PASSIVE SMOKING AND MENINGOCOCCAL DISEASE

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ABSTRACT

Neiserria meningitidis remains an important cause of morbidity and mortality in South Africa (SA). It is the sixth commonest cause of notified disease with a case fatality rate of 11% for the period 1990 - 1994. Identification of preventable risk factors is critical as no effective vaccine exists for serogroup B, the most prevalent serogroup in SA.

A case control study was undertaken to determine the risk factors associated with meningococcal disease. The study population consisted of all children under the age of 14 years who were residents of the Cape Town City Council and Cape Metropolitan Council areas of jurisdiction. Cases were identified from weekly notification reports and from admissions to the City Hospital for Infectious Diseases. Controls were selected from the trauma wards at Red Cross War Memorial Childrens Hospital. Data was analyzed using EPI INFO and SAS statistical software.

During the period October 1993 to January 1995 70 cases and 210 controls were interviewed. Cases were significantly younger than controls ($p = 0.0001$). On univariate analysis significant risk factors for meningococcal disease included: a household where 2 or more members smoked (odds ratio (OR) =1.8), recent upper respiratory tract infection (OR = 1.8), poor nutritional status (OR = 3.6), being breastfed for less than 3 months (OR = 2.7) and overcrowding (OR = 2.8).

After adjusting for confounders the main force of passive smoking as a risk factor for meningococcal disease appeared to be in the presence of a recent upper respiratory tract infection. Other factors that remained significant after adjusting for confounders included : being breastfed for less than three months (adjusted OR = 2.4) and being less than 4 years old (adjusted OR = 2.3).

This is the first case control study in South Africa examining risk factors associated with meningococcal disease. The study provides further evidence for the reduction of smoking, reduction of overcrowding and the promotion of breast-feeding as important public health measures. It also identifies children under the age of 4 years as an important target group should an effective vaccine become available.

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PASSIVE SMOKING AND MENINGOCOCCAL DISEASE

INTRODUCTION

Neisseria meningitidis is an important cause of morbidity and mortality in South Africa(SA). Meningococcal infection, a notifiable disease in SA since 1945, is the sixth commonest cause of notified disease and the second commonest cause of notified mortality in South Africa[1]. A review of the notification reports for the past ten years revealed that children under five years are the most severely affected, the case fatality ratio remains high and the highest incidence by region has been in the Western Cape[2-7]. The incidence in the Western Cape for the period 1983 - 1988 was consistently more than twice that for any other region in SA[5]. Geographical analysis of the notifications of the W.Cape for 1988 revealed the disease to be widespread with certain magisterial districts viz. Vredenberg, Prince Albert, Walvis Bay, Malmesbury, and Cape Town having a very high incidence[4]. In SA meningococcal disease has a cyclic seasonal occurrence with most cases occurring during winter and early spring[8]. There is a pressing need to identify and develop avenues for primary prevention of meningococcal disease in children.

The majority of infections in South Africa (SA) are due to serogroup B[9-11]. This serogroup has a relatively non - immunogenic polysaccharide capsule. Several outer membrane protein based serogroup B meningococcal vaccines have been developed and evaluated, but a highly immunogenic vaccine for children under

the age of five is not yet available[12-17].

In the absence of an effective vaccine identification, prevention and elimination of risk factors is one possible way of decreasing the incidence. Factors implicated as determinants of meningococcal disease are; complement[18-30] and immunoglobulin deficiency[31,32], preceding upper respiratory tract infection[33,34], stress[35,36], climate[37,38], overcrowded accommodation[39,40], poor socioeconomic status[41-44], contact with a case of meningococcal disease[39,45] and recently, passive smoking[35,36,39,46].

Passive smoking is now known to be a risk factor for acute respiratory infections[47-51] and acute otitis media in children[52]. Several studies have shown that the smoking prevalence in South Africa is high[53-58]. If passive smoking does increase the risk of meningococcal disease, this is then yet another reason to recommend a reduction in exposure to cigarette smoke as an important public health measure. The identification of other potential risk factors is also important in the primary prevention of meningococcal disease and in identifying target groups should an effective vaccine become available.

AIM

The aim of this study was to determine the association between exposure to tobacco smoke (passive) and meningococcal disease in children.

OBJECTIVES

1. To determine the degree of exposure to tobacco smoke in cases and controls.

2. To measure potential confounding and other exposure variables of interest in cases and controls.
These included:

a. Degree of household crowding
b. Type of dwelling
c. Attendance at a creche
d. Duration of breast feeding
e. Contact with a case
f. Nutritional status
g. Recent antibiotic usage
h. Recent upper respiratory tract infection

3. To determine the effect of smoking on meningococcal disease after adjusting for confounders.

4. LITERATURE REVIEW

4.1 Microbiology

Meningococcal meningitis was first described by Gaspard Viesseux in Geneva in 1805[59]. The organism, a Gram-negative diplococcus, was first isolated from cerebrospinal fluid in 1887 by Weischbaum[60]. The meningococcus is classified on the basis of its polysaccharides, outer membrane proteins (OMPs) and lipopolysaccharides. Capsular polysaccharides are classified into 12 serogroups: A, B, C, X, Y, Z, W135, 29E(Z'), H, I, K and L[61]. Unique serotypes are defined on the basis of antigenic differences in the Class 2 and 3 OMPs while differences in the Class 1 OMPs determine subtypes[62,63]. There are currently 20 serotypes and at least 10 class 1 subtypes[64].

4.2 Global Epidemiology

Of the 12 serogroups most illness is caused by serogroups A, B, and C. Epidemic group A meningococcal disease has been documented in various parts of the developing world. Outbreaks begin during the dry season and end with the onset of the rainy season. Attack rates generally range from 100 to 500 per 100 000[39]. Periodic outbreaks occur in sub- Saharan Africa in an area now named the meningitis belt of Africa. The borders of the belt were initially described by Lapeyssonnie[37] and later extended by Greenwood[38]. Although it was initially thought that epidemics occurred in

predictable cycles in the belt, it has now been established that cyclical patterns are not present in most countries included in the meningitis belt[64].

Group B meningococci are the major cause of sporadic disease in developed countries[65,66]. During the 1970s a group B clone was responsible for outbreaks in Norway, Denmark, the Netherlands and Great Britain[67]. Spread of this clone was later documented in Cuba, Chile, Rio de Janeiro and Sao Paulo[68]. The majority of infections in South Africa (SA) are due to serogroup B[9-11].

Group C meningococci have been implicated in large outbreaks[69] , small disease clusters[70] and sporadic infections. During the 1980s the proportion of sporadic disease caused by the Group C organisms increased in several European countries; a single strain was responsible for most of this increase[71].

4.3 Clinical Picture

Infection with the meningococcus results in one of four major clinical conditions[64].

1. Meningitis

This is the most common pathological presentation. Patients present with the classical signs of fever, headache, a stiff neck and frequently a petechial rash. Mortality, despite antimicrobial treatment and supportive care remains, at about 5 % in children younger than 5 years of age and between 10 to 15% in adults[64].

2. Meningococcaemia

This is the most severe form of the disease. Patients may present with a petechial or purpuric rash, hypotension, disseminated intravascular coagulation and/or multi-organ failure. The case fatality rate ranges from 15 to 30%. Poor prognostic signs include shock, coma, seizures, disseminated intravascular coagulation and thrombocytopenia[72].

3. Metastatic manifestations

These can include arthritis, pericarditis and endophthalmitis.

4. Asymptomatic nasopharyngeal carriage

This is the most common of the clinical conditions. The upper respiratory tract of humans is the only reservoir of *N meningitidis* and asymptomatic nasopharyngeal carriers are considered the usual source of infection. The prevalence of meningococci in asymptomatic carriers has been the subject of numerous studies in civilian and military populations[73-79]. Factors associated with carriage include age (15- 24 years)[77], male[77], active smoking[77,80-82], ABO secretor status[81] and passive cigarette smoking[77,83]. It is postulated that cigarette smoke interferes with ciliary action and this may predispose to the colonisation of the pharynx with *N meningitidis*[80]. The association between smoking and carriage could account for the increased risk of meningococcal disease in those who live with smokers and in children who live with a smoker[35,46]. Studies have also examined the relation between the incidence of meningococcal disease and meningococcal carriage[78,84,85]. The pressing needs of the military

situation in the first World War brought about a number of carrier studies. The World War one concept had it that prior to an outbreak of meningococcal disease - carriers rose from a normal of 2 - 4 % to 20 - 30%. Twenty percent was regarded as the danger point beyond which epidemics occurred. However the literature does not clearly bring out the facts on which this was based. Furthermore in spite of great care to detect and eliminate carriers the meningococcal incidence in troops were still much greater than in the civilian population[84]. In addition studies done on meningococcal carriage and disease from 1941 - 1945 showed that the incidence of disease was seasonal whilst the carriage rate remained constant[84]. In 1950 Agcock and Muller established that the incidence of illness did not appear to be a function of the percentage of carriers. This observation was corroborated by Wenzel et al[85] (1973). It is now believed that additional factors are important determinants of disease.

4.4 Risk Factors for Meningococcal Disease

4.4.1 Host Factors

Individual host factors that predispose to invasive meningococcal disease have been well described. These include : age, complement deficiency, immunoglobulin deficiency, preceding upper respiratory infections and stress.

Age

The risk of meningococcal disease decreases with increasing age. In a surveillance project in the United States, 49% of invasive meningococcal disease occurred in those under the age of two years[86]. A high incidence of meningococcal disease in childhood, with a peak in the first year of life has been reported in many studies[11,87,41]. This could be related to the lack of specific anti-meningococcal antibodies at this age.

Complement and Immunoglobulin Deficiencies

Deficiencies in the complement system[18,19], particularly the terminal components (C5to C8)[20-24], are known to predispose to meningococcal disease. Recently disease has been described in persons with deficiencies of C2[25], C3[21], homozygous C4b[26] and C9[27,28]. Persons with compliment deficiency have a lower case fatality rate than the overall case fatality rate for meningococcal disease.

Absent or dysfunctional properdin has also been shown to increase the risk of disease[29,30]. Properdin deficiency is associated with a higher case fatality rate compared to patients with terminal component complement deficiency[30].

Reports have found an association between IgM deficiency[31] and IgG2[32] subclass deficiency and meningococcal disease.

Upper Respiratory Tract Infection

The condition of the host pharyngeal mucosa may also be important in protecting against invasive disease. An association been influenza type A and meningococcal disease has been documented[33,34].

Stress

Recent studies have suggested an association between stress and meningococcal disease[35,36].

4.4.2 Environment

Climate

The peculiar borders of the African meningitis belt have prompted studies of the role of climate as a factor in epidemics.
Within the meningitis belt the greatest incidence of disease is in the dry season[37,38]. However dry seasons can pass without

epidemics. In the Western Cape meningococcal disease is seasonal with the majority of cases occurring in the wet winter months[8]. The role of climatic factors in precipitating outbreaks remains unclear.

Crowding

The role of crowding in the pathogenesis of meningococcal disease is controversial. Studies undertaken by Glover in barracks in the First World War[40] and by Stanwell-Smith et al[36] in England in 1988 suggested that overcrowding was associated with disease. However Stuart et al[46] and Greenwood BM et al[44] found that overcrowding was not associated with meningococcal disease.

Social Class

An association between lower social class, poverty and meningococcal disease has been demonstrated in the United States of America[41] and in Europe[42,43]. However this association was not found in a study in Africa[44]. The authors of the African study postulated that in the villages studied, inhabitants lived at a socio-economic level below which this factor begins to influence susceptibility to disease.

Passive Smoking

Recent studies have suggested an association between passive smoking and meningococcal disease[35,36,39,46]. In the study by Stanwell-Smith et al[36], the odds ratios for disease in children under the age of five years increased both with the number of cigarettes smoked and with the number of smokers in the household, suggesting a dose-response relationship. Active smoking has been shown to be associated with increased carriage of the meningococcus[82,83,85]. Thus children living in homes with smokers have higher exposure rates to meningococci and could thus have a greater chance of acquiring disease.

4.4.3 Organism

As discussed earlier different serogroups are responsible for different patterns of meningococcal disease. Strain characteristics also affect the pattern of disease. Some strains of meningococcal serogroups are more associated with epidemics than others. Olyhoek et al used isoenzyme electrophoresis and monoclonal typing to distinguish clonal populations in a large series of Group A meningococcal isolates from 28 different epidemics[88]. In all but one epidemic, a single clonal population was responsible for disease.

4.5 Prevention

4.5.1 Primary Prevention - Vaccine

Efforts to develop a successful vaccine against meningococcal disease began in the early 1900s[37]. Today vaccines are available against four meningococcal serogroups viz serogroups A, C, Y and W135[39,89]. Currently no effective vaccine against serogroup B is available and unfortunately the majority of infections in SA are due to serogroup B[9-11].

Serogroup B has a relatively non - immunogenic polysaccharide capsule. Several outer membrane protein based serogroup B meningococcal vaccines have been developed and evaluated[12-14]. However the only two vaccines that have demonstrated some protective efficacy have been a Norwegian and a Cuban developed vaccine.

The Norwegian vaccine was assessed in a placebo - controlled, randomised double blinded trial among children aged 12 to 16 years in Norway[14]. The estimated vaccine efficacy was 57% (lower confidence interval = 27%). On this basis the vaccine was not considered sufficiently efficacious to be considered for general use.

The Cuban vaccine was initially tested in children aged 10 to 16 years and was reported to have a vaccine efficacy (VE) of 81% in this age group[15]. Although the Cuban trial did not address VE in

children under the age of 10 years, over 850 000 Cuban children aged less than 6 have been vaccinated and the VE in this younger age group was estimated, based on vaccine coverage and incidence of meningococcal disease, to be 93%.

Two studies have been conducted in Brazil to test the VE of the Cuban vaccine[16,17]. The Sao Paulo study found the VE varied by age : in children older than 4 years of age VE was 74%, (95% CI 16% -92%), in those aged 24 to 47 months VE was 47% (95% CI -72% to 84%) and in those under the age of 24 months VE was - 37% (95% CI less than - 100% to 73%)[16].

The second study conducted in Rio de Janeiro, Brazil in 1990 in children aged 6 months to 9 years showed that the VE was 54% (95% CI 20% - 74%)[17]. VE also varied by age being 71% in children 4 years and older (95% CI 34% - 87%) , 14% in children 24 - 47 months (95% CI - 165% to 72%) and 41 % in children 6 - 23 months (95% CI - 96% to 82%) Despite the potential value in older children the public health impact has been disappointing - rates of disease have not changed much before and after the vaccine campaign in Sao Paulo[16].

The results from both studies suggest that the while the Cuban produced vaccine may be effective in older children it has a low efficacy in children younger than four years old[16,17] - the age group most seriously affected by serogroup B. Development of an effective group B vaccine remains a high priority for reducing disease

4.5.2 Secondary Prevention

Current recommendations of the Advisory Committee on Immunization Practices are that household members, day-care centre contacts and persons exposed to the oral secretions of the patient should receive prophylaxis[90]. The antibiotic of choice is rifampicin (600mg every 12 hours for adults for 2 days, 10mg/kg every 12 hours for 2 days for children one month and older and 5mg/kg every 12 hours for 2 days for children less than a month old).

4.6 Treatment

Serum therapy was the first successful treatment of meningococcal disease[91]. The discovery of sulfa in the 1930s and its success in treating meningococcal disease was a major advance and replaced serum therapy as the treatment of choice. When sulfa resistance developed,in the 1950s, penicillin became the treatment of choice. Penicillin resistant strains have however been reported from various countries[92-95]. Disease associated with these strains has a higher mortality rate[95]. Chloramphenicol is an alternative to penicillin for the treatment of meningococcal disease.

5. METHODS

5.1 STUDY DESIGN AND POPULATION

A case-control study was conducted between October 1993 and January 1995. The study population consisted of all children under the age of fourteen years who were permanent residents of the Cape Town metropolitan region (Cape Town Municipality (CTM) and Cape Metropolitan Council (CMC) areas of jurisdiction).

5.2 DEFINITION OF TERMS

Case Definition

Any child under 14 years and residing in the above areas was designated :

a definite case if:

N. meningitidis was isolated from the blood or cerebrospinal fluid (CSF) , or

clinical signs of meningitis or septicemia were accompanied by a haemorrhagic rash and Gram negative diplococci were detected in the CSF.

and a probable case if :

clinical signs of meningitis or septicemia were accompanied by a haemorrhagic rash, but N. meningitidis was not isolated by culture or gram stain.

Cases were identified using a combination of the passive statutory notification system and an active surveillance system consisting of weekly scrutinising the admission registers at the City Hospital for Infectious Diseases. This hospital is the main referral centre for infectious disease in the region.

Smoking Exposure

A child was considered to have been exposed to cigarette smoke if a household member smoked.

Household living density was measured in terms of a household crowding index. This crowding index is based on the work of Batson (where crowding is defined as the number of equivalent persons per number of sleeping rooms. A child 10 years or younger is considered half an equivalent person and a person older than 10 years as an equivalent person)[96]. A crowding index of greater than 2.5 was taken as an indication of overcrowding.

Type of dwelling was recorded as one of the following : brick house, apartment/flat, shack, tent, prefabricated building or other.

Nutritional status was measured in terms of weight for age. The growth reference charts developed by the National Centre for Statistics and Centre 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.

Duration of breastfeeding was measured as a categorical variable. The following categories were used :

not breastfed

< 3 months

≥ 3 < 6 months

≥ 6 < 12 months

≥ 12 months

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.

Contact with a case of meningitis was defined as a history of any contact with a person that had meningitis. Information was also collected on when the contact occurred.

Selection of controls

Controls were selected from the trauma wards at Red Cross War Memorial Childrens Hospital, the regional paediatric referral centre. Controls were under the age of 14 years and permanent residents in the area being studied ie the Cape Town Metropolitan region. Three controls were selected for each case, within a 3 month period from ascertainment of the corresponding case.

5.3 DATA COLLECTION

Trained medical staff at City Hospital, by means of a pre-tested questionnaire (see appendix), elicited case exposure histories and other relevant information from the parents or guardians. These interviews were conducted in the wards. Patients that were detected by the surveillance system but had not been admitted to City Hospital were contacted at their homes by the CMC or CTM district nurse. The district nurse administered the same questionnaire to the parent or guardian. A trained interviewer administered the same questionnaire to the parent or guardian of the selected controls.

A five percent random sub-sample was selected for repeatability testing of the measuring instrument. Different interviewers were used during the repeat interviews.

5.4 ETHICS

Approval for the study was obtained from the Ethics Committee of the University of Cape Town. Informed consent was obtained from the parents or guardians of all children. All data sheets and completed questionnaires were kept under the strict supervision of the field coordinator.

5.5 ANALYSIS

Analysis was done using SAS (version 6) and EPI INFO statistical software. The chi-squared test was used to test for significant differences between categorical variables. For numerical variables either the t test or the Wilcoxon sum of ranks test was used to test for significant differences. The Breslow - Day test was used to assess the homogeneity of the odds ratios across strata. Multiple logistic regression was performed to determine the association between passive smoking and meningococcal disease after adjusting for confounders. Crude odds ratios, adjusted odds ratios and 95% confidence intervals (CI) are reported.

6. 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. This difference was not significant (p=0.06). The percentage agreement between initial and repeat interviews for the questions relating to : the number of people per household was 92%, the number of rooms was 83% and the number of smokers was 75%.

UNIVARIATE RESULTS

Socio - demographic data

The median age of the cases was 27 months and that of the controls 60 months. This difference was significant (p = 0.0001). There was a male predominance amongst cases (64%) and controls (65%). There was no significant difference in residential distribution of the cases and controls. The majority of both cases and controls were from the Cape Flats area (35% and 42% respectively). Although there were more cases (13%) than controls (5%) from the West Coast area, this difference was not significant (p=0.059). The majority of cases (66%) and controls (69%) lived in brick houses.

Smoking Exposure

Data related to smoking exposure is summarized in tables 1, 2 and 3. Household exposure to cigarette smoke occurred among 78% of the cases and 74% of the controls. This difference was not significant ($p = 0.50$). However significantly more cases than controls came from homes with 2 or more smokers. The proportion of homes with 3 or more smokers per home was higher for cases than controls, although this difference was not significant. A higher proportion of cases than controls had main caregivers that smokers, but this difference was not significant.

Table 1 : Number of household smokers - univariate data

Household Smokers	Cases	Controls
Mean	1.8	1.5
Median	2.0	1.0
Range	1 - 7	1 - 6

$p = 0.111$

Table 2 : Proportion of households with smokers

Number of smokers	% of Cases (n = 68)	% of Controls (n = 210)
none	22	26
1	19	29
2	29	23
3	18	12
4	9	7
5	2	2
6	0	1
7	1	0

Table 3 : Smoking exposure

Variable	Cases %	Controls %	p value	OR	95% CI
Any household Exposure	78	74	0.50	1.25	0.65-2.40
⩾ 2 smokers per household	59	45	0.044	1.76	1.01-3.07
⩾ 3 smokers per household	29	22	0.206	1.49	0.80-2.75
Household exposure to moderate smokers	40	31	0.209	1.44	0.82-2.53
Household exposure to heavy smokers	18	11	0.184	1.66	0.78-3.53
Main care giver smokes	52	39	0.065	1.68	0.97-2.93

LEGEND

OR = odds ratio

Heavy smokers : use of > 20 cigarettes per day

Moderate smoking: use of > 10 ⩽ 20 cigarettes per day

Crowding

Data relating to crowding is summarised in tables 4, 5, 6 and 8. Case homes had significantly more rooms than control homes. The number of occupants per household did not differ significantly. Overcrowding was a significant risk factor for meningococcal disease (Table 8).

Table 4 : Number of rooms per household

Rooms per household	Cases	Controls
Mean	3.1	3.9
Median	3.0	4.0
Range	1 - 6	1 - 8

p = 0.0004

Table 5 : Occupants per household

Occupants per household	Cases	Controls
Mean	6.4	6.1
Median	6.0	6.0
Range	1 - 19	2 - 14

p = 0.74

Table 6 : Crowding index

Crowding Index	Cases	Controls
Mean	2.0	1.5
Median	1.7	1.3
Range	0.6 - 8	0.4 - 8

p = 0.0007

Duration of Breastfeeding

Data is summarised in Tables 7 and 8 . Controls tended to have been breastfed for longer periods than cases. There was a significant association between being breastfed for 3 months or less (including not being breastfed) and meningococcal disease (Table 8).

Table 7 : Duration of breastfeeding

Duration in months	% of Cases (n = 70)	% of Controls (n = 189)
0 (not breastfed)	6	10
< 3	41	15
⩾ 3 < 6	20	29
⩾ 6 < 12	9	18
⩾ 12	24	28

Contact with a case of meningitis

Significantly more cases than controls had a history of contact with a case of meningitis (Table 8). The median time of exposure to a case of meningitis was 6 months prior to the interview (range 1 to 36 months).

Other Risk Factors

As can be seen from Table 8 significant risk factors for meningococcal disease include : history of a recent URTI, history of contact with a case of meningitis, poor nutritional status, being breastfed for less than three months and living in overcrowded accommodation.

Table 8 : Risk factors for meningococcal disease

Variable	Cases % (n)	Controls % (n)	p value	OR	95% CI
History of previous URTI n = 273	59 (40)	45 (91)	0.043	1.77	1.02-3.09
Attendance at creche n = 175	25 (13)	18 (22)	0.283	1.53	0.65-3.59
Contact with a case of meningitis n = 260	16 (9)	4 (8)	0.003	4.57	1.7-12.5
recent antibiotic use n = 270	36 (25)	39 (78)	0.626	0.89	0.49-1.53
nutritional status WAZ < - 2 n=271	10 (6)	2.9 (6)	0.033	3.6	1.12-11.68
breastfed for < 3 months (including not breastfed) n = 259	47 (33)	25 (47)	0.001	2.69	1.45-5.01
CI > 2.5 n=280	29 (20)	12 (26)	0.002	2.83	1.46-5.49

LEGEND

WAZ = weight for age Z value

CI = crowding index

STRATIFIED ANALYSES

The association between exposure to cigarette smoke and meningococcal disease was modified by the presence of an URTI. Results are summarised in the tables below.

Table 9 : Crude association between exposure to 2 or more smokers and meningococcal disease

	Cases (n)	Controls (n)
Exposure to ≥ 2 smokers	40	94
Exposure to < 2 smokers	28	116

Odds Ratio = 1.8 95% CI 1.0 - 3.1

Table 10 : Association between exposure to 2 or more smokers and meningococcal disease among those with a history of a recent upper respiratory tract infection

	Cases (n)	Controls (n)
Exposure to ≥ 2 smokers	27	37
Exposure to < 2 smokers	13	55

Odds Ratio = 3.1 95% CI = 1.3 - 7.4

Table 11 : Association between exposure to 2 or more smokers and meningococcal disease among those with no history of a recent upper respiratory tract infection

	Cases (n)	Controls (n)
Exposure to ≥ 2 smokers	12	56
Exposure to < 2 smokers	16	58

Odds Ratio = 0.8 95% CI = 0.3 - 1.9

Breslow - Day test for homogeneity p = 0.024

The odds ratio in the presence of a history of a recent URTI was 3.1 compared to an odds of 0.8 if there was no history of a recent URTI.

Table 12 : Crude association between exposure to a main caregiver that smokes and meningococcal disease

	Cases (n)	Controls (n)
Main care giver smokes	35	82
Main care giver does not smoke	32	116

Odds Ratio = 1.7 95% CI = 0.9 - 3.1

Table 13 : Association between exposure to a main caregiver that smokes and meningococcal disease among those with a history of a recent upper respiratory tract infection

	Cases (n)	Controls (n)
Main care giver smokes	23	29
Main care giver does not smoke	16	63

Odds Ratio = 3.1 95% CI 1.3 - 7.3

Table 14 : Association between exposure to a main caregiver that smokes and meningococcal disease among those with no history of a recent upper respiratory tract infection

	Cases (n)	Controls (n)
Main care giver smokes	12	52
Main care giver does not smoke	14	60

Odds Ratio = 1.0 95% CI 0.4 - 2.5

Breslow - Day test for homogeneity p = 0.049

The odds ratio if the main caregiver smoked and there was recent exposure to a URTI was 3.1 and decreased to 1.0 in the absence of a recent URTI.

MULTIPLE LOGISTIC REGRESSION

Two multiple logistic regression models were fitted. The first was fitted to examine the association between the presence of 2 or more household smokers and meningococcal disease. The following variables were included in the model : overcrowding, nutritional status, age (as a categorical variable, with the overall median age used as a cut off point ie. $\leq$ 48 months or $>$ 48 months), breast feeding (as a categorical variable - $<$ 3 months (including not being breastfed) and $\geq$ 3 months), recent URTI and the URTI interaction with 2 or more household smokers. Contact with a case was excluded as a variable when logistic regression was performed as investigation into the time and type of contact as well as into the hospital records of some of the named primary cases, done only after the study was completed, showed that contact could not be reliably ascertained on history alone. Stepwise, forward and backward regression all yielded the same final model. The results are summarised in Table 15. The presence of 2 or more household smokers was no longer associated with meningococcal disease.

Table 15 : Results of logistic regression model fitted to examine the association between the presence of 2 or more household smokers and meningococcal disease

Variable	Odds Ratio	95% CI
2 or more smokers in household	0.6	0.25 - 1.48
breastfed	2.4	1.26 - 4.43
overcrowding	2.3	1.00 - 5.30
nutritional status	2.1	0.51 - 8.41
age	2.3	1.25 - 4.36
URTI	0.7	0.30 - 1.76
interaction :URTI and smoke exposure	5.0	1.44 - 17.31

The second model was fitted to examine the association between exposure to a main caregiver that smokes and meningococcal disease. The following variables were included in the model : overcrowding, nutritional status, age (as a categorical variable - $\leq$ 48 months or > 48 months), breast feeding (as a categorical variable - < 3 months (including not being breastfed and $\geq$ 3 months), recent URTI and the URTI interaction with 2 or more household smokers. Contact with a case was excluded as a variable when logistic regression was performed for reasons listed earlier. Stepwise, forward and backward regression all yielded the same final model. The results are summarised in Table 16. Exposure to a main caregiver that smoked was still not a risk factor for meningococcal disease.

Table 16 : Results of logistic regression model fitted to examine the association between exposure to a main caregiver that smokes and meningococcal disease

Variable	Odds Ratio	95% CI
main care giver smokes	0.9	0.38 - 2.25
breastfed	2.2	1.17 - 4.19
overcrowding	2.2	0.94 - 5.07
nutritional status	1.1	0.25 - 5.09
age	2.2	1.17 - 4.12
URTI	1.0	0.43 - 2.32
interaction :URTI and smoke exposure	3.5	1.01 - 12.01

7. DISCUSSION

7.1 Demography

The median age of the cases was 27 months. Seventy one percent of cases were under the age of 5 years. These findings are consistent with the age profile of cases of meningococcal infection in South Africa[2-7]. Children that were 4 years old and younger were twice as likely to develop meningococcal disease compared to those older than 4 years, confirming previous findings that the risk of meningococcal infection increases with decreasing age[64].

7.2 Passive Smoking

Passive smoking is known to be associated with an increased risk of respiratory disease in young children[47-51]. Cigarette smoke interferes with ciliary action, increases mucus production and decreases macrophage production, thereby decreasing the body's local defence against potential pathogens[97]. Previous studies have found as association between passive smoking and meningococcal disease[35,36,39,46]. More cases than controls had main caregivers that smoked (Table 3), however this difference was not statistically significant. Although significantly more cases than controls came from homes with 2 or more smokers, after adjusting for confounders exposure to 2 or more household smokers was no

longer a significantly associated with meningococcal disease. The prevalence of household smoking was high for both cases and controls. Lack of statistical power may therefore explain these findings, rather than a true lack of effect.

7.3 Upper Respiratory Tract Infection

Previous studies have implicated viral URTI as a co-factor and an association between influenza type A and meningococcal disease has been documented[33,34]. The main force of passive smoking as a risk factor for meningococal disease apperared to be in the presence of a recent upper respiratory tract infection. A possible explanation is that a recent URTI could denude the mucosa and, in the presence of already decreased local defence due to the action of cigarette smoke on the mucosa, increase the chances even further of invasion by the meningococcal organism. Further studies are needed to examine the association between passive smoking, upper respitatory tract infections and meningococcal disease.

7.4 Breastfeeding

Prolonged breast feeding has been found to protect infants against respiratory disease in general[98,99]. This is thought to be due to the transmission of specific human immunoglobulins in breast milk that improves the immunological defence mechanism of infants[100]. A study in the Gambia has suggested that breast feeding may protect infants against meningococcal disease[44]. In general controls were breastfed for longer periods than cases (Table 7) and breastfeeding was associated with meningococcal disease (Tables 15 and 16), confirming the postulate of the Gambian study. This study adds to the importance of encouraging public health measures that promote breastfeeding.

7.5 Contact with a Case

An increased risk of meningococcal disease has been reported following close contact with a case[39,45]. An attempt was made during the interview with the parent or guardian to determine whether there had been any contact with a case of meningococcal meningitis. Further investigation into the time and type of contact as well as into the hospital records of some of the named primary cases, done only after the study was completed, showed however that contact could not be reliably ascertained on history alone. Contact with a case was therefore excluded as a variable from the multiple logistic regression analysis. Future studies

need to obtain definitive evidence of contact with a true case of meningococcal disease.

7.6 Overcrowding

Overcrowding has been associated with ill health[101]. The mean crowding index was 2.0 for cases and 1.5 for controls (Table 6). The results of this study support the findings of other studies that overcrowding is associated with meningococcal disease[39,40].

7.7 Nutritional Status

Malnutrition and infection are closely linked[102]. Children that are malnourished are often more prone to certain infections than those that are well nourished. Ten percent of cases and three percent of controls had a low weight for their age (Table 8). However after controlling for confounders, nutritional status was not associated with meningococcal disease (Tables 15 and 16). This is in keeping with the findings of an earlier study done in Cape Town in which the presentation of 113 children that were admitted, between 1976 and 1982, to Red Cross Hospital with meningococcal infection was described, and children with malnutrition were found to be no different in their presentation, morbidity or mortality.

7.8 Data Quality, Limitations and Bias

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[103]. Cases were selected from the City Hospital for Infectious Diseases and controls from the trauma wards at Red Cross War Memorial Children's Hospital. Hospital controls were selected because of their logistic and financial convenience. Both of the hospitals used are referral centres for the Cape Metropole, thus the principle of comparability of study base is unlikely to have been violated. Controls from the trauma wards were selected so as to avoid any Berksons bias[104]. Controls were significantly older than the cases. However this difference was controlled for in the multiple logistic regression.

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

Smoking exposure was measured using a a questionnaire. 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 the exposed and unexposed[105]. The combination of a questionnaire about exposure to passive smoking and the use of biological markers eg. urinary cotinine, would perhaps offer the best method for accurate assessment of exposure to passive smoking[106].

7.9 Validity

Smoking exposure could have been validated by measuring urinary cotinine levels in the children, however this was not logistically or financially possible.

7.10 Reliability

An attempt was made to assess reliability by repeating selected questions in a randomly selected five percent sub sample. The questions repeated all had answers that were numerical variables and reliability was assessed by measuring the percentage of agreement between initial and repeat interviews. The percentage of agreement was acceptable.

8. RECOMMENDATIONS

8.1 Sample Size

The prevalence of passive smoking among cases and controls was much higher than anticipated. Future studies will need a much larger sample size to detect an association between passive smoking and meningococcal disease.

8.2 Measurement

Exposure to cigarette smoke was ascertained from questionnaires alone. Future studies should consider measuring urinary cotinine levels as this would give a more accurate assessment of exposure to cigarette smoke.

8.3 Public Health Policies

8.3.1 Vaccination

This study identified children under the age of 4 years as being at a much higher risk of developing meningococcal disease. When an effective vaccine becomes available, children under the age of 4 years should be targeted.

8.3.2 Passive Smoking

The extremely high prevalence of smoking is disturbing. Public health efforts that lower the prevalence of cigarette smoking by parents of young children, may reduce the incidence of meningococcal disease and should be encouraged.

8.3.3 Breastfeeding

Promotion of breastfeeding could have an impact on the incidence of meningococcal disease.

9. CONCLUSION

This is the first case-control study examining risk factors for meningococcal disease in South Africa and the high prevalence area of Cape Town in particular. 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 four have also been identified as an important target group, should an effective vaccine become available. Passive smoking was found to be a risk factor for meningococcal disease in the presence of a recent URTI. 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.

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11.1 QUESTIONNAIRE

RESEARCH BEING CONDUCTED BY THE DEPARTMENT OF COMMUNITY HEALTH AND THE DEPARTMENT OF PAEDIATRICS, UCT

CONTACT PERSONS :

DR GREG HUSSEY 4026911

DR JENNIFER MOODLEY 4066272 / 4066435

DR NICOL COETZEE 4066300

Interviewers Surname & initials _____

Person being interviewed :
Surname and initials _____
Relation to patient
(eg mother, father, guardian) _____

Date of Interview (dd/mm/yy) _____

Name of Hospital _____ Ward _____

Hospital number _____

Name of Patient: Surname _____

Firstname _____

Age : Yrs ____ Months____

Sex : Male ☐ Female ☐

Reason for Admission (diagnosis) _____

Was this patient referred from another hospital

Yes ☐ No ☐

If Yes : Which hospital _____

DO NOT FILL IN

CARD NO 1

2 ☐☐☐☐

6 ☐

7 ☐☐☐

10 ☐

11 ☐☐☐☐☐☐

17 ☐ 18 ☐☐☐

21 ☐☐☐☐☐☐☐

29 ☐☐ 31 ☐☐

33 ☐☐☐☐

37 ☐

38 ☐

39 ☐

40 ☐

QUESTIONNAIRE

Good morning/afternoon Mr/s _____. I am doing research for the community health and paediatric departments. I would like to ask you a few simple questions about this patient. Anything you tell us will remain totally confidential.

Do Not Fill In

Residential Address of patient

House Number _____
Street _____
Suburb _____
Telephone _____

41 ☐☐

Type of Dwelling of patient
(please tick)

Brick house	☐	Shack	☐
Flat/Apartment	☐	Prefab	☐
Tent	☐	Other (specify) _____	

43 ☐

How many rooms are there in the patient's household ?
(excluding bathrooms and toilets) _____ 44 ☐☐

How many of these rooms are used for sleeping ? _____ 46 ☐☐

How many people live in this household for at least 4 days of the week (including patient) :-

Total number _____ 48 ☐☐

Number of people age 10 years or less _____ 50 ☐☐

Number of people older than 10 years _____ 52 ☐☐

How long has this child lived in Cape Town ____Yrs ____ Mnths 54 ☐☐ 56 ☐☐

58 ☐☐☐☐

Does the child attend primary/high school
Yes ☐ No ☐ Don't Know ☐

62 ☐

Do Not Fill In

Does the child attend a creche/preschool/daymother/playcentre ?

Yes ☐ → If YES No ☐ Don't Know ☐ 63 ☐

How many children are in the class/centre

Less 5 children ☐

More than 5 children ☐ 64 ☐

How long does this child spend there

Half a day ☐

A full day ☐ 65 ☐

Don't know ☐

Does the daymother/teacher smoke whilst looking after the children ?

Yes ☐ No ☐ Don't Know ☐ 66 ☐

Who is the main care giver i.e(spends the most time with child)

(Relation to child) _____ 67 ☐☐

Does this person smoke ?

Yes ☐ No ☐ Don't Know ☐ 69 ☐

PAST CLINICAL HISTORY

How long was this child breastfed for ?

Less than 3 months ☐

From 3 to 6 months ☐

From 6 to 12 month ☐

More than 12 mnths ☐

Not Breastfed ☐

Don't Know ☐ 70 ☐

Has this child had a runny nose, cold, or flu in the past 1 month

Yes ☐ No ☐ Don't Know ☐ 71 ☐

DO NOT FILL IN
CARD NO 2

Has the child had any antibiotics in the past 1 month
Yes ☐ No ☐ Don't Know ☐ 2 ☐

Has this child had any operations in the last year ?
Yes ☐ → IF YES No ☐ Don't Know ☐ 3 ☐

Was this operation a tonsillectomy or an adenoidectomy
YES ☐ NO ☐ Don't Know ☐ 4 ☐

Has this child been in contact with anybody that has had meningitis
Yes ☐ → IF YES No ☐ Don't Know ☐ 5 ☐

State how long ago this was (in months) ——— 6 ☐☐☐
State who this person was (relationship to child) ——— 9 ☐
Did this person kiss the child ?
Yes ☐ No ☐ Don't Know ☐ 10 ☐

PRESENT CLINICAL DETAILS
(if necessary confirm with doctor)

Weight in kilograms to one decimal place ☐☐ , ☐ 11 ☐☐, ☐

Was N.Meningitidis isolated from the blood or CSF
Yes ☐ No ☐ 14 ☐

Were Gram negative diplococci detected in the CSF
Yes ☐ No ☐ 15 ☐

Haemorrhagic rash
Ever Present ☐ Never Present ☐ 16 ☐

Clinical signs of meningitis
Ever Present ☐ Never present ☐ 17 ☐

Fill in for all adults & children (excluding patient) living in the household for at least four days of the week

	1	2	3	4	5	6
1.Initials of person						
2.Relation to child (please tick)						
mother						
father						
sibling						
grandparent						
relative						
other						
3.Age of person in years						
4.Has this person slept in the same room as the patient for at least 4 nights a week in the past six months						
Yes						
No						
Don't Know						
5.Does he/she smoke cigarettes						
Yes						
No						
Don't Know						
IF HE/SHE SMOKES CIGARETTES						
6.How many cigarettes does he/she smoke per day						
less than 5						
from 5 to 10						
from 10 to 20						
more than 20						
don't know						
7.How long has he/she been smoking for						
less than 1 year						
from 1 to 5 years						
more than 5 years						
don't know						

Fill in for all adults & children (excluding patient) living in the patient's household for at least four days of the week

	7	8	9	10	11	12
1.Initials of person						
2.Relation to child (please tick)						
mother						
father						
sibling						
grandparent						
relative						
other						
3.Age of person in years						
4.Has this person slept in the same room as the patient for at least 4 nights a week in the past six months						
Yes						
No						
Don't Know						
5.Does he/she smoke cigarettes (tobacco cigarettes)						
Yes						
No						
Don't Know						
IF HE/SHE SMOKES CIGARETTES						
6.How many cigarettes does he/she smoke per day						
less than 5						
from 5 to 10						
from 10 to 20						
more than 20						
don't know						
7.How long has he/she been smoking for						
less than 1 year						
from 1 to 5 years						
more than 5 years						
don't know						