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Risk-factors for meningococcal disease in Victoria, Australia, in 1997

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SUMMARY

In Victoria between 1990 and 1996, meningococcal infections occurred in 1–2/100000 people each year, with sometimes devastating outcome. In 1997, a typical year, we conducted a case-control study of all cases notified to the State Disease Control Unit, to investigate personal, environmental and lifestyle risk factors. In bivariate analysis many exposures were statistically significantly different (at $P = 0{\cdot}01$) in cases and controls. The level of risk, and specific risks, differed between children (under 16) and adults (16 years and over). In multivariate analysis few exposures remained significant (at $P = 0{\cdot}05$). However, these included having a smoker amongst close contacts, exposure to construction dust, recent illness, a history of snoring and speech problems, and sharing a bedroom. Besides confirming some previously identified risk factors, this is the first time that snoring and speech problems have been identified as risk factors for meningococcal disease.

INTRODUCTION

Historically, descriptive studies largely attributed meningococcal disease to overcrowding, lack of ventilation, and poverty [1]. However, the few controlled studies that have been conducted have failed to support these early observations. Descriptive studies report higher attack rates in specific population groups, including young children and teenagers [2, 3], and family and close contacts of cases [4, 5]. Epidemics are known to occur periodically in defined geographic areas [6, 7], at specific times [3, 8], and in defined populations [2, 3, 5, 7, 9]. However, these studies do not address exposure to risk factors.

Controlled studies which have measured risk-factors for meningococcal disease have identified smokers, cigarette smoke, specific recreational venues (particularly bars and clubs), preceding influenza infection, mental and physical stress, and exposure to environmental dust [10–13] as significant exposures. Methodological concerns in some of these studies include unmatched study design, dissimiliar recruitment and interview methods for cases and controls, and the collection of data many months after the onset of disease. Few of these studies have examined the independent influence of these factors using multivariate analytical techniques.

Between 1990 and 1996, Victoria had a fairly consistent pattern of meningococcal disease, with about two-thirds of cases being attributable to serogroup B and one-third to serogroup C [14]. In the absence of a variance for population use, particularly in the prevention of serogroup B disease, we wished to identify local risk-factors to explore possible strategies for prevention campaigns based on health promotion.

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MATERIALS AND METHODS

A case-control study was designed to recruit all Victorian residents notified to the state disease control unit in 1997 with a microbiologically confirmed or probable clinical diagnosis of meningococcal disease according to previously defined criteria [15]. After seeking permission, cases were referred to the study immediately after notification.

The method of control selection was socio-geographic, with implicit socioeconomic as well as age and gender matching. Immediately after case recruitment, appropriate health and education professionals (maternal and child health nurses, head teachers and general practitioners) were asked to identify two controls, matched for age and gender, according to a strict protocol, and seek permission for the researcher to make contact. Alternative professionals were successfully approached for four who declined to participate.

We designed a model for development of meningococcal infection, in which the case must be susceptible to infection, be exposed to a meningococcus, and have damage to the nasopharynx so that invasion can take place. A pre-validated questionnaire [12] was adapted to our development of infection model for local use and piloted. Information was collected from all subjects about demographic characteristics; health status; the family, home and housing; exposure to smokers and smoke; dusts; and school, work and social activities during the 2 weeks prior to onset of disease in the case.

Because of the positive association between smoking and carriage [16], a smoker was defined as a person who had smoked at least one cigarette within the previous month. Exposure to cigarette smoke was defined as being in the presence of cigarette smoke for more than the length of time it took to pass a smoker in the street. Standing next to, or sitting with, smokers was considered exposed even if out of doors, whilst walking or running past was considered non-exposed. Alcoholic beverage intake was defined according to the Australian drug and alcohol standard measures [17]. Exposure to dust included visiting or working on a building site, or living in, on, or near a building site on an adjacent block, or a similar circumstance. Building trade workers were asked about contact with family members prior to bathing after work.

Oral muscle tone deficiencies were related to speech and pronounciation problems, snoring, mouth breathing and sleep dribbling. Speech and pronounciation problems were recorded as present if audible (including sound transpositions such as th for s, and missing hard consonants, especially at the ends of words, such a final k, d or t), or if the subject was currently receiving speech therapy. Snoring was recorded if it disrupted the sleep of the subject or other family member, and sleep dribbling was determined to be present if the sheet or pillow was usually wet on awaking.

To determine levels of crowding, room occupancy was calculated as the number of rooms in the dwelling divided by the number of inhabitants.

From first contact, subjects were informed of the nature of the interview (general health, lifestyle and recent family activities) and the time period of interest (the same 2-week exposure period was used for both cases and controls), in verbal and written communication. The case/control status of subjects was acknowledged, and incorporated in the interview structure by allowing time to discuss the reasons for agreeing to participate before the formal start of the interview. The same researcher (P. R.), who was not blinded to the status of the subjects, conducted all interviews, all but six within a month of date of onset. Validation techniques included the use of the Child Health Record, and school diaries and calendars. As far as practical, the case and matched controls were interviewed on the same day, in an order based on geographical practicalities. Where exposures were equivocal, cases were considered to be unexposed and controls exposed.

Australian Bureau of Statistics (ABS) occupational categories were collapsed into four main groups (managerial and professional; paraprofessional and skilled trades; office and service industries; and labourers, plant and machine operators and unskilled workers) [18]. Unemployed and retired people, and children and school students were designated as separate categories for analytical purposes.

At interview, a blood sample was collected and assayed for influenza antibodies. Sera were assayed against four reference antigens that were representative of influenza virus strains known to be prevalent locally and internationally during the period of the study, and one control strain. Antigens were prepared using standard methods [19].

A relational database was constructed in Microsoft Access 97 SR2 [20] and data exported to the STATA release 6 package [21] for statistical analysis. A matched analysis of exposures of interest using conditional logistic regression was performed and

comparisons of categorical and ordinal data between cases and controls were made using χ^2 statistics and signed rank tests. The formula for attributable fraction [(RR − 1)/RR], where RR (relative risk) = (incidence rate in exposed group/incidence rate in unexposed group) was applied for calculating fractions of disease in smokers attributable to smoking, using published data on smoking and smokers in Victoria in 1995 [22].

Eight areas of potential stress (deaths or illness in close friends and relatives, changes in lifestyle, personal habits or relationships, holidays, financial changes or law problems) were self-assessed in private using a visual analogue score, and subjected to a standard factor analysis. Factors with an eigenvalue greater than 1·0 were rotated, and uniqueness scores and Cronbach α reliability coefficient assessed before generating individual scores.

The study was designed to detect an odds ratio of at least 2 with a power of 80% and a significance level of 0·05, in a minimum of 63 cases with 2 controls per case (assuming at least a 15% exposure rate amongst controls). As some exposures were only relevant for either children or adults, subjects were stratified by age (children under 16 years and adults 16 years and over). Because of the large number of bivariate analyses undertaken, statistical significance was set at the 0·01 level. Variables with significance levels of 0·01 were included in conditional logistic regression models. A 0·05 level was used to define significance in the multivariate analyses.

RESULTS

The final study sample consisted of 87 cases (95% of eligible cases) and 174 controls (92% of those originally approached). Meningococcal disease was microbiologically confirmed in 62 cases (68%) (42 serogroup B, 9 serogroup C, 4 non-groupable and 7 microscopically confirmed), and the remaining 29 (32%) were clinical cases. Responses were obtained for all variables except for stress scores for 1 control, and blood specimens were not available for 11 cases and 18 controls. Comparison of confirmed and clinically diagnosed cases did not identify any variables in which there was a significant difference, and they were combined for the remainder of the analysis.

Cases and controls were similar in age, ethnic group, and religious belief. The work profile of adult cases and the fathers of child cases, and their controls, was similar to each other and to that of the Victorian working population.

Personal health risk factors

Child cases were more likely to be reported by parents to have had a recent illness (mainly respiratory infections), and were twice as likely to have had influenza. A similar proportion of cases (26%) and controls (22%) had consulted the family doctor in the 2 weeks before onset of disease in the case. The recent use of medications was similar, whilst a history of atopy and use of asthma inhalers or steroids was less likely in case compared with control children. Amongst infants under the age of 2 years, cases were much less likely to be currently breast fed (either exclusively or at all), although childhood immunization status was similar. A history of oral muscle tone deficiency was significantly more likely to reported by the parents of child cases. Three case children, compared with no control children, were smokers. Exposure to glues and other solvents in household contexts was similar in child cases and controls.

Adult cases were also more likely to report a recent illness. These were of a wide variety and included a range of operative procedures and fractures, as well as respiratory infections, including influenza. There was no significant difference in the recent use of medications, including asthma inhalers or steroids, although adult cases were more likely to have taken prescribed antibodies (23% compared with 8%) and cough mixtures (15% of cases compared with no controls), and were significantly more likely to self-report oral muscle tone deficiency.

Adult cases were more likely to smoke than their controls, and compared with the Victorian population, although stratification by gender identified a statistically significant difference only for women. In Victoria an estimated 23% of females and 27% of males 16 and over were smokers. In this study, 18 of the 40 adult cases were smokers, 12 of the 24 women and 6 of the 16 men. The fraction of disease in smokers attributable to smoking was 59%, but was much higher in women (at 70%) than men (at 38%). Although marijuana use was similar in cases and controls, the use of bongs (water pipes) was more common in cases (4 of 5 compared with 2 of 8). Alcohol consumption patterns were similar and cases were no more likely to report inebriation.

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Table 1. *Personal, environmental, and lifestyle risk factors for meningococcal infection, univariate analysis*

	Subjects < 16 yrs					Subjects ⩾ 16 yrs				
Risk factors	Cases $n = 47$ (%)	Controls $n = 94$ (%)	OR	95% CI	P	Cases $n = 40$ (%)	Controls $n = 80$ (%)	OR	95% CI	P
Personal health risk factors										
Any illness last 2 weeks	26 (55)	33 (35)	2·5	1·2, 5·3	0·02	21 (52)	20 (25)	3·4	1·4, 7·9	< 0·01
Any URTI/'flu last 2 weeks	16 (34)	22 (23)	2·4	1·0, 5·3	0·09	8 (20)	9 (11)	2·2	0·7, 7·1	< 0·01
1997 influenza vaccination	0 (0)	1 (1)	—	—		2 (5)	8 (10)	0·3	> 0·1, 2·8	0·25
Unimmunized and definite influenza infection*	15/42 (36)	17/78 (22)	2·0	0·9, 4·9	0·11	9/34 (26)	17/69 (25)	0·9	0·3, 2·3	0·81
Breast fed at all (< 2 years; 25 cases, 50 controls	3 (12)	14 (28)	0·2	0·1, 1·2	0·05	—	—	—	—	—
Oral muscle tone deficiency	27 (68)	35 (44)	2·1	1·0, 4·5	0·06	26 (55)	36 (38)	2·8	1·2, 6·5	0·02
Solvent use/exposure last (2 weeks)	6 (13)	8 (9)	1·6	0·5, 4·7	0·44	14 (35)	22 (28)	1·7	0·6, 4·7	0·30
Smoker	3 (6)	0				18(45)	26(33)	2·2	0·8, 5·8	0·11
Regular alcohol drinker (⩾ last month)	2 (4)	2 (2)	2·7	0·2, 33·0	0·42	32 (80)	54 (68)	4·0	0·9, 18·6	0·04
Environmental exposures										
Concrete, construction, or bush dust exposure, last 2 weeks	30 (64)	32 (34)	3·4	1·6, 7·0	< 0·01	26 (65)	34 (43)	2·4	1·1, 5·3	0·03
Participated in smoky indoor activities	20 (47)	14 (15)	1·7	1·1, 2·5	< 0·01	30 (75)	45 (66)	1·1	1·0, 1·2	0·16
Smoker amongst intimate contacts (parent or partner)	38 (81)	37 (39)	5·7	2·5, 13·3	< 0·01	15 (53)	18 (33)	4·7	1·3, 17·4	< 0·01
Daily median (range) cigarettes smoked nearby	Cases 0 (0–73·5)		Controls 0 (0–34·5)		0·05	Cases 3 (0–50)		Controls 1 (0–59·5)		0·03
Total (median, range) contacts who share drink cans, kiss, etc	Cases 6 (1–33)		Controls 4 (0–18)		0·02	Cases 4 (0–14)		Controls 4 (0–16)		0·27
Lifestyle risk factors										
Number in household (median, range) including subject	Cases 4 (3–12)		Controls 4 (3–8)		0·03	Cases 3·5 (1–8)		Controls 4 (1–10)		0·03
Number of people (median, range) per room	Cases 0·8 (0·4–2·4)		Controls 0·7 (0·4–1·3)		< 0·01	Cases 0·60 (0·22–5·0)		Controls 0·6 (0·2–2·0)		0·38
Normally shares a bedroom	25 (53)	30 (32)	2·78	1·3, 6·1	< 0·01	25 (63)	42 (53)	2·7	0·8, 9·5	0·10
Normally shares a bed with another person > 15 min night	12 (26)	23 (24)	1·06	0·5, 2·4	0·89	24 (60)	41 (51)	1·9	0·7, 5·6	0·22
Slept away from home last, 2 weeks	14 (30)	22 (23)	1·36	0·6, 2·9	0·43	20 (50)	25 (31)	2·1	1·0, 4·6	0·05
Aerobic activity during last 2 weeks	14 (30)	18 (19)	2·42	0·9, 6·8	0·09	14 (35)	35 (44)	0·6	0·2, 1·5	0·26
Regular contact with any pets	36 (77)	66 (70)	1·46	0·6, 3·5	0·39	28 (70)	59 (74)	0·8	0·3, 2·0	0·63
Owns family home	29 (62)	77 (82)	0·31	0·1, 0·8	< 0·01	33 (83)	69 (86)	0·7	0·2, 2·3	0·51

* Blood specimens were available for 232 subjects, 76 cases and 156 controls ($P = 0·73$). specimens were unavailable for a number of reasons (cases who had died, refusal by adult subject, refusal by children despite parental consent. There was no significant difference in the geometric mean titres between the case and control groups.

Table 2. *Multivariate analysis of exposures associated with meningococcal infection in children under 16, adults 16 and over, and all cases*

	Under 16 ($n = 47$)		16 years and over ($n = 40$)		All cases ($n = 87$)	
Risk factor	OR	95% CI, *P*-value	OR	95% CI, *P*-value	OR	95% CI, *P*-value
Smoker amongst intimate contacts	11·3	3·2, 39·9 (< 0·01)	1·84	0·6, 5·7 (0·29)	3·7	1·9, 7·5 (< 0·01)
Contact with building or bush dusts in prior 2 weeks	8·5	2·6, 28·1 (< 0·01)	3·60	1·2, 10·7 (0·02)	2·9	1·5, 5·4 (< 0·01)
Normally shares bedroom	5·4	1·7, 17·5 (< 0·01)	1·37	0·3, 6·2 (0·68)	2·7	1·2, 6·0 (0·01)
Any illness in prior 2 weeks	4·4	1·4, 14·3 (0·014)	3·41	1·3, 9·3 (0·02)	3·3	1·7, 6·6 (< 0·01)
Oral muscle tone deficiency	1·5	0·5, 4·4 (0·49)	3·53	1·3, 9·5 (0·01)	2·5	1·2, 4·9 (0·01)

Information about varicella and herpes virus infections was not specifically sought, however it is notable that 5 child and 11 adult cases had a coincidental infection for which antiviral therapy was prescribed (chicken pox, herpes zoster or herpatic gingivostomatitis). No controls mentioned such infections, which should have been identified by the questionnaire schedule. No difference in stress scores could be detected between cases and controls in either the families of children or in adults.

Environmental exposures

Child cases were significantly more likely than controls to have been exposed to construction dusts, smokers, and cigarette smoke, were far more likely to reside with smoker parents and to have other regular social contacts who were smokers. Case children were also significantly more likely to have been exposed to cigarette smoke in indoor settings away from home, and whilst 60% of case and 50% of control children had been taken to a café, the parents of case children were more likely to recall it a smoky, commenting on the difficulty of finding a smoke-free venue.

In adults, a significant increase in dust exposure in cases was associated with construction dusts (particularly wood and sawdust) but not bush dusts. Having an intimate partner (spouse or boy/girl friend) who smoked was more common in adult cases, as was exposure to cigarette smoke. Adult cases were significantly more likely to have visited a pub or club compared with controls.

Overall, child and adult cases and controls nominated a similar number of close contacts who kissed on the mouth. However, more cases than controls exchanged saliva with other people by using common equipment (such as drinking cups, water bottles, soft drink cans, smoking equipment such as cigarettes and bongs (water pipes), and dummies and babies bottles).

Lifestyle risk-factors

The construction of the homes of cases and controls was alike. However, whilst the living conditions of adult cases and controls were similar, the families of child cases had more people per room, the child was commonly shared a bedroom, and the family was less likely to own the home.

Cases were more likely to have stayed away from home than controls, but contact with pets, farm animals and wildlife was similar. Most subjects had taken part in a variety of social activities in the 2 weeks before onset of disease in the case. Both the type of recent activity (from sedentary occupations such as cinema visits, painting and knitting, and clubs such as scouts, to aerobic sports activities) and the amount of activity compared to usual, was similar in both cases and controls.

Table 1 summarizes bivariate statistics in cases and controls, for children and adults, for key personal health variables, environmental exposures and lifestyle risk factors.

Multivariate analysis

The exposures that were significant at $P = 0{\cdot}01$ level in univariate analysis were entered into a multivariate conditional logistic regression in order to examine their independent effect, in child and adult cases, and overall. The model that best fitted exposures in both children and adults is presented in Table 2. The model that best reflected statistically significant exposures in all cases included exposure to smokers amongst close contacts, exposure to building and bush dusts, recent

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illness, sharing a bedroom, oral muscle tone deficiency and renting the home.

DISCUSSION

This study included 95% of Victorian cases of invasive meningococcal disease in a typical year, and control selection was usually carried out according to the study protocol, minimizing recruitment bias. The demographic profile of cases and controls was very similar, and the age, sex distribution and microbiologically confirmed serogroup distribution of cases was as expected. This was an excellent group with which to study local risk-factors.

Recall bias was minimized by using several techniques. The time period for environmental exposures was identical for cases and their controls, and was identified to all subjects at the time of recruitment, within a few days of diagnosis. Almost all interviews were completed within a month of onset in the case. The information sought was either collected from diaries, identified established health and lifestyle patterns, or was about major recent events. Conducting interviews in the subjects' own homes afforded a degree of immediate validation of some information (particularly smoking status and construction dusts exposure), and enabled other data sources such as diaries to be accessed. During pre-interview discussion, many subjects said that had been given or sought information about meningococcal disease, which was reviewed for content to assess the potential for response bias. Website, hospital and health department materials mainly described diagnostic features and sequelae, whilst the media provided 'human interest' stories; risk-factors were ignored.

In our study, there were important differences in risk-factors between children and adults cases and their controls in recent health events, environmental exposures and lifestyle.

The overall increased risk associated with exposure to smokers, has been noted before [10, 12–13], although not in Australia. Although we identified an attributable fraction of 59% of disease in adult smokers, after stratification by sex, the doubling of risk identified in smokers only remained statistically significant for women. Attributable risks are only considered valid if there are no confounding effects, which is not true in this study as in multivariate analysis, smoking in adults did not remain a statistically significant risk-factor. In multivariate analysis whilst exposure to smokers was a significant risk-factor overall, and in children carried an odds ratio of 11·3, it was not significant in adults despite an odds ratio of 1·8. As this study was not powered to identify increased risks in the stratified groups, this question should be revisited in a larger adult case series.

Dust exposure was noted as a significant risk-factor in one previous study and [12]. It is notable that the major outbreaks of meningococcal disease occur in desert locations and in association with dust storms [8, 23]. In Australia population attack-rates are highest in the Northern Territory [24], an area consisting largely of desert with few sealed roads away from main highways. Dust exposure may damage the nasopharyngeal surfaces at the time of exposure to a meningococcus. Oral muscle tone deficiency may also facilitate bacterial adherence or increase the potential for nasopharygeal damage.

This is the first study to collect blood specimens for laboratory evidence of influenza infections as well as recent health data from the same individuals. All cases were more likely to have experienced recent illness than controls. In univariate analysis, whilst confirmed influenza infection was double in case children compared with controls (although failing to reach statistical significance), it was similar in unimmunized adult cases. The increase of influenza immunization in adults cases from 5% to 10% of controls suggests that immunization might be protective. A larger study to investigate specifically the potentially protective effect of influenza immunization would be an important contribution to understanding in this area. The association between respiratory syncytial virus has been demonstrated not to be associated with subsequent meningococcal infection [25], and no other potential associations with preceding viral infections have been reported. We conclude that influenza infection may be one of a variety of infections which sometimes precede and possibly facilitate invasive meningococcal infection.

The only lifestyle factor to be increased significantly in cases was an increase in visits to smoky cafés, bars and clubs. Although there were significantly more people per room in case households, at more than one room per person this cannot be described as overcrowding. It is interesting that cases came from larger households and were significantly more likely to share a bedroom than controls, confirming the findings of Stanwell-Smith et al. [12]. This is consistent with a disease associated with close contact with other people, rather than crowding *per se*; it is more likely

to occur in crowded populations, from refugees to bar patrons, simply because there are increased opportunities for transmission.

Our model for the development of meningococcal infection included susceptibility to infection (provided by recent illness), exposure to meningococci (increased intimate association with smokers, sharing a bedroom) and nasopharygeal damage (dust exposure, recent upper respiratory infections and oral muscle tone deficiency). We have identified significant independent exposures in all these areas.

This is the first controlled study to identify differences in risk-factors between children and adults. This study strengthens previous evidence of the more than threefold increased risk of disease in people who are exposed to smokers, especially for children, and confirms that specific types of dusts exposure constitute an environmental risk-factor. Lastly, this study it is the first which suggests that a history of oral muscle tone deficiency is a risk factor for meningococcal disease.

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