.0	6%
SE Thames	77	20	99	2.8	77	15	95	2.6	-4%
SW Thames	32	25	57	1.9	33	18	54	1.8	-5%
Wessex	37	21	59	2.1	32	20	57	2.0	-3%
Oxford	34	13	48	2.1	42	25	68	2.9	42%
S Western	63	21	88	2.9	68	28	100	3.2	14%
W Midlands	90	25	123	2.4	108	17	128	2.4	4%
Mersey	58	13	74	3.0	58	15	74	3.0	0%
N Western	87	31	124	3.8	88	23	113	2.8	-9%
Wales	76	10	92	3.3	81	20	101	3.6	10%
Others*	12	4	16	-	10	6	18	-	13%
Total	923	326	1301 †	2.6	929	319	1297 †	2.6	0%

* includes isolates received from HM forces laboratories and other sources.

† excludes serologically diagnosed cases.

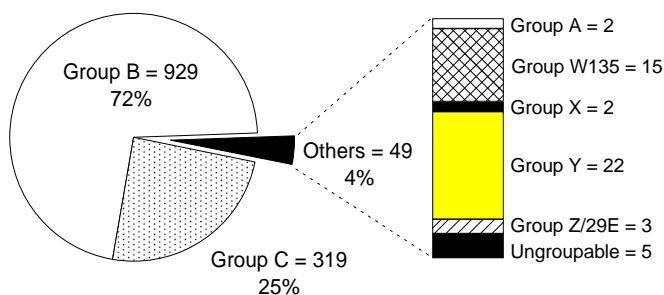
Table 2 Serotypes and subtypes of group B meningococci received in 1993

Subtype	Type								Total
	1	2a	2b	4	14	15	16	nt	
P1.1	-	-	-	-	-	-	-	8	8
P1.2	1	10	5	-	1	1	2	13	33
P1.4	1	-	-	20	4	1	-	182	208
P1.5	2	-	-	-	-	-	-	7	9
P1.6	2	-	3	1	1	-	1	20	28
P1.7	-	1	-	-	-	1	-	2	4
P1.9	1	2	2	-	-	-	-	16	21
P1.10	1	1	63	-	-	-	-	12	77
P1.12	-	1	-	-	-	2	-	5	8
P1.13	-	-	-	-	-	-	-	4	4
P1.14	2	-	-	-	-	-	-	20	22
P1.15	10	-	-	2	2	9	1	139	163
P1.16	-	-	5	-	-	132	8	37	182
nst	6	5	26	2	3	11	4	105	162
Total	26	20	104	25	11	157	16	570	929

nt - not typable.

nst - not subtypable.

Numbers emboldened appear in the main text.

Figure 5 Serogroups identified in 1993

Altogether, 570 strains (61%) could not be typed and 162 (17%) could not be subtyped using conventional monoclonal serotyping and subtyping methods. Using these antisera, 105 strains were not characterised beyond identifying the group. The 162 strains that could not be subtyped were examined using a DNA based subtyping system, which characterised 143 (88%) of them. A similar system for typing is being developed and much greater discrimination of group B strains should be possible in the future.

One hundred and forty-nine of the 319 group C strains (47%) were type 2a, 51 (16%) were type 2b, and 55 (17%) were not typable. The most common subtypes were P1.2 and P1.5 but 111 (35%) could not be subtyped. The DNA based subtyping system enabled all but six strains to be subtyped. This system has the potential to improve discrimination between strains in apparent clusters, and its contribution to epidemiological information is being evaluated.

Serology

Serological testing is carried out by an enzyme linked immunosorbent assay (ELISA) that uses an antigen prepared from outer membrane vesicles from three strains. The results are expressed in enzyme immunoassay units (EIU) calculated relative to a standard positive control. In 1993, 337 single specimens and 21 paired specimens of serum were examined from suspected cases. The criteria for serological diagnosis were either a rise in meningococcal antibody concentration (IgG or IgM) between acute and convalescent specimens of serum, or a raised level of IgM in a single specimen of serum, together with clear clinical signs of meningitis and/or septicaemia. Seventeen pairs and 54 single specimens fulfilled these criteria, and were accompanied by clear clinical evidence of meningococcal infection. During the evaluation of this test various control specimens of serum, including those collected from cases of invasive *Haemophilus influenzae* infection, were tested and found to be negative. What appears to be an anamnestic reaction was encountered in a

proportion of specimens from patients infected with the Epstein Barr virus (EBV), who produce both IgM and IgG antibody against meningococcal proteins. It is suggested that in doubtful clinical cases EBV infection should be excluded with a specific serological test.

Susceptibility to penicillin

The minimum inhibitory concentration (MIC) of penicillin was less than 0.1 mg/l for most strains of *N. meningitidis*, but 76 (6%) had an MIC in the range 0.16 to 1.28 mg/l. This is the same proportion as in 1992. This degree of reduced susceptibility is not clinically important when doses of penicillin recommended in the British National Formulary⁴ are given.

Rifampicin resistance

Isolates occasionally develop resistance after prophylaxis with rifampicin, but the incidence of clinical infections due to rifampicin resistant strains remains very low. In 1993 only three resistant strains (MIC 50 mg/l) were received from invasive infections.

Comment

Although the number of isolates received by MRU in 1993 was virtually the same as in 1992, the true incidence of meningococcal disease in 1993 may have been higher. Three observations support this hypothesis. Firstly, notifications to OPCS were higher in 1993 than in 1992. Secondly, notifications to OPCS exceeded isolates sent to MRU for the first time. This was probably due to increased early use of antibiotics in suspected cases and, hence, fewer isolates. Thirdly, meningococcal disease showed an unusual temporal distribution, associated with the influenza epidemic.

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Epidemiology of meningococcal disease and a community outbreak in Somerset

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Summary

We describe the epidemiology of meningococcal disease in Somerset and a community outbreak in one district. Fifty-seven cases of meningococcal disease occurred in residents of Somerset between 1 May 1990 and 30 April 1993 (incidence 4.7/100 000/year), of whom six died. Thirteen of the cases occurred in one local authority area in a six month period from 1 November 1992 to 30 April 1993; an incidence of 26.6/100 000/year. Twenty-seven patients were given benzylpenicillin before admission to hospital. General practitioners were significantly more likely to give benzylpenicillin to patients with rashes. The proportion that received prophylaxis tended to increase after a press release was issued and general practitioners were advised. The number of cases was too small to demonstrate the protective effect of early administration of benzylpenicillin. In five cases the consultant in communicable disease control was not informed for over 12 hours. Thirty-seven of the 48 index cases for whom information was available received rifampicin prophylaxis before discharge from hospital.

Introduction

The background incidence of meningococcal disease in England and Wales is 2.7/100 000/year¹. The incidence in Somerset Health District (population 406 000) rose from 2.1 to 6.1/100 000/year between the successive three year periods 1988 to 1990 and 1991 to 1993. The increase was particularly marked over a six month period in one district, Sedgemoor, which has a population of about 98 000.

On 21 December 1992, after seven cases had occurred in Sedgemoor in six weeks, a press release was issued to inform local people about the increased number of cases and the early symptoms of meningococcal disease. Local general practitioners were sent a newsletter reminding them of the need for vigilance and the benefits of giving parenteral penicillin before admitting suspected cases to hospital.

We reviewed the epidemiology, management, and clinical features of cases of meningococcal disease in Somerset from 1 May 1990 to 30 April 1993, including the community outbreak in Sedgemoor. As late notification of cases delays

public health advice and may lead to anxiety among contacts, we recorded the time between diagnosis of meningococcal disease and notification.

The protection given by the administration of benzylpenicillin before admission to hospital has been discussed²⁻⁴. We examined the use of penicillin before admission and its effect on mortality, morbidity, and length of admission. In addition, we assessed its use before and after general practitioners were advised and the press release about the outbreak was issued.

Methods

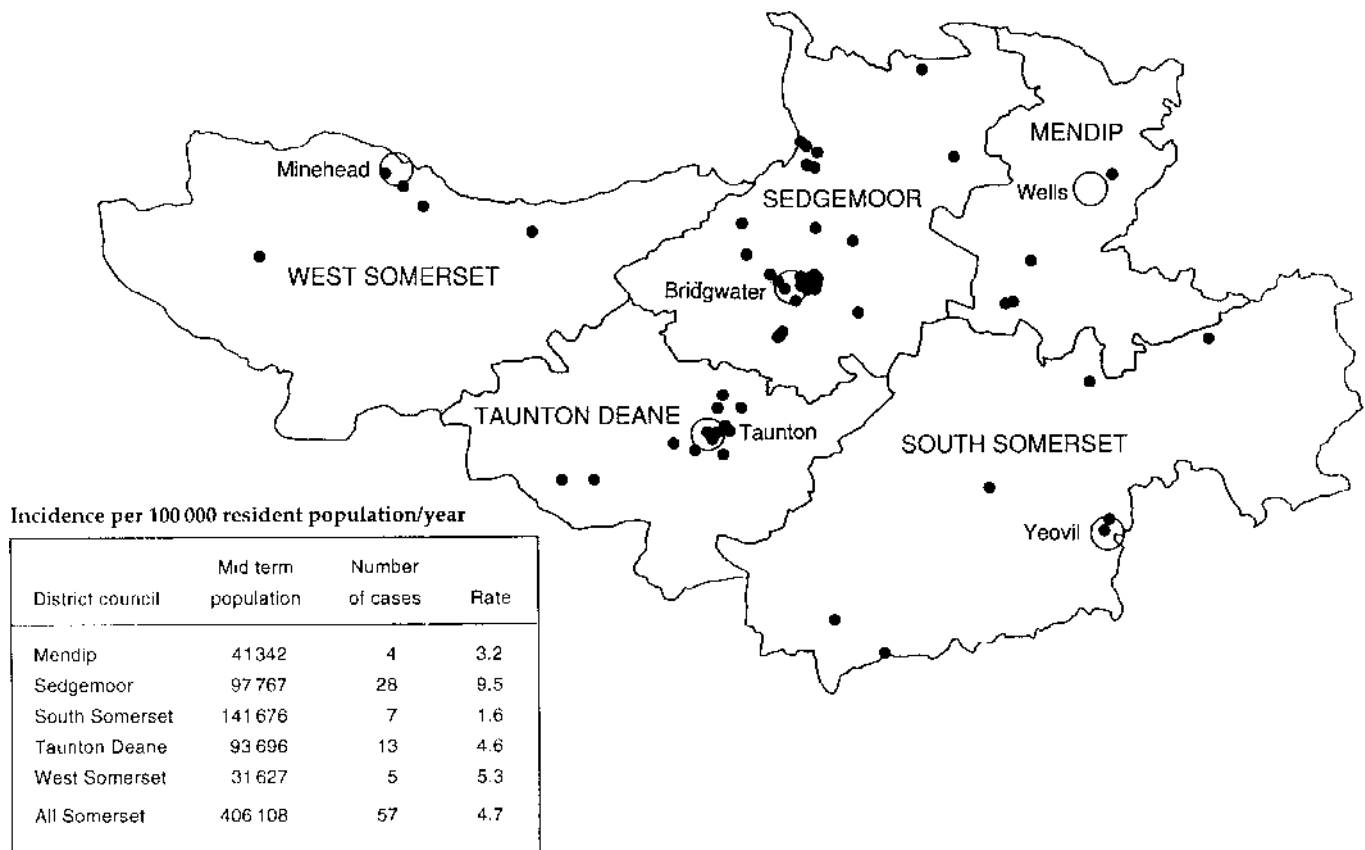
Cases were defined as those in whom *Neisseria meningitidis* was isolated from the blood and/or cerebrospinal fluid (CSF), or Gram negative diplococci were seen in the CSF, or clinical signs of meningitis or septicaemia were accompanied by a haemorrhagic rash⁵. Somerset residents who became ill within 10 days of leaving Somerset were included and information was sought from the hospitals to which they were admitted. People who lived outside Somerset and who became ill within less than 10 days of arrival in Somerset were excluded. These people might have been infected outside the district. One, for example, was admitted when she became ill on a coach driving through Somerset.

The consultant in communicable disease control (CCDC) for Somerset keeps detailed records of all notified episodes of meningococcal disease. These records were used as the source of cases and case ascertainment was checked for completeness against hospital admission data, notification data, and records from Taunton Public Health Laboratory. Hospital medical records and the public health department's case notes were reviewed; information was sought on the clinical features of the illness, demographic details, management before admission, and the results of microbiological investigations.

The outcomes of cases who did, or did not, receive benzylpenicillin before admission were compared, using Fisher's exact test, and their mean length of admission was compared with a two sample *t* test. The Chi squared test was used to compare the proportions of patients with rashes that received benzylpenicillin before and after general practitioners were advised.

Table Age distribution of cases of meningococcal disease in Somerset (May 1990 - April 1993) compared with that in England and Wales (1992)

Age (years)	Number of cases (%) in Sedgemoor	Number of cases (%) in the rest of Somerset	Number of cases (%) England and Wales 1992 ¹
<1	3 (11)	5 (17)	281 (21)
1-4	9 (32)	7 (24)	433 (32)
5-14	5 (18)	5 (17)	188 (14)
15-24	7 (25)	7 (24)	250 (19)
≥25	4 (14)	5 (17)	159 (12)
unknown	—	—	33 (2)
All ages	28 (100)	29 (100)	1344 (100)

Figure 1 Cases of meningococcal disease in Somerset District Health Authority – May 1990 to April 1993

Results

Epidemiology

Between 1 May 1990 and 30 April 1993 there were 57 cases of meningococcal disease in Somerset residents, 32 female and 25 male. Their age distribution is compared with that in England and Wales in the table. Four further cases of meningococcal disease admitted to hospitals in Somerset were holidaymakers who had been in Somerset for fewer than 10 days and were excluded from the study.

Twenty-eight of the cases were from Sedgemoor district (table; figure 1). Thirteen of these arose in the six months from 1 November 1992 to 30 April 1993 (incidence 26.6/100 000/year). The overall incidence for Sedgemoor for the three years was 9.5/100 000/year. No secondary cases were identified although, in the month after the study ended, a pupil at the same school as one of the study cases developed meningococcal meningitis. This pupil was in the same school year as the study case and was admitted three weeks later. Comparative bacteriology was not possible as the organism was not cultured, possibly because of early administration of benzylpenicillin.

Figure 2 traces the outbreak and shows the relative proportion of cases from the Sedgemoor area. *N. meningitidis* was cultured and grouped for 40 cases: 23 were group B; 15 were from groups A/C/Y; and two could not be grouped. Seven of the organisms isolated were resistant to sulphonamides; three of these were from cases in Sedgemoor. The proportion of group B infections in Sedgemoor was similar to that in the rest of Somerset. Six of the 13 typed isolates from Sedgemoor were group B, not typable, subtype

P1.15. Four of these were isolated during the six months from November 1992 to April 1993.

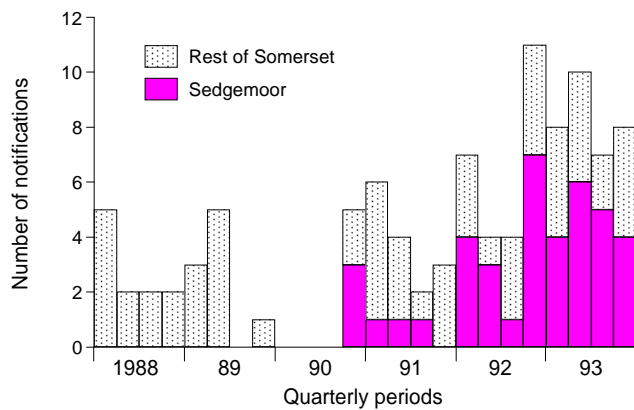
Clinical features and outcome

Six of the 57 cases died. Detailed reviews of medical records were possible in 52 cases. Three of the remaining five patients were admitted to hospitals outside the district and the notes of two could not be found; two had died. The presenting features were as follows: vomiting in 35; purpuric or petechial skin rashes in 33; convulsions in six; headache in 27 (although 20 were too young to report this); and examination for neck stiffness (recorded for 49 patients) was positive in 34. The clinical features of cases from Sedgemoor were the same as those in the rest of Somerset. The median length of hospital admission was nine days. Sequelae of more than three months duration were recorded for eight patients. These included partial deafness in two (both adults), oculomotor nerve palsy in one, seizures in one, impaired motor skills in two, arthritis in one, and problems at school in one. All the young children had a hearing test after discharge from hospital, and none was reported to have hearing loss when followed up at three months (older cases were presumed to be able to report hearing loss).

Management of cases and efficacy of benzylpenicillin

The medical records of 46 cases admitted by general practitioners clearly indicated whether or not benzylpenicillin had been given before admission. Twenty-seven of these were given benzylpenicillin before admission.

Figure 2 Meningococcal disease in Somerset: 1988-1993
(quarterly data)



Three of those who received the antibiotic, and two of the 19 who did not, died. The frequency of long term sequelae did not differ significantly between those who had received benzylpenicillin before admission and those who had not. Three cases with long term sequelae had received the antibiotic before admission and four had not; in the other case no information was available. The mean length of hospital admission for those discharged alive who received benzylpenicillin was 9.3 days (median 9), compared with 10.4 days (median 8.5) for those who did not. The mean lengths of admission were not significantly different.

Records of 49 patients enabled us to look for an association between the presence of a rash and the administration of benzylpenicillin before admission. Twenty-two of the 32 patients who had a rash on admission had received benzylpenicillin from their general practitioner, compared with only four of the 17 without a rash (95% confidence interval for the difference: 19.4% to 71.0%; $\chi^2 = 9.12$, $p = 0.003$). Five of the eight patients who presented with the combination of rash, vomiting, neck stiffness, and irritability on admission had been given benzylpenicillin before admission. After the press release was issued and general practitioners were advised, eight of the 11 subsequent cases were given benzylpenicillin compared with 18 of 35 in the preceding 30 months. Rifampicin was administered to the index case by clinicians before discharge from hospital in 37 of the 48 cases in whose medical records this information was recorded.

The time after diagnosis and before the CCDC was informed was known in 50 cases. The median interval was four hours, with a range from less than 1 hour to 110 hours. CCDCs were first informed by paediatricians in 14 cases; the public health laboratory in 34 cases; other CCDCs in three cases; general practitioners in two cases; the press in one case; and a school in another. In five cases it was more than 12 hours (16,19,39,48,110 hours) before the CCDC was informed and prophylaxis and advice may have been delayed.

Discussion

The Sedgemoor outbreak of meningococcal disease differed from another recent outbreak in a district nearby (Stroud) in the age distribution of cases. In Sedgemoor this followed the national pattern, with only a slight excess of cases in the 15 to 24 year age group. In contrast, teenagers were the main

group affected in Stroud (71% of cases were aged 10 to 24)⁵. No particular types or serotypes predominated, although *N. meningitidis* group B, not typable, subtype P1.15 was isolated from four cases in Sedgemoor in the six months from November 1992 to April 1993. Such organisms account for 13% of meningococcal group B isolates nationally⁶. The case fatality rate of 10% in this outbreak is similar to that reported in other series^{4,7-9}.

In 1988 the chief medical officer wrote to all general practitioners advocating the administration of benzylpenicillin to suspected cases of meningococcal disease before admission¹⁰. Shortly afterwards, a survey of general practitioners showed that less than half carried benzylpenicillin in their bags¹¹. Overall, 59% of the patients admitted by general practitioners in our study were given benzylpenicillin before admission. This proportion exceeds that reported in some recent studies: 27% in Gloucestershire, Plymouth, and Bath¹², and 26% in Denmark⁴. One study showed that, after local publicity, 86% of patients received benzylpenicillin before admission¹³; this compares with 73% after publicity in Somerset.

The number of cases studied was too small for a protective effect from the administration of benzylpenicillin before admission to be demonstrated. The rationale for such treatment is that earlier antibiotic treatment is associated with a better outcome³. It is argued, however, that patients with more severe illness – florid signs of meningococcal disease – are more likely to be given benzylpenicillin. This group may have a worse prognosis and, if studies fail to control for the severity of the disease, any protective effect is likely to be underestimated or missed⁴. We found that those with a rash on admission were more likely to have received benzylpenicillin, but only five of the eight patients with rash, vomiting, neck stiffness, and irritability on admission (florid signs of serious infection) were given benzylpenicillin before admission.

CCDCs were usually informed promptly, but delays – when they occurred – might have increased the risk of secondary cases, which most often occur soon after the index case¹⁴. If contacts are not warned that they are at increased risk they may delay seeking medical help for early symptoms of meningococcal disease. In addition, anxiety in local communities and schools might have been allayed in some instances by prompt notification.

Meningococcal meningitis continues to be a common and frightening cause of severe, often fatal, illness that particularly affects young children. An effective vaccine against group B *N. meningitidis*, the commonest group to cause illness in this country, is not available. The cluster described caused much public alarm in our community and has not been explained. Somerset Health District has continued to experience a greater than expected number of cases of meningococcal disease. At the time of writing (22 July 1994) a further 39 cases have occurred since 1 May 1993.

Acknowledgements

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Age specific antibody prevalence to parvovirus B19: how many women are infected in pregnancy?

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Summary

Infection with parvovirus B19 is an important cause of late fetal mortality in the second trimester, and many infections in pregnancy remain undiagnosed. A serological survey stratified by age has been used to estimate the incidence of maternal infection with parvovirus B19 in pregnancy. Serum remaining from specimens submitted for diagnosis from 6864 people of all ages to seven public health laboratories in England was tested for antibody to parvovirus B19. The antibody prevalence rose with age to 45% at 10 years and 60% to 70% in adults. The age specific force of infection was highest in children aged less than 10 years and lowest in adults. Maternal infection with parvovirus B19 is estimated to occur in approximately one pregnancy in 400. It has been estimated that fetal death occurs in 9% of these cases, which suggests that parvovirus B19 may cause more than 150 fetal deaths in England and Wales each year. Testing for evidence of recent infection with parvovirus B19 should be considered for unexplained cases of fetal hydrops in the second trimester, especially in years of parvovirus B19 epidemics.

Introduction

Parvovirus B19 causes erythema infectiosum¹, commonly known as slapped cheek syndrome or fifth disease. It is clinically similar to rubella and the diseases can be distinguished reliably only by laboratory tests. The disease

is usually mild, but infection during pregnancy has been estimated to cause fetal death in about 9% of cases². There is no evidence to suggest that parvovirus B19 is associated with congenital abnormality. A serological survey was performed in 1991 and the results, stratified by age, were analysed to estimate the incidence of parvovirus B19 infection in pregnant women.

Methods

Laboratory methods

Serum remaining from specimens submitted from patients of all ages for routine diagnostic examination to seven public health laboratories (Ashford, Birmingham, Exeter, Leeds, Manchester, Preston, and Reading) during 1991 was tested. Specimens from immunocompromised patients and samples sent for testing for hepatitis B virus and antibodies to the human immunodeficiency virus were excluded.

The serum specimens were tested for anti-B19 IgG using an enzyme linked immunosorbent assay (ELISA) (MRL Diagnostics, Cypress, California) at Preston Public Health Laboratory. Preliminary studies at the Virus Reference Division at the PHLS Central Public Health Laboratory had shown that the sensitivity and specificity of the ELISA was similar to that of antibody capture radioimmunoassay for anti-B19 IgG³. Results were expressed as an index calculated as the ratio of the optical densities of test specimens to a reference specimen provided with the ELISA kit. The kit manufacturer recommends that specimens with index values greater than 1.2 be considered seropositive; those between 0.8 and 1.2, equivocal; and those less than 0.8, seronegative.

In a serological survey it is essential to ensure that the correct proportions of specimens are classified as positive or negative in each age group, but not that every individual specimen is correctly classified as positive or negative. A cut off point should be chosen to balance false negatives against false positives. Force of infection estimates were derived using cut off ratios of 0.8, 0.9, and 1.0: ratios greater than the cut off were classified as seropositive and values less than the cut off as seronegative. A cut off of 1.0 divides the equivocal range equally between positive and negative, whereas a cut off of 0.8 assigns all equivocal results as positive, which may be more appropriate if the test is insensitive.

Epidemiological methods

The force of infection, λ , is defined as the rate at which susceptible people acquire infection⁴. The probability that a susceptible person will be infected in a short period of time is the product of the force of infection and time. The force of infection changes in the course of an epidemic cycle: it is greater at the height of an epidemic. We calculate its mean value, averaged over epidemic and non-epidemic periods. The force of infection varies with age for most directly transmitted diseases, and is typically highest in primary school children and lowest in adults. The age specific force of infection, (a), is related to the prevalence at age a, P(a), by the equation:

$$P(a) = 1 - \exp \left(- \int_0^a \lambda(a') da' \right)$$

This is a generalisation of the relationship for an age independent force of infection: $P(a)=1 - \exp(-\lambda a)$. The equation above was used to estimate the age specific force of infection from serological data in age groups 0 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 44 years using a maximum likelihood technique⁵.

The value derived for the force of infection in adults (15 to 44 years) was used to estimate the average annual number of infections in pregnancy in England and Wales, thus:

Number of infections in pregnancy = Number of births x Proportion of adults susceptible x Force of infection in adults x Duration of pregnancy

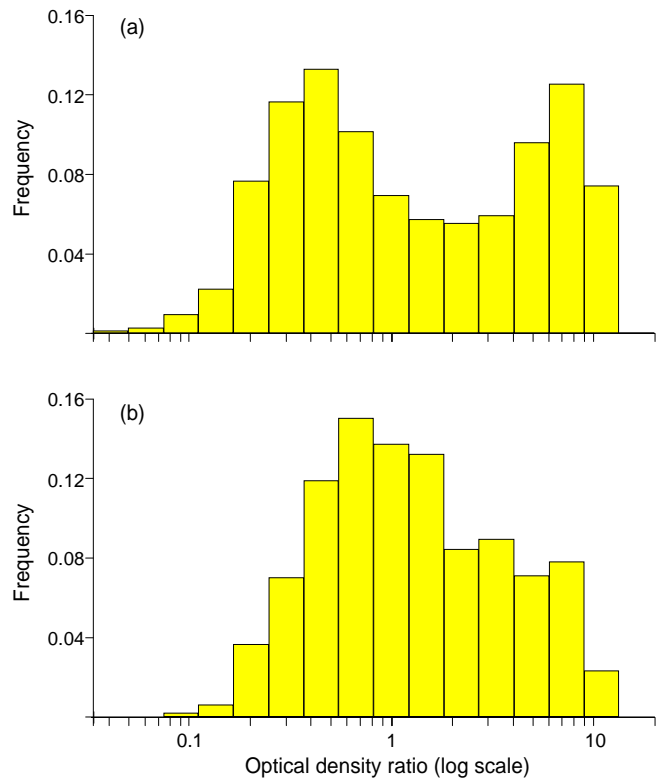
The annual number of births was taken as 700 000 and the duration of pregnancy as nine months.

Results

A total of 6864 specimens of serum was examined. Of these, 1223 were from people aged 1 to 14 years, 3133 from people aged 15 to 29, 1481 from people aged 30 to 44, and 1027 from people aged 45 years or over. Specimens from males numbered 2701 and from females, 4163.

ELISA tests on specimens from one laboratory (Leeds, 636 specimens) yielded different results from specimens from other laboratories. Almost all gave an optical density ratio greater than one. Investigation revealed that Leeds was the only laboratory where specimens were inactivated by heat, and it was thought that this treatment might have invalidated the test results. Consequently, these results were excluded from the analysis. There were no significant differences between the results from the other laboratories,

Figure 1 Distribution of optical density ratios: a) ages 1 to 44 years, b) ages 45 to 99 years.



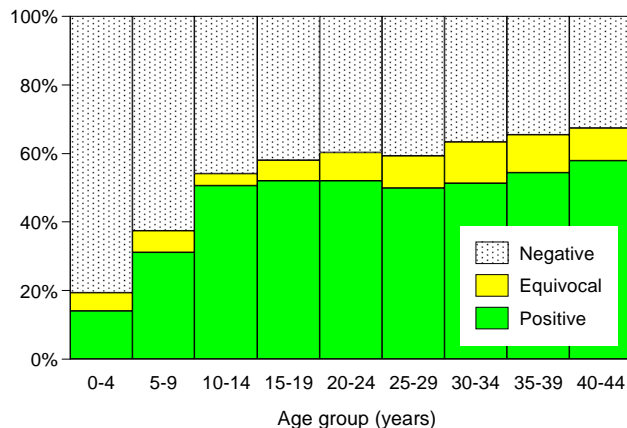
or between the results for males and females.

The optical density ratios for people aged 1 to 44 (5244 specimens) show two distinct peaks, due to positive and negative specimens, but many results fall between the peaks (figure 1a). In the 45 to 99 year age group (984 specimens), no clear division can be seen between positive and negative specimens (figure 1b). This suggests that the assay used does not distinguish specimens with low concentrations of antibody (generally indicative of an infection many years ago) from those with no antibody.

The proportions of positive, negative, and equivocal test results (according to the manufacturer's definitions), in five year age groups, are shown in figure 2. Eight per cent of specimens from 1 to 44 year olds yielded equivocal results. The proportion of equivocal results increased with age, confirming that the test lacks sensitivity in detecting antibody in older people.

Table 1 Estimated force of infection in adults, and annual number of parvovirus B19 infections in pregnancy in England and Wales, using different cut off points

Cut off	Force of infection in adults per year	Infections per 100 000 pregnancies	Average annual total in England and Wales
0.8	0.0081	310	2200
0.9	0.0051	230	1600
1.0	0.0038	170	1200

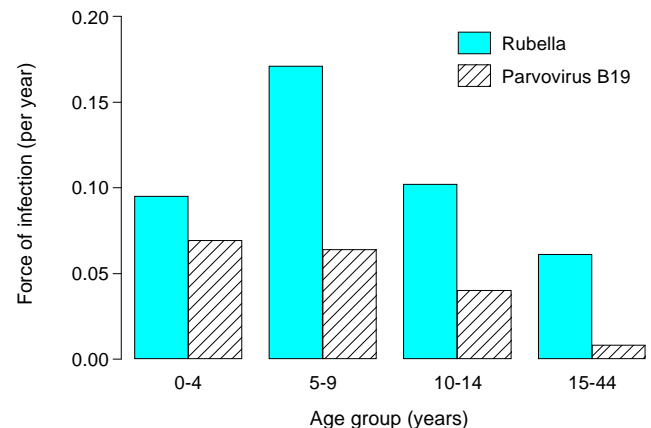
Figure 2 Antibody prevalence to parvovirus B19 by age

Different ELISA cut off points were used to derive the force of infection in adults and estimate the incidence and annual number of parvovirus B19 infections in pregnancy in England and Wales (table 1). The force of infection is greatest in children aged less than 10 years (0.07/year); that is, in a year the probability of a susceptible child under ten becoming infected is 0.07. In adults the force of infection falls to less than 0.01/year. The choice of cut off has only a small effect on the estimated force of infection in children under 15, but has a greater effect in adults. The age specific forces of infection of parvovirus B19 (calculated using a cut off of 0.8) and rubella are compared in figure 3.

Discussion

This serological survey is the most comprehensive yet undertaken for parvovirus B19 and establishes the prevalence of antibody in all age groups. Although the people from whom the specimens were taken were not a random sample of the population, there is no reason to believe that they were unrepresentative in terms of their history of exposure to parvovirus B19. Similar studies of measles, mumps, rubella, and hepatitis A have yielded valuable information about the epidemiology of these diseases⁵⁻⁷. Analysis of the serological profile suggests that, on average, slightly fewer than 1% of susceptible adults are infected each year. We estimate from this that 1600 to 2200 mothers are infected in pregnancy each year in England and Wales; that is, approximately one infection in every 400 pregnancies. The total in a particular year will reflect the three to four year epidemic cycle of parvovirus B19: in an epidemic year there may be two or three times more cases than in an average year. An equivalent analysis of serological data for rubella suggests that, before vaccination began, rubella caused about twice as many infections in pregnancy as parvovirus B19.

Our results suggest that the ELISA used was unsuitable for use with serum specimens inactivated by heat, and that its sensitivity was insufficient to detect low concentrations of anti-B19 IgG. A more sensitive test is needed to ascertain the immune status of individuals and would enable the force of infection in adults to be determined more precisely. The test's insensitivity and the changing prevalence of infection with age suggest that an age dependent cut off might improve the analysis by enabling the criterion of equal numbers of false positives and false negatives to be applied in each age

Figure 3 Estimated age specific force of infection for parvovirus B19 (using a cut off ratio of 0.8) and rubella (PHLS data)

group. Methods for determining age specific cut offs are being developed, based on mixture modelling techniques⁸.

The force of infection for parvovirus B19 was estimated previously to be 0.004/year in hospital employees and 0.029/year in school employees in a study of seroconversions, over a 42 month non-epidemic period, in Virginia⁹. The risk in hospital workers corresponds well with the overall population estimates from our study, while school employees' higher degree of contact with children puts them at greater risk. Parous women may be at greater risk than nulliparous women for the same reason. This effect has been documented for rubella¹⁰, for which the risk in parous women was two to three times greater than for nulliparous women.

In 1993, an epidemic year for parvovirus B19 in England and Wales, 310 laboratory confirmed infections in pregnancy were reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre. This represents at most 10% of the 3000 to 6000 infections that are estimated to occur in an epidemic year, and this highlights the extent to which B19 infection is undiagnosed. The outcomes of these pregnancies are being studied prospectively in order to provide a better understanding of the consequences of maternal infection during pregnancy.

In a previous study, 180 out of 186 cases were symptomatic and it was estimated that fetal death resulted from maternal infection in pregnancy in 9% of cases, with an excess in the second trimester². Applying this fetal death rate to the estimated number of infections suggests that 150 to 200 fetal deaths are caused by parvovirus B19 each year. It has been suggested, however, that asymptomatic maternal infection is associated with an increased risk of fetal death¹¹, so this figure could be regarded as a minimum estimate. Symptoms of parvovirus B19, such as rash and arthralgia, are caused by the antigen antibody complex rather than the virus itself. Symptomatic cases may, therefore, have a stronger antibody response than asymptomatic cases, with shorter viraemia and a smaller risk of fetal infection. A study to measure the frequency and consequences of asymptomatic infection in pregnancy is needed.

Parvovirus B19 is an important cause of fetal mortality in the second trimester. Testing for evidence of recent B19 infection should be considered for otherwise unexplained cases of fetal hydrops in the second trimester, especially in epidemic years. The appropriate serological tests on the

mother would include B19 specific IgM and IgG. IgM may, however, not be detected since fetal death associated with parvovirus B19 often occurs two or more months after maternal infection, when B19 IgM has fallen to concentrations difficult to detect with currently available assays. It is important, therefore, to compare IgG in current and antenatal booking specimens, looking for seroconversion to diagnose gestational infection with parvovirus B19.

Diagnosis of fetal infection with parvovirus B19 by the detection of IgM is also of limited value. The most effective method for diagnosing fetal infection is by direct observation of the virus using electron microscopy¹², and/or by parvovirus B19 DNA and antigen assay¹³. These techniques enable fetal viraemia to be detected in pre-natal blood specimens. Infection can also be demonstrated in amniotic fluid or fetal tissues collected at necropsy. Fresh or formalin fixed specimens are suitable for DNA testing, and fetal liver (with a high concentration of the target erythroid cells), is the most useful tissue for confirming the infection. Placenta is not helpful for this investigation.

Although a vaccine against parvovirus B19 is being developed¹⁴, there is no immediate prospect of its use. Greater knowledge of the morbidity and fetal mortality caused by the virus is needed, so that appropriate immunisation strategies may be developed.

Acknowledgements

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Serological surveillance in the Netherlands

M Esveld

The Netherlands Immunisation Programme (NIP) has greatly reduced the incidence of target childhood diseases and their complications. The current programme and coverage are shown in the table. Particular vigilance is needed, however, in communities where a high proportion of people are unvaccinated and herd immunity may not be sufficient to protect those who are not immune. Vaccination reduces the circulation of microorganisms, with paradoxical effects: infections occur later in life and may have more complications,

natural immunity may not persist because rechallenge occurs less frequently, and immunity in the elderly may decline. Surveillance of immunisation programmes should include the following components: disease incidence, adverse events following vaccination, vaccine efficacy, coverage, and serological surveillance.

A recent pilot study by the National Institute of Public Health and Environmental Protection, in cooperation with the public health services in four municipalities in Utrecht, investigated the feasibility and the management of setting up a serum bank. Factors considered in the protocol included randomisation, assessment of the characteristics of non-

Table Immunisation programme and coverage in the Netherlands

- diphtheria, pertussis, tetanus, and polio: 3, 4, 5, and 12 months
(coverage: 97% by January 1992)
- diphtheria, tetanus, and polio: 4 and 9 years
(coverage: 94% by January 1992)
- measles, mumps, and rubella: 14 months and 9 years
(coverage: 94% by January 1992)
- *Haemophilus influenzae* type b: 3, 4, 5, and 12 months
(from April 1993)

responders and whether responders represent the population, compliance, informed consent, confidentiality, and the questionnaire.

A random sample of 2040 people aged up to 79 years was chosen. They received an invitation by post, with a consent form, appointment card for blood sampling, and a questionnaire. The questions focused on socioeconomic status, health and disease, vaccinations, and attitudes towards vaccination. Blood samples were taken from all participants who consented. Data were anonymised, apart from the information used to investigate non-responders.

The collection of data for the pilot study has just been completed and results are not yet available. If successful, the study will be expanded nationally. It is proposed that, every five years, a sample of about 20 000 people in all age groups will be tested. Further information is available from Dr M A E Conyn-van Spaendouck, Center for Infectious Diseases Epidemiology, PBI, 3720 BA, Bilthoven, Netherlands (telephone 010 31 30 743018; fax 010 31 30 283944).

Annual collection of specimens of serum stratified by age for serological surveillance was established in England in 1987, before the introduction of measles, mumps, and

rubella vaccine¹. The data on changing levels of susceptibility provided by this programme has been instrumental in guiding changes to vaccination policy. The specimens of serum have also been tested for antibodies to other pathogens, including parvovirus B19², hepatitis A³ and Norwalk virus⁴. Analysis of these surveys of infections, against which little or no vaccination has occurred, can provide the age specific incidence of infection⁵, enabling, for example, the incidence of parvovirus B19 infection in pregnancy to be estimated². The specimens of serum collected in this programme were tested recently to assess diphtheria immunity, and this indicated the need for a booster dose in teenagers⁶.

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