RISK FACTORS FOR MENINGOCOCCAL DISEASE IN CAPE TOWN

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Objective. To determine the risk factors associated with meningococcal disease among children living in Cape Town.

Design. A case-control study was conducted from October 1993 to January 1995.

Setting. The study population consisted of all children under the age of 14 years who were resident in the Cape Town metropolitan region. Cases and controls were selected from Red Cross War Memorial Children's Hospital.

Results. A total of 70 cases and 210 controls were interviewed. Significant risk factors for meningococcal disease included being breast-fed for less than 3 months (adjusted odds ratio (OR) 2.4); overcrowding (adjusted OR 2.3); and age less than 4 years (adjusted OR 2.3). Exposure to two or more household members who smoked was also a risk factor, but only in the presence of a recent upper respiratory tract infection (adjusted OR 5.0).

Conclusion. This is the first case-control study in South Africa examining risk factors for meningococcal disease. It provides further evidence for reduction of smoking, reduction of overcrowding and promotion of breast-feeding as important public health measures.

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Neisseria meningitidis is an important cause of morbidity and mortality in South Africa.[1] A review of the notification reports for the past few years revealed that children under 5 years are the most severely affected, the case fatality ratio remains high, and the highest incidence by region has been in the Western Cape.[2-4] The incidence in the Western Cape for the period 1983 to 1988 was consistently more than twice that for any other region in South Africa.[4]

The majority of infections in South Africa are due to serogroup B.[5-7] This serogroup has a relatively non-immunogenic polysaccharide capsule. Although several outer membrane protein-based serogroup B meningococcal vaccines have been developed and evaluated, a highly immunogenic vaccine is not yet available.[8-10] The recently developed Cuban vaccine was initially thought to be efficacious in all age groups.[11] However, recent studies have shown that while the vaccine may be effective in older children, it has a low efficacy in children younger than 4 years[12,13] — the age group with the highest incidence of serogroup B.

In the absence of a vaccine, identification, prevention and elimination of risk factors for meningococcal disease is one way of decreasing the incidence of the disease. Symptom-free nasopharyngeal carriers are considered the usual source of infection.[14] However, studies have shown that the incidence of disease does not appear to be a function of the prevalence of carriers.[14] Additional factors are believed to be important determinants of disease.[15] Factors implicated elsewhere as determinants of meningococcal disease include overcrowded accommodation,[16,17] close contact with a confirmed case,[16,18] lower socio-economic status,[19] climate,[16] complement deficiency,[20,21] stressful events[22] and, recently, passive smoking.[16,19,22,23] The aim of this study was to determine the risk factors associated with meningococcal disease among children living in Cape Town.

METHODS

A case-control study was conducted between October 1993 and January 1995. The study population consisted of all children under the age of 14 years who were resident in the Cape Town metropolitan region for 6 months or more.

Any child under 14 years residing in the above area was designated a definite case if *N. meningitidis* was isolated from the blood or cerebrospinal fluid (CSF), or if clinical signs of meningitis or septicaemia were accompanied by a haemorrhagic rash and Gram-negative diplococci were detected in the CSF. A probable case was designated if clinical signs of meningitis or septicaemia were accompanied by a haemorrhagic rash, but *N. meningitidis* was not isolated from culture or a Gram stain. Cases were identified using a combination of the passive statutory notification system and an active surveillance system consisting of daily scrutiny of admission registers at Red Cross War Memorial Children's Hospital and at City Hospital for Infectious Diseases.

Controls were selected from the trauma wards at Red Cross War Memorial Children's Hospital. Three controls were selected for each case within 3 months of ascertaining the corresponding case.

Interviewers, trained by the authors, elicited exposure histories and other relevant information from the parents or guardians of the patients using a pretested questionnaire. Household living density was measured in terms of a household crowding index, defined as the number of equivalent persons per number of sleeping rooms.[24] A child 10 years or younger was considered half an equivalent person,

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and anyone older than 10 years an equivalent person. A crowding index of greater than 2.5 was taken as an indication of overcrowding. A child was considered to have been exposed to cigarette smoke if a household member smoked. Nutritional status was measured in terms of weight for age. The growth reference charts developed by the National Center for Health Statistics and Centers for Disease Control (the 1976 NCHS charts) were used and the cut-off point to determine nutritional status was the median minus 2 standard deviations (SDs). Poor nutritional status was therefore defined as a weight-for-age Z value of less than –2.0. Recent antibiotic use was defined as a history of any antibiotic use in the preceding month. Upper respiratory tract infection (URTI) was defined as a runny or stuffy nose in the preceding month. Duration of breast-feeding was measured as a categorical variable. The following categories were used: not breast-fed, breast-fed for < 3 months, breast-fed for ≥ 3 months. Type of dwelling was recorded as brick house, apartment/flat, shack, tent, prefabricated building, or other.

A 5% random subsample was selected for repeatability testing of the measuring instrument. Different interviewers were used during the repeat interviews.

Informed consent was obtained from the parents or guardians of all children, and approval for the study was obtained from the Ethics Committee of the University of Cape Town.

ANALYSIS

Analysis was done using SAS (version 6) statistical software. The chi-square test was used to test for significant differences ($P < 0.05$) between categorical variables. For numerical variables either the t-test or the Wilcoxon sum of ranks test was used to test for significant differences ($P < 0.05$). The role of possible effect-modifying variables was examined by stratified analysis. The Breslow-Day test was used to assess the homogeneity of the ORs across strata. Multiple logistic regression was performed to determine the adjusted ORs.

Crude ORs, adjusted ORs and 95% confidence intervals (CIs) are reported.

RESULTS

Information was collected on 70 cases and 210 controls. There were 35 definite cases and 35 probable cases. All cases were analysed together. The interviewee was the parent for 91% of cases and 81% of controls ($P = 0.06$). The percentage agreement between the initial and repeat interviews for the questions relating to the number of people per household was 92%; for the number of rooms it was 83%; and for the number of smokers it was 75%.

The median age of the cases was 27 months and that of the controls 60 months ($P = 0.0001$). There was a male predominance among cases (64%) and controls (65%). The residential distribution was similar in both cases and controls, and the majority of cases (66%) and controls (69%) lived in brick houses.

Risk factors for meningococcal disease are summarised in Table I. On univariate analysis significant risk factors included being breast-fed for less than 3 months, overcrowding, poor nutritional status, a household where two or more members smoked, and recent URTI.

Stratified analysis showed that the association between exposure to cigarette smoke and meningococcal disease was modified by the presence of an URTI. The OR for meningococcal disease if there were two or more smokers per household and a history of a recent URTI was 3.1 compared with an OR of 0.9 if there was no history of a recent URTI. The OR for meningococcal disease if the main caregiver smoked and there was recent exposure to an URTI was 3.1; this decreased to 1.0 in the absence of a recent URTI.

A multiple logistic regression model was fitted with the following variables: overcrowding, nutritional status, age, breast-feeding, exposure to two or more household smokers, a recent URTI, and the URTI interaction with two or more household smokers. The results are summarised in Table II.

Table I. Risk factors for meningococcal disease

Variable	Cases		Controls		P-value	Crude OR	95% CI
	%	N	%	N			
Recent URTI	59	40	45	91	0.043	1.8	1.0 - 3.1
At a creche	25	13	18	22	0.283	1.5	0.7 - 3.6
Recent antibiotics	36	25	39	78	0.626	0.9	0.5 - 1.5
Nutritional status WAZ < –2.0	10	06	2.9	06	0.033	3.6	1.1 - 11.7
Breast-fed < 3 mo.	47	33	25	47	0.001	2.7	1.5 - 5.0
Crowding index > 2.5	29	20	12	26	0.002	2.8	1.5 - 5.5
> 2 smokers/household	59	40	45	94	0.044	1.8	1.0 - 3.0
Main caregiver smokes	52	35	39	82	0.065	1.7	1.0 - 3.0

WAZ = weight-for-age Z value.

Table II. Results of logistic regression model

Variable	Adjusted OR	95% CI
> 2 smokers/household	0.7	0.2 - 1.5
Breast-fed < 3 mo.	2.4	1.3 - 4.4
Crowding index > 2.5	2.3	1.0 - 5.3
WAZ < –2.0	2.0	0.5 - 8.4
Age < 48 months	2.3	1.2 - 4.4
Recent URTI	0.7	0.3 - 1.8
Interaction: URTI and smoke exposure	3.6	1.4 - 17.3

WAZ = weight-for-age Z value.

DISCUSSION

Prolonged breast-feeding has been found to protect infants against respiratory disease in general.[25] This is thought to be due to the transmission of specific human immunoglobulins in breast-milk, which improves the immunological defence mechanism of infants.[26] A study in Gambia has suggested that breast-feeding may protect infants against meningococcal disease.[27] Our study, unlike the study by Stanwell-Smith *et al.*,[23] confirmed this postulate.

An increased risk of meningococcal disease has been reported following close contact with a confirmed case of the disease.[18] In our study we attempted, during the interview with the parent or guardian, to determine whether there had been such contact. However, this measure proved to be unreliable and for this reason contact with a confirmed case was omitted as a variable during analysis. Future studies need to obtain definitive evidence regarding contact with a true case of meningococcal disease.

Our results support the findings of other studies that overcrowding is associated with meningococcal disease.[17,23] Recent antibiotic use, type of dwelling and nutritional status were not associated with meningococcal disease.

Passive smoking is known to be associated with an increased risk of respiratory disease in young children.[28-31] Cigarette smoke interferes with ciliary action, increases mucus production and decreases macrophage production, thereby decreasing the body's local defence against potential pathogens.[32] In our study more cases than controls had main caregivers who smoked; however this difference was not statistically significant. Significantly more cases than controls came from homes with two or more smokers, but after adjusting for confounders, exposure to two or more household smokers was no longer associated with meningococcal disease. In our study the prevalence of household smoking was high for both cases and controls. Lack of statistical power may therefore explain our findings, rather than a true lack of effect.

Previous studies have implicated viral URTI as a co-factor and an association between influenza type A and meningococcal disease.[33,34] In our study the main force of passive smoking as a risk factor for meningococcal disease appears to be in the presence of a recent URTI. A possible explanation is that a recent URTI could denude the mucosa, and that this together with the decreased local defences due to the action of cigarette smoke on the mucosa, would increase the chances of invasion by the meningococcal organism even further. Further studies are needed to examine the association between passive smoking, URTI and meningococcal disease. The definition of URTI used in this study could have resulted in children with nasal allergy being labelled as having an URTI. Future studies must therefore consider a more specific definition for an URTI.

The selection of an appropriate comparison group is perhaps the most critical issue in the design of a case-control study. A crucial requirement is that the controls be comparable to the source population of the cases.[35] In our study both cases and controls were selected from the regional paediatric referral hospital; therefore the principle of comparability of study base is unlikely to have been violated. Controls were selected from the trauma wards so as to avoid any Berkson's bias.[36] Although cases were significantly younger than the controls, the difference was adjusted for during the logistic regression.

Information about exposure status and other variables of interest were obtained by interviews. Interviewers were blinded to the hypothesis to minimise the possibility of observation bias. Risk factors for meningococcal disease are not widely known and since both cases and controls were in hospital, differential recall bias is unlikely.

It is possible that misclassification of smoking exposure status could have occurred. If this did occur it is likely to have been a random misclassification. In general random misclassification reduces the chances of observing any difference between meningococcal disease in exposed and unexposed subjects.[37] In our study it was not financially feasible to measure biological markers of smoking exposure. A questionnaire investigating exposure to passive smoking combined with the use of biological markers, e.g. urinary cotinine, would perhaps offer the best method for accurate assessment of exposure to passive smoking.[38]

This is the first case-control study to examine risk factors for meningococcal disease in South Africa. The study provides further evidence for the promotion of breast-feeding and reduction of overcrowding as important public health measures. Children under the age of 4 have also been identified as an important target group, should an effective vaccine become available. Passive smoking was found to be an independent risk factor for meningococcal disease among those who had had a recent URTI. Although tentative, this finding adds weight to the evidence that passive smoking is harmful to human health. Passive smoking is a risk factor that should be given greater attention in further studies on meningococcal disease.

References

1. Ferrinho P, Buch E, Reinach SG. Mortality due to meningococcal infection in South Africa, 1968 - 1986. *S Afr J Epidemiol Infect* 1993; **8**(2): 52-54.

2. Department of National Health and Population Development (DNHPD). Notifiable Medical Conditions. *Epidemiological Comments* 1995; **22**(2): 41-42.

3. DNHPD. Meningococcal infection update. *Epidemiological Comments* 1989; **16**(5): 13-17.

4. DNHPD. Meningococcal infection. *Epidemiological Comments* 1985; **12**(1): 13-21.

5. Donald PR, Burger PJ, Van Zyl LE. Meningococcal disease at Tygerberg Hospital. *S Afr Med J* 1981; **60**: 271-275.

6. Potter PC, Donald PR, Moodie J, Slater C, Kibel MA. Meningitis in Cape Town children. *S Afr Med J* 1984; **66**: 759-763.

7. Ryder PC, Beatty DW, de V Heese H. Group B meningococcal infection in children during an epidemic in Cape Town, South Africa. *Ann Trop Paediatr* 1987; **7**: 47-53.

8. Frasch CE, Coetzee GJ, Zahradnik JM, Feldman HA, Koornhof HJ. Development and evaluation of a group B serotype 2 protein vaccine: report of a group B field trial. *Med Trop* 1983; **43**: 177-183.

9. Zollinger WD, Boslego J, Morgan E, *et al.* Meningococcal serogroup B vaccine protection trial and follow-up studies in Chile. *NIPH Ann* 1991; **14**: 211-213.

10. Bjune G, Hiby EA, Gronnesby JK, Arnesen O. Effect of an outer membrane vesicle vaccine against serogroup B meningococcal disease in Norway. *Lancet* 1991; **338**: 1093-1096.

11. Sierra GVG, Campa HC, Varcacel NW, *et al.* Vaccine against Gram negative *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. *NIPH Ann* 1991; **14**: 195-207.

12. De Moraes JC, Perkins BA, Camargo MCC, *et al.* Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil. *Lancet* 1992; **340**: 1074-1078.

13. Noronha CP, Struchiner CJ, Halloran ME. Assessment of the direct effectiveness of BC meningococcal vaccine in Rio de Janeiro, Brazil: A case-control study. *Int J Epidemiol* 1995; **24**(5): 1050-1057.

14. Broome CV. The carrier state: *Neisseria meningitidis*. *J Antimicrob Chemother* 1986; **18**: suppl A, 25-34.

15. Fraser PK, Bailey GK, Abbot JD. The meningococcal carrier-rate. *Lancet* 1973; **1**: 1235-1237.

16. Schwartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. *Clin Microbiol Rev* 1989; **2**: S118-S124.

17. Kaiser AB, Hennekens CH, Saslaw MS, Hayers PS, Bennet JV. Sero-epidemiology and chemoprophylaxis of disease due to sulphonamide resistant *Neisseria meningitidis* in a civilian population. *J Infect Dis* 1974; **130**: 217-224.

18. Munford RS, Taunay ADE, Morais JSD, Fraser DW, Feldman FA. Spread of meningococcal infection in households. *Lancet* 1974; **1**: 1275.

19. Stuart JM, Cartwright KAV, Dawson JA, Rickard J, Noah ND. Risk factors for meningococcal disease: a case control study in south west England. *Community Med* 1988; **10**: 139-146.

20. Ellison RT, Kohler PF, Curd JG, Judson FN, Reller LB. Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. *N Engl J Med* 1983; **308**: 913-916.

21. Braconier JH, Sjoholm AG, Soderstrom C. Fulminant meningococcal infections in a family with inherited deficiency of properdin. *Scand J Infect Dis* 1983; **15**: 339-345.

22. Haneberg B, Tonjum T, Rodahl K, Gedde-Dahl TW. Factors preceding the onset of meningococcal disease with special emphasis on passive smoking, stressful events, physical fitness and general symptoms of ill health. *NIPH Ann* 1983; **6**: 169-174.

23. Stanwell-Smith RE, Stuart JM, Hughes AO, Robinson P, Griffin MB, Cartwright K. Smoking, the environment and meningococcal disease: a case control study. *Epidemiol Infect* 1994; **112**: 315-328.

24. Batson E. Notes on the concept and measurement of overcrowding. In: *The Social Survey of Cape Town* (Report ss27). Cape Town: Department of Social Science, University of Cape Town, 1944.

25. Watkins CJ, Leeder SR, Corkhill RT. The relationship between breast and bottle feeding and respiratory illness in the first year of life. *J Epidemiol Community Health* 1979; **33**: 180-182.

26. Welsh JK, May JT. Anti-infective properties of breast milk. *J Pediatr* 1979; **94**: 1-9.

27. Greenwood BM, Greenwood AM, Bradley AK, *et al.* Factors influencing susceptibility to meningococcal disease during an epidemic in The Gambia, West Africa. *J Infect* 1987; **14**: 167-184.

28. Bland M, Bewley BR, Pollard V, Banks MH. Effect of children's and parent's smoking on respiratory symptoms. *Arch Dis Child* 1978; **53**: 100-105.

29. Fielding JE, Phenow KJ. Health effects of involuntary smoking. *N Engl J Med* 1988; **319**: 1452-1460.

30. Ehrlich R, Kattan M, Godbold J, *et al.* Childhood asthma and passive smoking. *Am Rev Respir Dis* 1992; **145**: 594-599.

31. Richards GA, Terblanche APS, Theron AJ, *et al.* Health effects of passive smoking in adolescent children. *S Afr Med J* 1996; **86**: 143-147.

32. Crofton J, Douglas A. *Respiratory Diseases.* Oxford: Blackwell Scientific Publications, 1981: 353.

33. Cartwright KAV, Jones DM, Stuart JM, Kachzmarski EB, Palmer SR. Influenza A and meningococcal disease. *Lancet* 1992; **338**: 554-557.

34. Moore PS, Hierholzer J, De Witt W, *et al.* Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. *JAMA* 1990; **264**: 1271-1275.

35. Wacholder A, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 1992; **135**: 1019-1028.

36. Last JM, ed. *A Dictionary of Epidemiology.* 3rd ed. New York: Oxford University Press, 1995: 15.

37. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? *Am J Epidemiol* 1990; **132**: 746-748.

38. Marbury MC, Hammond SK, Haley NJ. Measuring exposure to environmental tobacco smoke in studies of acute health effects. *Am J Epidemiol* 1993; **137**: 1089-1097.