Modifiable Risk Factors for Invasive Meningococcal Disease During an Edmonton, Alberta Outbreak, 1999-2002

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ABSTRACT

Background: An outbreak of invasive meningococcal disease (IMD) in metro Edmonton, Alberta, Canada between December 1999 and June 2002 resulted in 84 laboratory-confirmed cases. Most cases were infected with *Neisseria meningitidis* serogroup C, and the highest age-specific incidence was observed in the 15-19 year age group.

Methods: A case-control study was conducted to identify modifiable IMD risk factors among outbreak cases. Two controls were matched to each case on age and sex, and were recruited through random-digit dialing. A questionnaire was telephone-administered to 132 study participants (44 cases, 88 controls). Conditional logistic regression was utilized to calculate risk measures.

Results: Multivariate analysis revealed three statistically significant risk factors: bar patronage (OR 35.2; 95% CI: 2.64-468), "rave" attendance (OR 12.8; 95% CI: 1.47-111) and maternal smoking (OR 8.88; 95% CI: 1.67-47.4). Humidifier use in the home was protective (OR 0.07; 95% CI: 0.009-0.64).

Conclusion: While the precision of risk estimates was low in the multivariate model, this study has identified rave attendance as an emergent IMD risk factor.

Key words: Meningococcal infections; risk factors; case-control studies

La traduction du résumé se trouve à la fin de l'article.

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Invasive meningococcal disease (IMD) is a bacterial infection caused by *Neisseria meningitidis*, and is spread through direct contact or inhalation of respiratory droplets.[1] IMD usually manifests as meningitis (meningococcal meningitis) and/or septicemia (meningococcemia). These syndromes account for approximately 50% and 20% of IMD cases respectively, and have a combined mortality rate of approximately 10%; in another approximately 10% of cases, serious sequelae result, including hearing impairment, neurological disability, and loss of digits/limbs.[2] Immunization is the primary method of control of IMD in high-risk groups, including those less than 19 years of age, the group in which more than half of IMD cases are reported.[3] Several modifiable IMD risk factors have been identified in well-designed and controlled studies in the literature.[4-19]

An outbreak of IMD in metro Edmonton, Alberta, Canada between December 1999 and June 2002 (described elsewhere)[20,21] resulted in 84 laboratory-confirmed cases. Most cases (89%) were infected with serogroup C, and the highest age-specific incidence was observed in the 15-19 year age group (32% of cases). The outbreak elicited a mass immunization campaign, with over 250,000 of approximately 800,000 in the region receiving meningococcal vaccine. This paper summarizes the findings of a population-based matched case-control study conducted to identify modifiable IMD risk factors among cases in this outbreak.

MATERIALS AND METHODS

Participant recruitment

Ethics approval was granted by the University of Alberta Health Research Ethics Board. The local health department provided the researcher (LH) with information on characteristics of IMD cases (minus personal identifiers pending informed consent) reported during the outbreak. Cases were defined by diagnostic criteria:

- isolation of *N. meningitidis* from a normally sterile site (blood, cerebrospinal fluid (CSF), joint, pleural or pericardial fluid), or
- demonstration of *N. meningitidis* antigen in blood or CSF, or
- positive *N. meningitidis* polymerase chain reaction (PCR) test in blood or CSF.

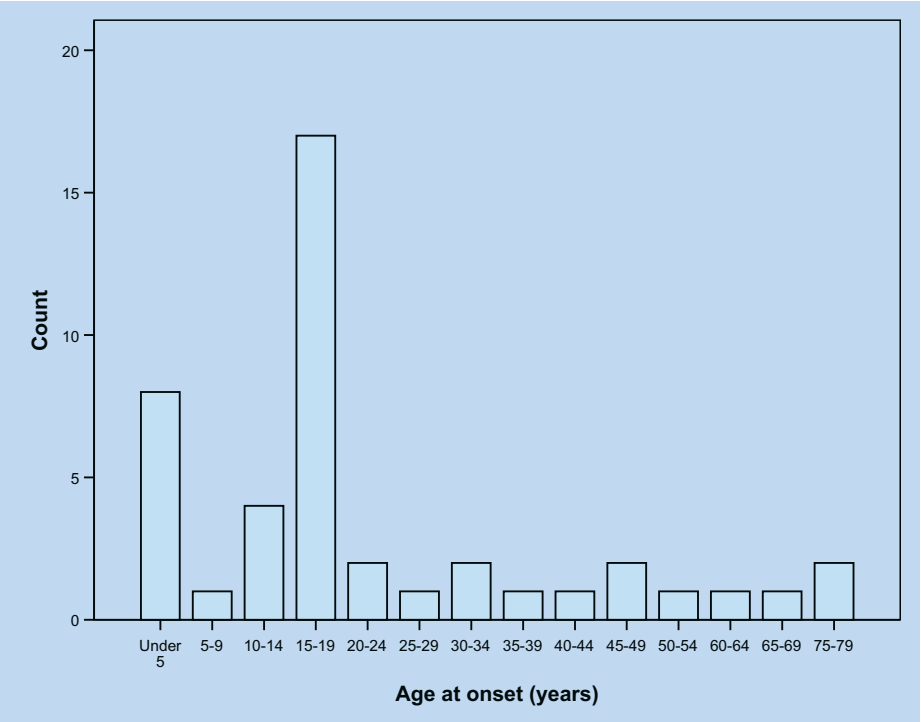

Figure 1. Age distribution (at onset) of recruited Edmonton IMD outbreak cases (n=44)

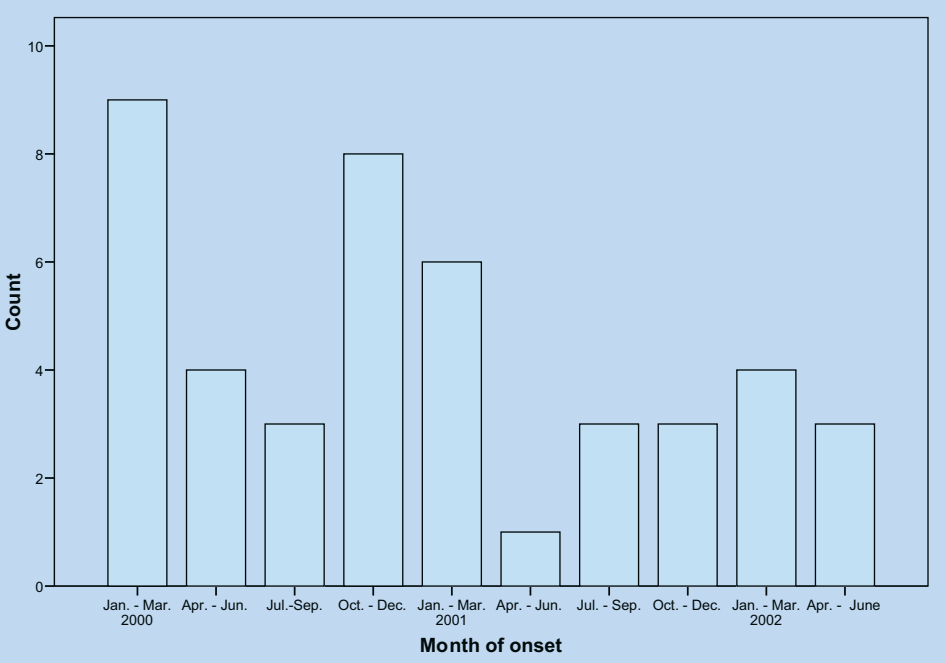

Figure 2. Epidemic curve for recruited Edmonton IMD outbreak cases (n=44)

Cases were recruited by telephone. Proxy respondents (parents, guardians or loved ones) were sought for fatal cases. Of 84 eligible cases, 44 (52%) participated in the study. Reasons for non-recruitment included no correct participant telephone number found, unable to contact the participant by telephone, and refusal to participate (48%, 42% and 10% of those not recruited, respectively). A recruitment letter was also sent to all cases if unable to contact by telephone. It is unknown what proportion of those not successfully contacted received study notification but refused to participate.

Controls were recruited via random-digit dialing (sampling and dialing methods published elsewhere)[22] and computer-assisted telephone interviewing. Of those contacted and deemed to be eligible, 32% agreed to participate. Two controls were matched to each case on age and sex. Controls were matched to cases greater than two years of age at onset by exact age (in years) of the case on the approximate date of control recruitment, and to cases less than two years of age based on their age (to the ranges 0-6 months, 6-12 months or 12-24 months) as of the date of onset. Other eligibility criteria were self-report of

- never having been ill with meningococcal meningitis nor meningococcemia, and
- residing in the metro Edmonton area continuously since 1999.

Data collection

Study data were collected using an interviewer- (telephone) administered questionnaire. No validated questionnaire suited for this research was available; however, the instrument was adapted from questionnaires used in similar studies.[5,8,14] The exposure period of interest was the month before illness onset in case participants, and for controls, the calendar month of illness onset for the case to which each control was matched. Age-correlated exposures were measured only for participants in appropriate age categories, e.g., those less than 12 years of age were classified as not exposed to raves or active smoking, those less than 16 years of age were classified as not exposed to bars. The mean time period between month of interest and date of study questionnaire administration to participants was 3.1 years (cases) and 3.4 years (controls); this difference was significant (p=0.046).

Information was collected on factors affecting IMD and/or immune status identified in the literature,[4-19] as well as attendance at "raves". Raves have been defined as all-night youth-oriented electronic music dance events held in makeshift dance halls,[23] and are a relatively recent phenomenon. Public health investigators determined that two Edmonton outbreak IMD cases were thought to have attended the same "rave-like event",[24] and thus, this exposure was included in the questionnaire as a potential new risk factor.

An IMD immunization program (serogroup A, C or A, C, W-135, Y poly-

TABLE I

Descriptive Analysis and Likelihood Ratio Test for Important Exposures Measured Among Edmonton IMD Cases and Controls

Variable†	Number (no.), Frequency (%) or Mean, Standard Error (SE)		
	Cases (n=44) No. (%) or Mean (SE)	Controls (n=88) No. (%) or Mean (SE)	p-value*
Lived in Canada entire life	42 (95.5)	72 (81.8)	0.005
Household population density‡,§	1.1 (0.06)	1.1 (0.05)	0.71
Humidifier on furnace	12 (27.3)	42 (47.7)	0.011
Other (external) humidifier used in home	6 (13.6)	20 (22.7)	0.21
Vaccine-mediated immunity	11 (25.0)	26 (29.5)	0.67
Chronic health condition‖	5 (11.4)	25 (28.4)	0.01
Lived with or in same room as someone sick with meningococcal disease	2 (4.5)	2 (2.3)	0.49
Age in months when breastfeeding stopped‡,¶	4.3 (1.4)	10.4 (3.0)	0.16
Household income <$15,000 CDN annually	4 (9.1)	5 (5.7)	0.46
Lived with smoker of following category:			
• mother	11 (25.0)	9 (10.2)	0.02
• father	7 (15.9)	15 (17.0)	0.87
• roommate	2 (4.5)	2 (2.3)	0.49
• husband, wife, boyfriend or girlfriend	3 (6.8)	5 (5.7)	0.80
• son or daughter	0 (0.0)	4 (4.5)	0.076
• brother or sister	4 (9.1)	6 (6.8)	0.66
• other relative/friend	2 (4.5)	2 (2.3)	0.49
Visited place(s) outside the home where other people smoking at least once per week	26 (59.1)	38 (43.2)	0.074
Smoked cigarettes on most days**	10 (22.7)	17 (19.3)	0.64
Attended a service at a church, synagogue or mosque	12 (27.3)	48 (54.5)	0.005
Attended a rave**	8 (18.2)	4 (4.54)	0.013
Went to a bar or other establishment where alcoholic drinks served††	23 (52.3)	26 (29.5)	<0.001
Attended college or university††	6 (13.6)	14 (15.9)	0.69

* likelihood ratio test from the conditional logistic regression
† during month of interest, unless otherwise stated
‡ for continuous variables, mean and standard error are shown among those participants with at least one unit of exposure
§ household density=number of household residents aged 10 years of age or more + 0.5 (number of household residents less than 10 years of age)/number of bedrooms in household
‖ conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV
¶ exposure information collected only from participants less than 5 years of age at onset (cases) or equivalent calendar month (controls)
** exposure information collected only from participants 12 years of age or more at onset (cases) or equivalent calendar month (controls)
†† exposure information collected only from participants 16 years of age or more at onset (cases) or equivalent calendar month (controls)

saccharide vaccine formats) for residents 2-24 years of age was initiated in the local health region early in the Edmonton outbreak (February 2000). In September 2001, residents 2-23 months of age were also eligible to receive a newly licenced serogroup C conjugate vaccine. All study participants were asked if they had ever received the meningococcal meningitis "shot". Participants who had received the immunization prior to onset (cases) or prior to the month of onset of matched case (controls), and had been infected (cases) or had a matched case that had been infected (controls) with IMD serogroup A, C, W-135 or Y were classified as vaccinated. If a control's matched case was known to have been infected with serogroup B, both the control and the case were classified as non-vaccinated, regardless of IMD immunization status, as no vaccine format provided protection for this serogroup.

Statistical methods

Recruited IMD cases were compared with those not recruited on age (t-test) as well as sex, fatality rate and IMD immunization rate (Pearson χ^2 test). Conditional logistic regression was used in testing associations between exposures and development of IMD. Polychotomous variables with an unstable category were collapsed into a dichotomous variable. Vaccine-mediated IMD immunity was forced into the model. Matched odds ratios (OR) were calculated as the risk estimates.

The association between each of the exposure variables and development of IMD was determined one at a time. The significance of point estimates was assessed utilizing a comparison of the Wald statistic χ^2 test. "Purposeful" selection methods (using the Likelihood Ratio χ^2 test) were employed in building the multivariate model.[25] Variables exhibiting complete separation (12 of 67) were not included in the model-building process because the odds ratios were not estimable for these variables. Variables dropped from the model were re-introduced individually and kept in the model as confounders if the logistic regression coefficient (β) of any of the variables in the model changed by more than 15%. Tests were conducted for linearity of continuous variables and significance of plausible interactions was assessed. The statistical package SPSS 12.0 for Windows[26] was used for the statistical analyses.

RESULTS

Case-descriptive analysis

As compared with non-recruited cases, recruited cases had a slightly younger mean age (23 vs. 24 years), a higher proportion of males (52 vs. 45%), were less likely to be fatal (4.5 vs. 5.0%) and more likely to have been immunized for IMD at onset (30 vs. 15%). However, recruited and non-recruited cases were not significantly different from each other on any of these characteristics. Among recruited cases, the highest age-specific incidence was in the 15-19 year age group (Figure 1). There was no significant difference in the sex-specific age distribution for recruited cases. The mean (standard deviation) age of all recruited cases was 23.1 years (19.4 years), respectively. The epidemic curve for recruited cases is seen in Figure 2, which was similar to the curve for all outbreak cases.

Significant factors

The descriptive analysis for selected exposures appears in Table I. Eight variables were significantly associated with IMD in the univariate analysis (Table II). Variables in the final multivariate model

TABLE II

Risk Factors for Edmonton IMD Outbreak Cases, Univariate Analysis

Exposure†	Odds Ratio‡		95% Confidence Interval	p-value*
Lived in Canada for all of his/her life	10.0		1.23, 81.4	0.03
Participant's home was heated with a furnace that had a humidifier attached	0.32		0.12, 0.83	0.02
Participant had chronic health condition (other than six conditions specifically asked) § prior to month of interest	0.25		0.07, 0.88	0.03
Participant's mother lived in participant's home and was a smoker	3.84		1.18, 12.5	0.03
Frequency of visits by participant to places outside participant's home where other people were smoking	<1/month:	1.00		
	≥1/month,<1/week:	2.40	0.68, 8.50	0.17
	≥1/week:	2.93	1.09, 7.86	0.03
Participant attended a service at a church, synagogue or mosque	0.36		0.17, 0.76	0.008
Participant attended rave‖	4.88		1.28, 18.6	0.02
Participant visited bars or other establishments where alcoholic drinks are served more than once in a month¶	16.0		2.06, 124	0.008

* Wald statistic, χ^2 distribution
† during month of interest, unless otherwise stated
‡ odds ratio for exposure, relative to reference category of no exposure (odds ratio=1.00), unless otherwise stated
§ conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV
‖ exposure information collected only from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)
¶ exposure information collected only from participants ≥16 years of age at onset (cases) or equivalent calendar month (controls)

TABLE III

Risk Factors for Edmonton IMD Outbreak Cases, Multivariate Analysis

Exposure†		Odds Ratio‡	95% Confidence Interval	p-value*
Use of external humidifier in home		0.07	0.009, 0.64	0.02
Smoking mother lived with participant		8.88	1.67, 47.4	0.01
Attended rave§		12.8	1.47, 111	0.02
More than one visit per month to bars‖		35.2	2.64, 468	0.007
Mother's education less than high school diploma¶,**		6.18	0.65, 58.5	0.11
Visits to places where smoking is allowed:**	<1/month	1.00		
	≥1/month,<1/week	2.79	0.61, 12.8	0.19
	≥1/week	1.39	0.37, 5.17	0.63
Vaccine-mediated immunity††		1.21	0.22, 6.57	0.82

* Wald statistic, χ^2 distribution
† during month of interest, unless otherwise stated
‡ odds ratio for exposure, relative to reference category of no exposure (odds ratio=1.00), unless otherwise stated
§ exposure information collected from participants ≥12 years of age at onset (cases) or equivalent calendar month (controls)
‖ exposure information collected from participants ≥16 years of age at onset (cases) or equivalent calendar month (controls)
¶ exposure information collected from participants <18 years of age at onset (cases) or equivalent calendar month (controls)
** included in the model due to statistical confounding
†† forced into the model

appear in Table III. Three factors significant in univariate analysis (rave attendance, bar attendance, residing with mother who was a smoker) were also significant after multivariate analysis. Two of these factors (rave attendance, bar attendance) exhibited instability (i.e., value above 100 at upper end of 95% confidence interval) and thus the associations should be interpreted with caution. When two variables (mother's education level, and passive exposure to cigarette smoke outside the home) were removed, they significantly affected the β coefficients of other variables in the model and thus were retained in the final model. IMD immunization status, as in univariate analysis, was not a significant predictor even when forced into the multivariate model. Rave attendance remained a significant association when bar attendance was removed from the model.

DISCUSSION

This is the first epidemiologic study to identify participation at "raves" as a significant risk factor for IMD. During 2000, there were at least four rave clubs reportedly operating in Edmonton, with monthly attendance in the thousands.[27] It is unlikely that the risk was associated with one rave event – the eight cases who reported this exposure in the month before IMD onset had onset during different calendar months. The risk appears to be independent of exposure to bar environments. Crowding in bar and rave facilities may ultimately be responsible for increased IMD risk, because such conditions promote respiratory droplet transmission and passive tobacco smoke exposure.[14]

Passive tobacco smoke exposure both inside and outside the home were significant risk factors for IMD, consistent with other studies.[4-13] The association with exposure to a mother (and not a father or other household member) who smokes is also consistent with other key IMD studies,[5,7,11] and with research suggesting that maternal smoking contributes more to overall passive tobacco smoke exposure in children than paternal smoking.[28] Tobacco smoke has also been cited as a risk factor for meningococcal bacteria carriage,[29-33] and thus, exposure to smokers may increase the likelihood of exposure to the pathogen.

Home humidifier use (univariate, furnace humidifier; multivariate, non-furnace humidifier) was found to be protective. While use of a humidifier may be collinear with other factors such as socio-economic status, this finding is consistent with other research.[5] Humidity may also act as a cofactor with antecedent respiratory infection. Antecedent respiratory infection in

study participants could not be controlled in the analysis, and thus the independent protective effect of humidity could not be calculated.

Vaccine-mediated IMD immunity was not protective in the study group, possibly a result of low statistical power. However, it has been observed that meningococcal polysaccharide vaccines, while effective in controlling serogroup C IMD outbreaks, are only 65% effective after two years in children and young adults.[34] This study was not designed to evaluate the effectiveness of the vaccine or vaccine implementation campaign; such an evaluation should be conducted for future meningococcal immunization programs, for which conjugate vaccines will likely be used.

This research is subject to limitations, including low statistical power and the potential for recall bias presented by the length of time between exposure period of interest and questionnaire administration. This work is based on the Master of Science thesis successfully defended by the first author,[35] the timing of which precluded earlier initiation of the research. One would expect cases to exhibit superior recall as compared with controls, which could have biased results away from the null.

Modifiable risk factors for invasive meningococcal disease were, however, revealed. Subject to corroboration, these findings could be used in the prevention of IMD in the community, such as smoking cessation programs targeting mothers (which is also important for the prevention other diseases), and promoting home humidifier use. The associations identified with rave and bar attendance may be used in preventing the secondary spread of IMD. If not currently doing so, public health officials may consider collecting information on rave and bar attendance from all sporadic IMD cases and, subject to further confirmatory evidence, offer IMD prophylaxis to all individuals who patronized like facilities concurrently with a confirmed case.

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RÉSUMÉ

Contexte : Une éclosion de maladie invasive à méningocoque (MIM) survenue dans le Grand Edmonton (Alberta), au Canada, entre décembre 1999 et juin 2002 avait entraîné 84 cas confirmés en laboratoire. La plupart des cas étaient infectés par *Neisseria meningitidis* du sérogroupe C, et le plus haut taux d'incidence selon l'âge avait été observé dans le groupe des 15 à 19 ans.

Méthode : Nous avons mené une étude cas-témoin pour déterminer les facteurs de risque de MIM modifiables chez les cas liés à l'éclosion. Deux témoins recrutés par composition aléatoire ont été assortis par âge et par sexe à chaque cas. Un questionnaire téléphonique a été administré aux 132 participants (44 cas et 88 témoins). Les mesures du risque ont été obtenues par régression logistique conditionnelle.

Résultats : L'analyse multivariée a mis au jour trois facteurs de risque significatifs : la fréquentation des bars (RC=35,2; IC de 95 % = 2,64–468), la participation à des fêtes techno (RC=12,8; IC de 95 % = 1,47–111) et le tabagisme maternel (RC=8,88; IC de 95 % = 1,67–47,4). L'utilisation d'un humidificateur à la maison était un facteur de protection (RC=0,07; IC de 95 % = 0,009–0,64).

Conclusion : Malgré le manque de précision des estimations du risque dans le modèle multivarié, l'étude a décelé un nouveau facteur de risque de MIM : la participation à des fêtes techno.

Mots clés : infections à méningocoques; facteurs de risque; études cas-témoins

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5th World Conference on Breast Cancer
Heart, Soul, & Science: "It's a Small World After All"
4-8 June 2008 Winnipeg, MB
Contact: Tel: 204-480-4588
E-mail: mail@wcbcf.ca www.wcbcf.ca

18th World Conference on Disaster Management
Resiliency – Individual, Community, Business
The Canadian Centre for Emergency Preparedness
15-18 June 2008 Toronto, ON
Contact:
www.wcdm.org

International Nursing Research Conference
Facing the Challenge of Health Care Systems in Transition
29 June-3 July 2008 Jerusalem, Israel
Contact: Diesenhaus Unitours – Convention Department
Tel: 972-3-5651313
Fax: 972-3-5610152
E-mail: meetings@diesenhaus.com
www.d-convention.com/israelnursing

Beyond the Horizon
74th Annual Educational Conference of the Canadian Institute of Public Health Inspectors (CIPHI)
20-23 July 2008 St. John's, NL
Contact:
www.ciphi.ca/events.htm

29th ICOH, International Congress on Occupational Health /
29e CIST, Congrès International de la Santé au Travail
Occupational Health: A Basic Right at Work – An Asset to Society / Santé au travail : un droit fondamental au travail – un atout à la société
22-27 March/mars 2009
Cape Town, South Africa / Afrique du Sud
Contact: Congress Secretariat / Secrétariat du Congrès
Tel/Tél :+27(0)21-938-9238/9245/9082/9651
Fax/Téléc : +27(0)21 933 2649
E-mail/Courriel : admin@icoh2009.co.za
www.icoh2009.co.za