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Meningococcal disease at the University of Southampton: outbreak investigation

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SUMMARY

In October 1997, an outbreak of meningococcal disease occurred at the University of Southampton. All six cases were first year students living in halls of residence. Microbiological characterization of case and carrier strains, case interviews, and a meningococcal carriage prevalence survey were used to investigate the outbreak. Five cases were due to serogroup C strains, one case was unconfirmed. Serotyping did not distinguish between the strains but gene sequencing permitted identification of two distinct strains in the outbreak. Although none of the cases was known to each other, three had attended the same nightclub one evening 3–4 days before illness. Meningococcal carriage rates in undergraduates were within the range expected (147/587, 25%), but no carriers of outbreak strains were identified in this sample. The findings suggest that in communities with a high degree of social interaction, the introduction of highly virulent meningococcal strains may result in enhanced transmission with clustering of cases.

INTRODUCTION

The epidemiology of meningococcal disease in England and Wales has changed markedly in recent years. In 1997, notifications of meningococcal meningitis and septicaemia reached a provisional total of 2660, whereas average yearly notifications for the 5-year periods 1983–7, 1988–92 and 1993–7 were 665, 1363 and 1925 respectively (Office for National Statistics), a highly significant upward trend ($P < 0{\cdot}00001$). Since winter 1995/6, there has been an increase in the proportion of cases caused by serogroup C strains, the proportion in older children and adults [1, 2] and the number of school-based clusters of meningococcal disease [3].

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Several clusters have been reported in university settings. The largest were at the University of Wales, Cardiff in October/November 1996, in which 2 of 7 student cases died (Evans, unpublished report) and at the University of Southampton in October 1997, where 3 deaths occurred amongst 6 student cases. Both outbreaks were caused by serogroup C strains and were characterized by the short time interval between most cases, a high case fatality rate and extensive media coverage.

The University of Southampton outbreak comprised six cases of meningococcal disease that occurred over a 3-week period in October 1997. The university term started on 25 September. The first case was found dead on 11 October. Two weeks later, Cases 2–5 occurred in rapid succession, all four becoming ill between 26 and 27 October. The last case

was admitted to hospital on 30 October. All six cases occurred in first-year undergraduates aged between 18 and 19 years, living in University accommodation. Five were resident in the same accommodation complex (Wessex Lane Halls) consisting of 20 blocks of flats/rooms, although only two were resident in the same block. The sixth case was resident in a separate accommodation area some miles distant. Contact tracing for each case identified 117 total contacts; none of the cases or their close contacts was a close contact of any other case.

We describe the outbreak investigation and discuss implications of these findings.

METHODS

Definitions

Probable case. A case in which meningococcal meningitis or septicaemia was considered the likeliest diagnosis in the absence of microbiological confirmation [3].

Confirmed case. A case with a clinical diagnosis of meningococcal disease and microbiological confirmation of meningococcal infection [3].

Characterization of meningococci. *Neisseria meningitidis* isolates were characterized by the convention of serogroup:type:subtype. Isolates that could not be characterized or failed some aspect of characterization were identified as non-groupable (NG), non-typable (NT) or non-subtypable (NST).

Microbiology

Cases were confirmed by isolation of meningococci or detection of meningococcal DNA by polymerase chain reaction (PCR) from blood or CSF. Specimens were cultured using standard Public Health Laboratory Service (PHLS) operating procedures (B.SOPs 9, 27, 37, Technical Services PHLS HQ, Colindale, London). Pharyngeal swabs taken from university students and staff were inoculated immediately onto chocolate agar and modified New York City selective medium. The identity of potential meningococcal isolates was confirmed using an apiNH test system (BioMerieux s.a., Lyon, France). Isolates identified as *Neisseria meningitidis* were sent to the Meningococcal Reference Unit (MRU), Manchester PHL, for characterization of serogroup, type and subtype antigens. Detection of meningococcal DNA by PCR was also performed by the MRU.

For serogroup C isolates, DNA sequences of *porA* and *porB* genes, which determine subtype and type specificity respectively, were analysed at the National Institute for Biological Standards and Control, Potters Bar and the Wellcome Trust Centre for the Epidemiology of Infectious Disease at the University of Oxford.

Case investigation

Social activity of the cases in the 7 days prior to onset of illness was investigated. A questionnaire was formulated covering details of social events and places attended, the amount of time spent at each place, the level of overcrowding and smokiness. On 5 and 6 November 1997, the questionnaire was administered in person by a single researcher (A.G.) to the closest contacts of the three deceased cases and by telephone to the three surviving cases.

Carriage studies

Swabs were taken at three antibiotic/vaccination sessions on 28 October, 4 and 6 November 1997. On 28 October, swabs were taken from students as part of an existing university research project. On 4 and 6 November, posters and information leaflets requesting swabs were circulated and specimens taken from student and staff volunteers. All swabs were taken from the posterior pharyngeal wall by PHL staff. Participants were asked to complete a brief questionnaire giving details of year of study, course and faculty for students, job description for staff, age, address or hall of residence. In addition, pharyngeal swabs were taken from 21 close contacts of the first 2 cases. These were placed in transport medium, then plated and identified as described above.

Statistical analysis of carriage study

Data were entered twice for validation and single variable analysis performed using Epi-Info version 6.01b [4]. Age was categorized into four groups, and $2 \times n$ tables derived for all variables. Factors potentially associated with carriage were assessed using Yates' corrected χ^2 test, by comparing exposure between carriers and non-carriers. Those found to be significantly related ($P < 0{\cdot}05$) were incorporated into a multivariable model. Multivariable logistic

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regression was performed using the statistical package GLIM [5].

RESULTS

Outbreak control

Case 1 was managed as a single case [6]. Two weeks later, on 27 October, Cases 2 and 3 were reported from the same Wessex Lane accommodation complex (Table 1). By the morning of 28 October, Case 1 had been confirmed as serogroup C disease, Case 2 remained a probable case, and Case 3 was confirmed, serogroup unknown. The outbreak control team (comprising Health Authority, University and PHLS representatives) recommended offering prophylaxis (ciprofloxacin 500 mg and meningococcal A&C vaccine) immediately to all 1160 first-year students resident in the Wessex Lane Halls. Distribution of antibiotics commenced that afternoon, 28 October, at the same time as Cases 4 and 5, both within the defined target group for prophylaxis, were admitted to hospital.

Case 6, was admitted on the evening of Thursday 30 October with a clinical diagnosis of viral meningitis. Meningococcal disease was not confirmed until after her death on Sunday 2 November. Three students had now died and Case 6 had arisen in a student outside the original target group. At an emergency outbreak control team meeting, an extension of antibiotic prophylaxis and vaccination was recommended to include all first-year undergraduates and all students and staff living or working in halls of residence, an estimated additional 3300 students and 100 staff. The decision to include staff was not based on evidence of increased risk, but on the extreme levels of anxiety in this group. Antibiotic and vaccine distribution commenced on Monday 3 November. Across the widened target group of 4460 students, 4100 received antibiotics and 4086 vaccine, a coverage rate of 92%. No further cases of meningococcal disease occurred amongst this group during the remainder of the academic year.

The University also took the decision to offer immunization but not antibiotics to all other students and staff. This action reflected the wider concerns the University authorities had to take into account and was not recommended on public health grounds. The additional vaccination sessions commenced on Wednesday 5 November. A further 3800 people received immunization, out of an estimated potential 17500 (a 22% uptake rate).

Microbiology

Five cases were confirmed as due to serogroup C meningococcal infection. Cases 1, 3 and 6 were confirmed on culture, Cases 2 and 5 by PCR testing (Table 2). Case 4 was a probable case.

The isolate from Case 1 was characterized as C:2a:NST, and those from Cases 3 and 6 as C:NT:P1.5. Expression of serotype and serosubtype by the same strain can be intermittent, and given the close clustering in time, these strains were initially assumed to be the same. DNA sequencing for these isolates later showed that two distinct serogroup C strains were involved in this outbreak. The Case 3 and 6 isolates had identical *porA* and *porB* sequences, (designated the outbreak strain) that were different from those of the Case 1 isolate.

A pharyngeal swab taken from a contact, 2 days after performing mouth to mouth resuscitation on Case 1, grew meningococci genetically indistinguishable from the Case 1 isolate. Of 20 other close contacts of Cases 1 and 2 that were swabbed, only 2 were found to be carriers but neither was carrying the Case 1 nor outbreak strains.

Case investigation

The most notable finding of the case investigation was that although none of the cases or their close contacts were known to each other, Cases 2, 4 and 5 all attended nightclub X on the same night and became ill 3–4 days later (Table 1). The club was described as very crowded and smoky. All three had spent 4–6 h there. Although 4 cases had also visited Bar 1, the bar of their halls of residence, no 2 were definitely there at the same time. No other link was found between any of the cases.

Carriage study

A total of 646 swabs were taken, 86 (13·3%) on 28 October from students in the initial target group, 193 (29·9%) on 4 November and 367 (56·8%) on 6 November from students and staff of the expanded target group. Of all swabs, 634 (98·1%) were taken from students, of whom 587 (92·6%) were undergraduates. The overall carriage rate was 23·8% (154/646), 25% (147/587) in undergraduates and

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Table 1. *Details of cases and results of case investigation*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	19	18	18	19	19	18
Sex	F	F	M	M	M	F
Date of admission	N/A	27 Oct. 98	26 Oct. 98	28 Oct. 98	28 Oct. 98	30 Oct. 98
Date Health Authority informed	13 Oct. 98	27 Oct. 98 (a.m.)	27 Oct. 98 (p.m.)	28 Oct. 98	28 Oct. 98	31 Oct. 98
Outcome	Died 11 Oct. 97	Died 27 Oct. 97	Alive	Alive	Alive	Died 2 Nov. 97
Halls of residence*	A1 (self catering)	B (catered)	A2 (self catering)	A3 (self catering)	A2 (self catering)	C (catered)
Nightclub X						
Visited in 7 days before illness†	Y	Y	N	Y	Y	N
Date(s) visited (October 1997)‡	9	23		23	23	
Gap between visit and onset of symptoms (days)	1	3		4	4	
Bar 1 (Bars to Halls A1–3)						
Visited in 7 days before illness†	Y	N	Y	Y M	Y M	N
Date(s) visited (October 1997)‡	4, 5, 6, 7, 9		21, 22	23 (other dates)	20 (23)	
Gap between visit & onset of symptoms (days)	1–6		4–5	4	7 (4)	
Bar 2 (Bar to Hall B)						
Visited in 7 days before illness†	M	Y	N	N	N	N
Date(s) visited (October 1997)‡	(6)	22, 23, 25				
Gap between visit & onset of symptoms (days)	(4)	1–4				

* Halls A1–3 and B are part of the Wessex Lane Complex.

† Y = Yes; N = no; M = maybe.

‡ Parentheses used to indicate where there is uncertainty whether the venue was visited on that date.

Table 2. *Summary of microbiological data from cases*

Case	Antibiotics prior to admission	Isolation of meningococci			PCR result	Serological characterization	*porA* subtype sequence	*porB* type sequence
		CSF	Blood	Throat				
1	N	+	NA	NA	NA	C:2a:NST	5,2	2–36
2	Y	—	—	—	+	C	—	—
3	N	—	+	+	NA	C:NT:P1.5	5a,10d	2–37
4	Y	—	—	—	—	—	—	—
5	Y	—	—	—	+	C	—	—
6	Y	—	+	—	—	C:NT:P1.5	5a,10d	2–37

NA, not available; NT, non-typable; NST, non-subtypable.

Table 3. *Carriage rates by serogroup in undergraduates.*

Serogroup	B	C	29E	W135	X	Y	Z	NG	Total
Number of carriers									
First years	17	0	1	5	0	5	1	21	50
Second years	13	4	6	4	3	7	0	32	69
Third, fourth and fifth years	6	1	1	3	2	3	0	11	27
Total	36	5	8	12	5	15	1	65*	147*
Overall serogroup carriage rate (%) ($n = 587$)	6·1	0·9	1·4	2·0	0·9	2·6	0·2	11·1	25
Proportion of carriers positive for each serogroup (%)	24·5	3·4	5·4	8·2	3·4	10·2	0·7	44·2	100

* Includes one non-groupable carrier where year of study not specified.

Table 4. *Factors associated with meningococcal carriage in undergraduates: results of single variable analysis*

Factor	No. of carriers (% carriage)	No. of non-carriers	OR (95% CI)	*P* value
Age (years)				
17–18	23 (21·9)	82	1·00	< 0·001
19	57 (37·3)	96	2·12 (1·16–3·89)	
20	34 (24·1)	107	1·13 (0·6–2·16)	
21+	33 (17·6)	154	0·76 (0·4–1·45)	
Sex*				
Female	55 (19·8)	223	1·00	0·003
Male	92 (31·1)	204	1·83 (1·22–2·75)	
Year of study†				
1	50 (19·4)	208	1·00	0·01
2	69 (30·9)	154	1·86 (1·23–2·84)	
3, 4 or 5	27 (26·2)	76	1·48 (0·86–2·53)	
Date				
28 Oct. 97	13 (15·1)	73	1·00	0·008
4 Nov. 97	37 (21·3)	137	1·52 (0·76–3·03)	
6 Nov. 97	97 (29·7)	230	2·37 (1·25–4·47)	
Place of residence‡				
Living out	105 (28·8)	260	1·00	0·01
Living in	41 (18·9)	176	0·58 (0·37–0·89)	
Hall of residence				
Glen Eyre and New College	28 (21·5)	102	1·00	0·3
Wessex Lane	13 (14·9)	74	0·64 (0·29–1·39)	

* Data missing on 13 students.
† Data missing on 3 students.
‡ Data missing on 5 students.

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Table 5. *Factors associated with meningococcal carriage in undergraduates: results of multivariable analysis*

Factor	OR (95% CI)	*P* value
Age (years)		
17–18	1·00	< 0·001
19	1·38 (0·67–2·85)	
20	0·6 (0·27–1·32)	
21+	0·44 (0·21–0·93)	
Sex (male)	1·80 (1·19–2·71)	0·004

13·2% (5/38) in postgraduates. The mean age of carriers was significantly lower than that of non-carriers (20·0 *vs.* 21·9 years, $P = 0{\cdot}004$), the mode age of carriage being 19 (range 17–49 years).

The undergraduate carriage rates by serogroup are shown in Table 3. Five (3·4%) of the carriers identified were colonized with serogroup C strains. All five were second- and third-year undergraduates. None was carrying the Case 1 or outbreak strain (as confirmed by serological characterization and gene sequencing). There was no significant difference in serogroup carriage rate by year.

Carriage rates in undergraduates varied significantly with age, sex, year of study and date of specimen (Table 4). Carriage rates increased from the age of 17–19 years, decreasing thereafter, were higher in males than females ($P = 0{\cdot}003$) and in second-year than first-year students ($P = 0{\cdot}01$). Carriage rates increased over time and were significantly higher on the third sampling date than the first ($P = 0{\cdot}008$). Those living in halls of residence had significantly lower carriage rates than those living out ($P = 0{\cdot}01$). No significant difference in carriage rates was seen between students of different faculties or halls of residence.

Age, sex, date of swab, year of study and whether living in or out were incorporated in the multivariable model. Only age and sex remained significantly associated with carriage rate (Table 5). Carriage rates were significantly lower in those aged 21 years and over than in those aged 17–18 years, and in females compared with males.

DISCUSSION

Rapid microbiological results are essential to the successful and timely management of both individual cases and clusters of meningococcal disease. The decision to advocate immunization of all first-year students resident in Wessex Lane Halls was made on the basis of a single confirmed serogroup C culture from a case. Although this decision was supported by subsequent results, it would have been made easier had serogroup confirmation been available for the two other cases that had occurred by this stage. We re-emphasize the importance of the recommendation to collect a full range of specimens (including blood culture, throat swab and plasma for PCR) from all suspected cases on admission to hospital [7].

This is the first outbreak in this country where gene sequencing has been used to characterize outbreak strains. It highlights the value of this technique in distinguishing between strains that are difficult to differentiate phenotypically. Such results would be invaluable if available early in the course of outbreaks. The likely explanation of the results is that Case 1 was an isolated case due to a genetically distinct strain, which was followed 2 weeks later by an outbreak of five cases. Although detailed strain characterization was available for only 2 of these 5 cases, their close temporal relationship makes it highly likely that the same strain was responsible. Moreover, isolates from two geographically distant cases, linked to, but not part of the University outbreak, were genetically identical (M. Maiden et al., unpublished data). Close clustering of cases in time is typical of institutional outbreaks. In North America where genetic characterization of strains has been used for some time, outbreak isolates have generally been shown to be indistinguishable [8].

Carriage rates were within the expected range, peaked in young adults, declined thereafter, and were higher in males than females, consistent with previous studies [9–11]. No carriers of the outbreak strain were identified amongst the 646 people or 21 close contacts swabbed. Carriage of the Case 1 isolate in the contact performing mouth-to-mouth resuscitation is assumed to have followed the resuscitation. Low carriage rates of serogroup C outbreak strains have been observed in many serogroup C outbreaks, whether based in community [12], prison [13], school [9], (A. Rushdy, unpublished data) or university [14].

Explanations for the occurrence of outbreaks in the context of low carriage rates of the outbreak strain include high virulence of outbreak organisms, enhanced transmission of meningococci, and the clustering of susceptibles. The high case fatality rate in this and the University of Wales outbreaks, 50 and 28% respectively, compared with an average age specific case fatality rate over the 7-year period

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1989–95 of 13% in 15 to 24-year-olds [1] suggests high virulence of these organisms, although outbreak case numbers are low. In a Danish outbreak study, acquisition of the serogroup C outbreak strain was low despite frequent changes in carriage of other meningococcal strains [9]. However, in this and the University of Wales outbreak (M. Evans, unpublished data), low carriage rates of outbreak organisms and tight clustering of cases in time suggest a high acquisition rate. In the Welsh outbreak all seven cases formed part of a diffuse social network. Although the Southampton cases had no such links, the case investigation linked three cases to a nightclub. Overcrowding [15, 16] and passive smoking are recognized risk factors for both carriage [10, 17] and disease [18, 19]. A number of outbreaks have now been linked to similar settings and it has been suggested that the crowded and/or smoky environments of bars and nightclubs may facilitate transmission of meningococci [14, 20–22].

A recent review demonstrated significantly higher rates of meningococcal disease amongst UK university students compared with the general population of the same age [23]. Disease rates were shown to be highest in first-year students living in halls of residence and disease occurred predominantly in the first semester. The Southampton University outbreak was consistent with this pattern, yet our carriage study found lower carriage rates in first-year than second-year students. The predominance of disease amongst first-year students, despite higher carriage rates in second years, may indicate that immunity is lower and acquisition higher amongst first-year students. The higher rate of meningococcal disease among first-year university students in halls of residence may arise through a combination of clustering of non-immunes and increased exposure to different meningococcal strains consequent upon the rapid increase in intense socializing that accompanies a move to group residential living. For similar reasons, outbreaks may arise when highly virulent strains are introduced to these settings.

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