

A retrospective survey of clusters of meningococcal disease in England and Wales, 1993 to 1995: estimated risks of further cases in household and educational settings

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Summary

Information about the epidemiology of meningococcal disease case clusters and the risk of further cases is sparse. Data on clusters in household and educational settings from 1 January 1993 to 31 March 1995 was requested from consultants in communicable disease control in England and Wales through a retrospective postal survey. Ninety-three per cent (122/131) responded. Of the 114 cases in 45 reported clusters, 77 (67.5%) were microbiologically confirmed. The case fatality rate in index cases was higher than in associated cases (18.2% vs 4.5%; $p=0.02$). Five out of 11 clusters in household settings consisted only of index and co-primary cases. No further cases occurred within two weeks after giving chemoprophylaxis to household contacts. The relative risks of further cases in the week after the index case arose were estimated to be 1200 for contacts in the household, 160 in secondary schools, 60 in primary schools, 1.8 in universities/colleges, and 0 in nurseries. Between seven and 30 days the relative risks were lower; 150 in households, and between 0 and 13 in all other settings. Beyond 30 days, the relative risk in the household setting was 8 and lower than this in all other settings. The absolute risk of further cases in the month following the index case was calculated as 210 per 100 000 in household members, $7\text{--}10/10^5$ in pupils at the same school, and $0.6/10^5$ in students at the same university or college. The current policy in England and Wales to recommend chemoprophylaxis for household members may prevent half of the further cases in this setting. Raised awareness may have contributed to the lower case fatality rate among household contacts who developed meningococcal disease, but the number of co-primary

cases observed should prompt urgent enquiries about current illness in household contacts of index cases. The relative risk of further cases in preschool groups was low and apparently unaffected by changes in chemoprophylactic policy. The relative risk in school settings was raised in the month following a case, but the absolute risk was still low. Further study to quantify the risk in university settings is needed.

Key words: disease outbreaks – meningitis, meningococcal – meningococcal infections – *Neisseria meningitidis* – risk factors

Introduction

Meningococcal disease is an important cause of illness and death in England and Wales. Between 1990 and 1994 between 1344 and 1451 cases were officially notified each year¹, representing an annual notification rate of about 3/100 000. Most cases were children under 5 years. Age specific attack rates are highest in infancy with a smaller peak in late teenage years². Crude case fatality rates (derived from deaths reported to the Office of Population Censuses and Surveys (now the Office for National Statistics, ONS) as caused by meningococcal disease and notifications of meningococcal meningitis and septicaemia) varied between 11% and 12% during this period¹. The case fatality rates are likely to be falsely high due to the incompleteness of notification in England and Wales³.

The spread of meningococcal disease is difficult to predict; even the occurrence of a single case can readily evoke fear in a community and unease for those concerned with diagnosis and control of the disease⁴. The management of clusters of meningococcal disease is made

Box Survey definitions

Cluster: two or more clinical or confirmed cases of meningococcal disease arising within 12 months in the same defined setting – household, nursery/playgroup, primary school, secondary school, or university/college.

Clinical case: clinical diagnosis of meningococcal meningitis and/or septicaemia reported to the CCDC.

Confirmed case: clinical case with microbiological confirmation of infection with *Neisseria meningitidis* (by culture from blood or cerebrospinal fluid (CSF), the presence of Gram negative diplococci in CSF, meningococcal DNA on polymerase chain reaction (PCR) testing or meningococcal antigen in blood or CSF, or serological evidence of meningococcal infection).

Clusters were grouped as 'same strain' (consisting of two or more confirmed cases of the same serogroup and serotype), 'possibly same strain' (consisting of two or more clinical or confirmed cases in which the microbiological data were insufficient to classify strains as the same or different), or 'different strain' (consisting

of two or more confirmed cases caused by strains of different serogroups and/or serotypes).

Index case: the first case of meningococcal disease diagnosed in a defined setting.

Associated case: a subsequent case of meningococcal disease in the same setting in the 12 months after the diagnosis of an index case. The word 'associated' was chosen in preference to 'secondary' since the source of infection is usually unknown and 'secondary' implies that the source of infection was the index case.

Co-primary case: an associated case occurring within 24 hours of diagnosis of the index case.

Nursery/playgroup (referred to as nursery): preschool learning group for children mostly under 4 years of age

Primary school: school with pupils mostly aged between 4 and 10 years

Secondary school: school with pupils mostly aged between 11 and 16 (or 18) years

University/college (referred to as university): an institution of further or higher education for students over 16 years of age.

Table 1 Population and incidence data (England and Wales) used for calculations

Group	Age	Mean group size	Estimated number of such groups	Estimated annual incidence per 100 000	Total index cases annually*	Contacts annually (index cases x group size -1)
Household	All ages	4	12819250	2.46	1261	3783
Nursery	2-3	41	20822	14.62	125	5000
Primary schools	4-10	209	20381	3.56	152	31616
Secondary schools	11-15	809	3856	1.94	61	49288
Independent schools	4-17	243	2330	3.04	17	4114
Special schools	4-17	75	1370	3.04	3.1	229
Colleges	16-20	5030	498	4.21	105	528045
University	18-22	7850	158	3.24	40	313960

* index cases = (incidence/100 000) x group size x number of groups

more difficult because of the lack of evidence to indicate the risk of secondary spread or the effectiveness of control measures^{5,6}. Reported studies of the secondary spread of meningococcal disease use different case and cluster definitions, making comparisons between studies difficult⁷⁻⁹.

We report the results of a retrospective survey of all consultants in communicable disease control (CCDCs) in England and Wales. The objective was to obtain information about clusters of meningococcal disease in household and educational settings from 1 January 1993 to 31 March 1995 and estimate the risk of further cases in these settings.

Methods

The terms used in this paper are defined in the Box.

Survey

A short postal questionnaire was sent to all CCDCs in England and Wales listed in the PHLS Communicable Disease Surveillance Centre directory in May 1995. The purpose of the questionnaire was to ascertain if any clusters of meningococcal disease had occurred in each CCDC's health district between 1 January 1993 and 31 March 1995. CCDCs who reported clusters were contacted by telephone and sent a follow up questionnaire requesting details

about the index and associated cases in each cluster. CCDCs who had not responded within three weeks were sent a further letter.

Data from completed questionnaires were entered twice on a database using Epi-Info version 6¹⁰ and validated. A copy of the PHLS Meningococcal Reference Unit (MRU) database relating to the study period was obtained; in some cases this enabled us to supplement information obtained from the questionnaires.

Expected numbers of chance clusters were calculated using the relevant age specific incidence of culture confirmed cases in England and Wales during the study period, which were obtained from MRU (table 1). Estimates of the average sizes of households and educational settings and the numbers of such settings were obtained for 1993/94 from Department of Education Statistics, the Welsh Office, the Further Education Funding Council, the Preschool Learning Alliance, and for 1994/95 from the Resources of Higher Education Statistics for the United Kingdom (table 1). Relative risks were estimated from the observed and expected number of clusters in each setting for each time period. Confidence intervals were calculated assuming that the observed numbers of clusters were consistent with Poisson processes that were constant within intervals of one week, one week to one month and one month, to one year for each setting.

Table 2 Clusters of meningococcal disease reported by CCDCs from 1 January 1993 to 31 March 1995 showing the number of cases in each setting

Setting	Number of clusters = no. index cases (% of total no. of clusters)	Number of associated cases	Mean no. of cases per cluster (range)
Household	11 (24.4)	20	2.8 (2-6)
Nursery	3 (6.7)	4	2.3 (2-3)
Primary school	7 (15.5)	7	2.0 (2)
Secondary school	12 (26.7)	18	2.5 (2-4)
University	12 (26.7)	20	2.7 (2-4)
All settings	45 (100)	69	2.5 (2.6)

Table 3 Index and associated cases: age, sex, presence of the rash and outcome

	Index cases	Associated cases
Total number of cases	45	69
Mean age	12.9 yrs	13.2 yrs
Age range	5 mnths to 58 yrs	5 mnths to 54 yrs
Sex	males 17:females 27 m:f ratio of 0.63 (not known=1)	males 30:females 38 m:f ratio of 0.79 (not known=1)
Presence of rash on admission	n=29 (91%) (not known=13)	n=44 (75%) (not known=10)
Outcome:death	n=8 (not known=1)	n=3 (not known=2)
Fatality rate*	18%	4%

* Fisher's exact test, 2 tailed p value = 0.02
– other differences not statistically significant

Table 4 Observed (O) and expected (E) clusters of cases of meningococcal disease by setting and within different epochs 1993-5 with relative risks (RR) and 95% confidence intervals (CI)

Setting	Within one week (0-6 days)				One week to one month (7-30 days)				One month to one year (31-365 days)			
	O	E	RR	(CI)	O	E	RR	(CI)	O	E	RR	(CI)
Household*	6	0.005	1200	(400-2400)	3	0.02	150	(30-480)	2	0.25	8	(1.0-30)
Nursery	0	0.03	0	(0-110)	0	0.11	0	(0-30)	3	1.5	2.0	(0.4-6)
Primary school	3	0.05	60	(10-180)	2	0.15	13	(1.5-4.0)	2	2.3	0.9	(0.1-3)
Secondary school	8	0.05	160	(75-350)	1	0.15	7	(0.2-35)	3	2.2	1.4	(0.3-4)
University	2	1.1	1.8	(0.2-6)	6	4.0	1.5	(0.6-3)	4	50	0.1	(0.02-0.2)

* assumes mean case household size of four people

Results

The initial postal questionnaire was sent to 131 CCDCs in the 122 health authority districts in England and Wales. The response rate to a single mailing was 93% (122/131) and represented 96% (117/122) coverage of all district health authorities. Forty-six (38%) CCDCs reported clusters between 1 January 1993 and 31 March 1995. All 46 returned data on 53 clusters in response to the second questionnaire. Eight responses were excluded from the analysis, as the clusters did not meet the defined criteria, leaving 45 clusters – comprising 114 cases – for analysis. The mean number of cases per cluster ranged from 2.0 to 2.8 (table 2), depending on the setting; the median was 2 overall. The median intervals between the development of index and second cases were 1.5 days (range 0-96) in household clusters, 5 days (range 0-225) in primary and secondary schools, and 23 days (range 1-290) in universities. In total, 77 (68%) diagnoses were confirmed by laboratory tests, and the serogroup was confirmed in 64 cases, 45 of which were group B and 19 group C. No other serogroups were identified. Group B cases were commoner in all settings.

A total of 11 deaths occurred among the 111 cases whose outcome was reported, an overall case fatality rate of 10%. Age specific death rates were 8% (5/63) in children aged 0 to 14 years and 13% (5/39) in 15 to 24 year olds. Index cases were more likely to die than associated cases (table 3). When analysis was restricted to confirmed cases, the difference in case fatality rates remained – 21% (7/33)

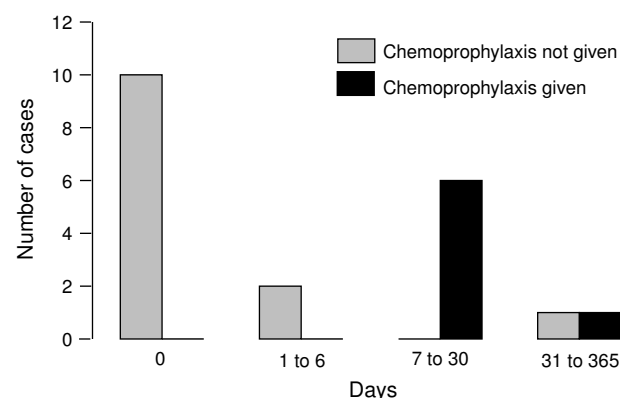
in index cases, and 7% (3/44) in associated cases. The age profile and sex ratio of index and associated cases were similar. Three associated cases died, all within nine days of the index case becoming ill; one occurred in a school and the other two in university settings.

Twenty-nine clusters (64%) consisted of two or more confirmed cases, 13 of one confirmed and one or more clinical cases, and three of two or more clinical cases only. Ten of the 45 clusters were 'same strain', 28 were 'possibly same strain', and seven were 'different strain' clusters. Twenty-nine of the 30 clusters in household or school settings were 'same strain' or 'possibly same strain' clusters. The seven 'different strain' clusters occurred in four universities, one secondary school, and two nurseries. In each of the four university and the single school clusters, either the index case was of group C and the second of group B or vice versa; the intervals between index and second cases were 1, 8, 36, and 42 days in the universities and 190 days in the school. In both 'different strain' clusters in nurseries, the index and second cases were caused by group B strains of different serotype and serosubtype separated by 42 and 100 days, respectively. In the first of these nursery clusters a third case caused by a group C strain occurred after a further 198 days.

The observed number of clusters in each setting apart from nurseries was higher than expected during the week after diagnosis of the index case (table 4). The relative risk was highest in households, but was significantly raised in both primary and secondary schools. No significant excess

Table 5 Absolute risk of an individual becoming a case in month after index case, by setting

Setting	No of clusters	No of cases	Absolute risk/10 ⁵	(95% CI)	95% CI for odds
Household	9	18	210	(130-330)	1 in 300 to 1 in 800
Nursery	0	0	–	(0-30)	>1 in 3000
Primary school	5	5	7	(2.5-16)	1 in 6000 to 1 in 40000
Secondary school	9	12	10	(5-17)	1 in 6000 to 1 in 20000
University	8	11	0.6	(0.3-1.0)	1 in 100000 to 1 in 350000

Figure 1 Associated cases in household clusters

risk was observed in universities. Between seven and 30 days the relative risk declined in all settings. Beyond one month observed numbers were close to the expected figures and were lower than expected in universities. The absolute risk of associated cases within one month in the same setting was much higher in households than in educational settings (table 5).

Forty-two (93%) of the 45 household contact groups were reported to have been given chemoprophylaxis. Dates of administration were recorded for 27 of the 45 contact groups, 23 (85%) of which received chemoprophylaxis on the day the index case was admitted to hospital. Nineteen of the 37 index cases who survived were known to have received chemoprophylaxis before leaving hospital. Of the remaining cases, CCDCs commented that local policy was to give such prophylaxis, but could not confirm whether it had been carried out.

Five of the 11 clusters in households consisted only of index and 10 co-primary cases (figure 1). Only one of the remaining six clusters included associated cases that arose within the first week. Neither of the two associated cases in this cluster had received chemoprophylaxis. In those clusters in which associated cases occurred after prophylaxis had been given, six cases occurred after intervals of 18 to 28 days, and the seventh was diagnosed after 92 days.

Discussion

This survey provides comprehensive information about the occurrence of case clusters of meningococcal disease in England and Wales. Our aim was to provide information of relevance to the practical decisions faced by CCDCs when managing a cluster. Often in such situations decisions have to be made without microbiological confirmation of the responsible organism, serogroup, or serotype. At the time of our survey cases of meningococcal disease were less likely to be microbiologically confirmed than in previous years because lumbar punctures were performed less often and the administration of benzylpenicillin to suspected cases before admission to hospital was becoming commoner¹¹. In an intensively investigated case series of meningococcal disease in an English health district, the proportion of clinical cases in 1989-95 was not dissimilar to the proportion of this study (23% vs 32.5%)¹¹. Thus we decided to include clusters of clinical and confirmed cases in the analysis, accepting that this could overestimate the true risk. The response rate was high but this study was retrospective and underascertainment was likely, which would tend to underestimate risk. Other relevant factors not accounted for in this analysis were temporal and geographical variations in disease incidence. We emphasise therefore that the risk estimates were inexact, but believe that they provide useful comparative data of the risks in different settings. Clusters are rare compared with sporadic cases, and continuing analysis of clusters is important to increase the validity of risk calculations. It is difficult to compare reported studies on clusters because definitions of cases and clusters differ^{7,8,9,12}, and it would be helpful if an international agreement on methodology could be reached.

Previous studies of household contacts have shown that associated cases caused by the same strain can occur

several months after the index case^{8,13}. For this reason we decided to use a cut-off of 12 months so as not to lose potentially relevant information. The longer the time interval between consecutive cases and/or the larger the population in which they arise, however, the more likely it is that clusters are due to unrelated sporadic infections. Outside the household setting, relative risk was not raised beyond a one month period, and cases in 'different strain' clusters were either all separated by intervals of more than one month or occurred in settings with relatively large denominator populations (colleges/universities).

The proportions of disease known to be caused by group B (70%) and group C (30%) in cluster cases was very close to the proportion attributable to these groups in culture confirmed cases for England and Wales in 1993 and 1994¹⁴. Sixty-nine associated cases (including co-primary cases) were identified, about 3% of the number of cases of meningococcal disease notified during the study period.

The most striking difference observed between index and associated cases relates to the higher case fatality rate among index cases, especially in clusters within a household. The difference remained when only microbiologically confirmed cases were analysed. A possible explanation for the difference is that the index case serves to raise awareness of meningococcal disease in the household. Prompt recognition of suspicious symptoms by household members and general practitioners could result in earlier treatment and a better prognosis for subsequent cases. A study undertaken in Belgium before administration of penicillin before admission to hospital was advocated in the management of meningococcal disease showed a similar but less marked difference in case fatality rates between primary cases (9.8%) and secondary cases (4.7%)⁷.

Some CCDC respondents questioned the appropriateness of including university clusters in this survey because of the large denominator populations in these settings. Underreporting of university clusters was therefore more likely than of school or household clusters, and cases that arose during university vacations were unlikely to be ascertained. The relative risk of university clusters, however, was only slightly raised in the seven days after the index case, a time when the risk of a second case was highest in households and schools. Four of the 12 university clusters reported were 'different strain' clusters. This incidence pattern may be explained by sporadic disease, and further surveys are needed to quantify the risk in higher educational institutions¹⁵.

The relative risk of clusters in the school setting was considerably higher than calculated from a survey of school based clusters in the United States¹². In the American study clusters were confined to cases of the same serogroup. Relative risks were calculated by comparing monthly incidence in cluster schools with annual age specific attack rates. Applying these criteria in our study would have reduced the relative risk to a similar level. In our survey the relative risk of a subsequent case within one month of an index case was high, but the absolute risk of an individual in a school developing meningococcal disease was low and considerably lower than the equivalent risk to a household member.

Guidance introduced in England and Wales in November 1992 recommended that nursery contacts should be given chemoprophylaxis after one case in a nursery¹⁶. This guidance was based on one Belgian study in which four secondary cases occurred in two nurseries⁷. In our study, which was conducted after the policy changed, three clusters – two caused by different strains – were observed in nurseries. One additional cluster occurred at the end of the study period (index case March 1995, second case April 1995) in which two cases caused by indistinguishable group B strains arose within three weeks after giving antibiotics to all staff and children at the nursery¹⁷. Between 1989 and 1992, before the change in guidance, 149 primary cases and three associated cases (at intervals of two days, two months, and 10 months) were identified in 5725 nursery contacts in the 50% of health districts that responded (D Killalea, unpublished data). There was therefore no evidence that the risk had changed following the change in policy in 1992. Indeed the excess risk of further cases in nurseries appears to be very low in England and Wales with or without prophylaxis. Children of this age group are more likely to be carrying *N. lactamica* than *N. meningitidis*, and clearance of carriage in this setting may impair the development of immunity against meningococcal infection¹⁸. The guidance given in November 1992 was rescinded in 1995⁶.

Seven associated cases occurred in households after chemoprophylaxis was given, six after intervals of 16 to 28 days. Similar intervals between the occurrence of co-primary and further cases in the household have been observed following chemoprophylaxis in other studies^{8,12}; one hypothesis was that chemoprophylaxis simply postpones the onset of disease in household members. In this study, the number of co-primary cases (ten) in the household setting was similar to the number of associated cases one to 60 days after the index case (nine). If the findings from the Belgian study⁷ in which chemoprophylaxis was not given had applied, ten co-primary cases would have been followed by 13 cases in the first seven days, and another 10 in the eight to 60 day period. This contrasting experience does not support the postponed disease hypothesis and suggests that chemoprophylaxis may prevent about 50% of further cases within households. Similar findings and conclusions were reported from a Norwegian study on the effectiveness of giving a seven day course of oral penicillin to household contacts aged under 15 years¹⁹. Giving rifampicin to eradicate carriage or penicillin to treat early infection may have similar effectiveness in preventing further cases in the household. It would be useful to see further evaluation of the Norwegian policy but we see no reason on present evidence to change current policy in England and Wales. Since co-primary cases remain an important feature of household clusters, a diagnosis of meningococcal disease should prompt urgent enquiry about current illness in household contacts as well as chemoprophylaxis.

Acknowledgements

We would like to thank all the CCDCs who took time to provide detailed information for this study, the MRU Manchester PHL for providing data on confirmed cases, and Professors Keith Cartwright and Norman Noah for their helpful comments on the manuscript.

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