Epidemiol. Infect. (2001), **127**, 435–441. © 2001 Cambridge University Press
DOI: 10.1017/S0950268801005817 Printed in the United Kingdom

Day-care and meningococcal disease in young children

T. GREIN[1]* AND D. O'FLANAGAN[2]

[1] *European Programme for Intervention Epidemiology Training (EPIET), 12, rue du Val d'Osne, F-94415 Saint Maurice, France*
[2] *National Disease Surveillance Centre, Dublin, Ireland*

(*Accepted 1 June 2001*)

SUMMARY

The Republic of Ireland has the highest incidence of meningococcal disease in Europe with 40% of all cases occurring in children under the age of 5 years. Attending day-care increases the risk of certain infections, including *Haemophilus influenzae* type b (Hib) meningitis. The risk of meningococcal disease associated with day-care is not known. We conducted a case-control study among pre-school children with 130 laboratory-confirmed cases and 390 controls, matched on age, gender and place of residence, to determine if day-care attendance was a risk factor for meningococcal disease. Multivariate analysis showed that day-care attenders had a lower risk of disease than non-attenders (OR 0·3, 95% CI 0·1–0·7) whereas the number of adults in a household, and household crowding were independent risk factors for disease. Asymptomatic carriers of *Neisseria meningitidis* are the main source of transmission and these carriers are usually adults. Regular day-care attendance may reduce this risk by removing children from close and prolonged contact with adults.

INTRODUCTION

Since 1997, the Republic of Ireland has experienced the highest incidence of meningococcal disease (MD) in Europe. In 1999, the crude incidence of laboratory-confirmed cases was 10·5 per 10^5 population per annum compared with 1·7 cases per 10^5 for the rest of Europe [1]. Two-thirds of these cases were due to *N. meningitidis* serogroup B.

In 1999, nearly 40% of all reported cases of MD in the Republic of Ireland were in children under the age of 5 years. Age-specific incidence rates were 170 (< 1 year) and 71 (1–4 years) per 10^5 per annum, these children again being at much higher risk of MD than their European counterparts [2].

Day-care is mainly attended by children under the age of 5 years. It is well described that day-care attendance increases the risk of droplet-transmitted infections such as upper respiratory tract illness [3] or infections caused by Hib, including meningitis [4–6]. Contributing factors may be the high child population density in day-care centres, the close physical proximity of young children to each other when playing, and their age-related higher immunological susceptibility.

While an increased risk of MD has been documented for contacts of cases in school settings [7], studies of the risk of MD in day-care attenders are inconclusive [7–11]. We conducted a study to determine if children attending day-care were at higher risk of MD than those who did not attend, and if duration of day-care and size and type of day-care facility were associated with illness.

METHODS

We studied all reported cases of laboratory-confirmed MD in pre-school children (under the age of 6 years) in the Eastern Regional Health Authority (ERHA) in

* Author for correspondence.

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press

the Republic of Ireland. The ERHA serves close to one-third of the total population of the Republic, its area including the counties of Dublin, Kildare and Wicklow. The study was carried out between November 1997 and April 1998.

We used a case-control study design with 130 cases and 390 controls matched for age, gender and area of residence. Sample size calculations were based on the total number of cases diagnosed over a 2-year period, a type I error of 5%, a type II error of 20% and an expected 30% of controls attending day-care. Matching three controls to one case allowed us to detect odds ratios of 2·0 or higher.

Case definition

A case was defined as a child aged under 6 years with laboratory-confirmed MD diagnosed between 1 January 1996 and 31 December 1997, and having lived in the ERHA area for at least 2 months prior to diagnosis of the illness (or since birth for children younger than 2 months).

Laboratory confirmation of MD was defined as isolation of *N. meningitidis* (1) from blood, cerebrospinal fluid or other normally sterile body site, or (2) from petechial or purpuric lesions, or (3) by a positive polymerase chain reaction (PCR) for *N. meningitidis* in blood, cerebrospinal fluid or other normally sterile site from a patient with a clinical diagnosis of meningitis or septicaemia.

Case finding

Cases were identified through the MD register of the ERHA. This register compiles MD cases reported by statutory and voluntary clinical and laboratory surveillance systems, including the meningococcal reference laboratory in Dublin. Age, place of residence, date of diagnosis and relevant laboratory results were determined through this register. One hundred and thirty laboratory-confirmed non-fatal cases were identified during the study period. Three laboratory-confirmed fatal cases were excluded to avoid causing distress to relatives.

Control definition

Controls were children without a history of MD, matched to cases by age (within 3 months), gender and socio-economic class (SEC). Controls had to be resident in the ERHA area at the time when MD was diagnosed and had not to have received meningococcal vaccine before recruitment. We excluded vaccinated children because it is ERHA policy to offer vaccination as well as chemoprophylaxis to all children in day-care facilities whenever a case occurs due to a vaccine preventable-strain.

Socio-economic status was determined using district electoral divisions (DED) of residence. Previous studies conducted in the ERHA area had demonstrated that determining SEC by district electoral division led to similar results to those obtained when using parental profession or household income [12]. SEC was measured in five classes, with class 1 being the highest and class 5 being the lowest class.

Control selection

Controls were selected from the Regional Interactive Child Health System (RICHS) on which all children resident in the ERHA area are registered and which provides information about important personal details. For each case, up to six controls were randomly selected from the computerized database, of whom the first three were recruited into the study. If any of these three were not eligible, refused participation, or could not be located, a questionnaire was sent to one of the other selected controls.

Definition of day-care

Day-care was defined as attending a crèche, being childminded, or both. Crèche attendance was defined as a child attending a planned pre-school programme for at least 4 h per week. Childminding was defined as a child being looked after outside his or her own home by an unrelated person for at least 4 h per week with two or more other unrelated children being childminded at the same time. Children who attended a crèche and who were childminded for less than 4 h per week each but, when cumulated, had day-care for more than 4 h, were regarded as day-care attenders, whereas those with less than 4 h were regarded as non-attenders.

Other risk factors examined were size of the day-care centre and play group, time spent in day-care, and household characteristics (size, composition, crowding, smoking).

Data collection

A piloted, self-administered questionnaire was sent to the parents or guardians of cases and controls together with an explanatory letter, a leaflet about MD and a

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press

pre-paid envelope for return of the questionnaire. No inducements to participate in the study were offered and the right to refuse participation was clearly stated in the explanatory letter.

The questionnaire elicited demographic and household details, and history of day-care attendance in the 7 days prior to onset of illness for cases. The same information was obtained for controls except that details of day-care attendance were sought for the calendar month in which illness occurred in the matched case. After 4 weeks a reminder letter and a second questionnaire were sent to all non-responders.

Data analysis

Epi Info version 6.04 [13] was used for descriptive analysis. Means of continuous variables were compared with the one-way ANOVA (*F*-test) and proportions with the Mantel–Haenszel χ^2 test. To compare exposures between cases and controls, crude matched odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by conditional logistic regression using EGRET for Windows version 2.02 [14]. For categorized variables, likelihood ratio tests were used to assess statistical significance of the variable across its categories.

Variables that were associated with illness in univariate analysis, and potential confounders, were included in a multivariate model to obtain adjusted odds ratio estimates.

The effects of age, gender and socio-economic class could not be investigated because of matching on these variables. However, their possible effect modification on day-care attendance and other key exposures was examined by stratified analysis.

RESULTS

Study participants

We received completed questionnaires from 87/130 (69%) cases and 261/390 (67%) controls. The 261 controls included 32 (8%) replacements: 14 because those originally selected could no longer be located, 14 who were ineligible (meningococcal vaccine in the past, lived outside the study area for the period of interest), and 4 who refused participation.

Two cases had to be discarded because none of the matched controls responded to the questionnaire. The remaining 85 cases and their matched controls (varying between 1 and 3 controls per case) led to 182 matched pairs for primary analyses.

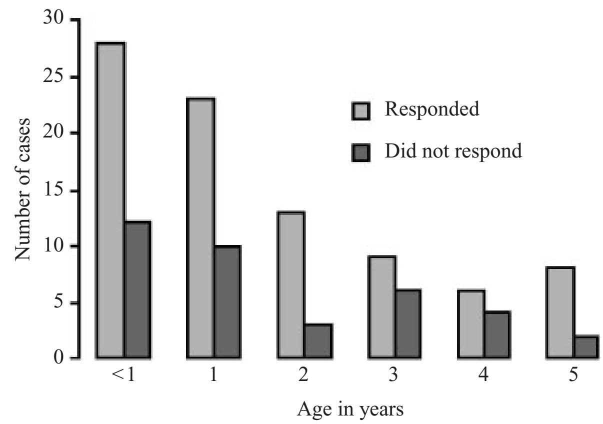

Fig. 1. Age distribution and study participation of laboratory-confirmed MD ($n = 130$) cases under the age of 6 years; EHRA, 1996–7

Table 1. *Characteristics of study participants, ERHA, Dublin, 1997–8*

	Cases ($n = 87$)	Controls ($n = 267$)
Age (in years)		
Mean (SD)	2·1 (1·6)	2·0 (1·5)
Sex		
Female	45 (52)	118 (44)
Male	42 (48)	149 (56)
Socio-economic class*		
1–3	52 (60)	153 (57)
4–6	35 (40)	114 (43)
N. meningitidis		
Serogroup B	60 (69)	
Serogroup C	18 (21)	
Not grouped	9 (10)	
Onset of illness		
January–March	28 (32)	
April–June	25 (29)	
July–September	18 (21)	
October–December	16 (18)	

Data are expressed as numbers (percent) unless indicated otherwise.

* As determined by District Electoral Division of residence.

The mean age of the 87 cases from whom questionnaires were received was 2·0 years and similar to those who did not respond (mean 1·9 years). Fifty-two (60%) of the 87 cases were children under the age of 2 years (Fig. 1), 45 (52%) were female, 52 (60%) lived in residential areas classified as belonging to SEC 1–3 (Table 1). Response rates varied by SEC: 79% for SEC 1–3 compared with 55% for SEC 4–5 (MHχ^2 8.5, $P = 0{\cdot}03$).

Sixty (69%) of the 87 cases had infection with *N.*

Table 2. *Day-care characteristics of MD cases and controls, matched odds ratios (OR) and 95% confidence intervals (95% CI); ERHA, Dublin, 1997–8*

	Cases ($n = 87$)	Controls ($n = 267$)	OR (95% CI)
Day-care	18 (21)	84 (31)	0·4 (0·2, 0·9)
Hours per week in day-care*			
0–3·9	58 (67)	150 (56)	Reference
4–19·9	16 (18)	48 (18)	0·8 (0·4, 1·7)
⩾ 20	13 (15)	69 (26)	0·5 (0·2, 1·1)
Attending crèche	16 (18)	74 (28)	0·4 (0·2, 1·0)
Hours per week in crèche†			
0–3·9	71 (82)	192 (72)	Reference
4–19·9	11 (13)	48 (18)	0·5 (0·2, 1·4)
⩾ 20	5 (5)	27 (10)	0·2 (0·1, 1·0)
Number of children in crèche‡			
1–15	4 (25)	38 (51)	Reference
⩾ 16	7 (44)	36 (49)	2·1 (0·3, 12·8)
Unknown	5 (31)	0 (0)	
Number of children in playgroup§			
1–10	4 (25)	43 (58)	Reference
⩾ 11	8 (50)	31 (42)	1·0 (0·2–6·4)
Unknown	4 (25)	0 (0)	
Being childminded	3 (3)	10 (4)	0·9 (0·2, 3·9)

Data are expressed as numbers (percent).
* Likelihood ratio statistic (LRS) 2·93 (2 D.F.), $P = 0{\cdot}23$.
† LRS 4·99(1 D.F.), $P = 0{\cdot}025$.
‡ LRS 0·67 (1 D.F.), $P = 0{\cdot}41$.
§ LRS 0 (1 D.F.), $P = 1{\cdot}0$.

meningitidis serogroup B, 18 (21%) with serogroup C, while 9 (10%) were laboratory-confirmed by PCR but not grouped. The seasonal distribution of the cases is shown in Table 1.

Risk factors

Day-care

Eighteen (21%) cases and 83 (32%) controls met the definition of day-care: 16 cases and 74 controls attended a crèche, 2 cases and 9 controls were childminded, and 1 case and 1 control had both forms of day-care.

Cases were less likely to attend day-care than controls (OR 0·4, 95% CI 0·2–0·9) while no statistically significant association was found between the number of hours per week spent in day-care and risk of MD (Table 2).

Cases were also less likely than controls to attend crèche (OR 0·4, 95% CI 0·2–1·0) with an odds ratio of 0·2 (95% CI 0·1–1·0) for spending 20 or more hours per week in a crèche. The actual number of days per week or number of hours per day spent in a crèche were not associated with MD, nor was the total number of children in a crèche nor the average number of children in a playgroup (Table 2).

Prevalence of crèche attendance in the study population was 15% for children under 2 years of age and 41% for children 2–5 years of age (MHχ^2 30·2, $P = 0{\cdot}3^{-8}$). To assess if age modified the effect of crèche attendance, odds ratios were calculated separately for both age groups but the results did not differ from the crude measure (OR = 0·4 for children 0–1 year of age, 0·5 for children aged 2–5 years). The potential effect of age as a confounder was addressed by the matched study design.

Prevalence of crèche attendance was not influenced by SEC (26% for children of lower SEC compared with 24% for children of higher SEC) or single parenthood (34% for children in households with one adult compared with 29% in households with two or more adults).

With only 3 (3%) cases and 10 (4%) controls meeting the definition of being childminded, measures of association could not be calculated and child-

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press

Table 3. *Household characteristics of MD cases and controls, matched odds ratios (OR) and 95% confidence intervals (95% CI); ERHA, Dublin, 1997–8*

	Cases ($n = 87$)	Controls ($n = 267$)	OR (95% CI)
Adults (⩾ 18 years) in household*			
1–2	59 (68)	216 (81)	Reference
3–4	18 (21)	36 (14)	2·2 (1·0, 4·7)
⩾ 5	9 (10)	7 (3)	5·4 (1·5, 19·5)
Unknown	1 (1)	6 (2)	
Children (< 6 years) in household†			
1	66 (76)	167 (63)	Reference
⩾ 2	21 (24)	96 (36)	0·5 (0·3, 0·9)
Unknown	0 (0)	4 (1)	
Crowding index‡			
< 2·0	56 (64)	183 (79)	Reference
⩾ 2·0	30 (34)	77 (28)	1·8 (1·0, 3·4)
Unknown	1 (2)	7 (3)	
Household smoking	62 (71)	171 (66)	1·4 (0·8, 2·5)
Number of smokers in household§			
0	25 (29)	90 (34)	Reference
1–2	49 (56)	160 (60)	1·3 (0·7, 2·2)
⩾ 3	13 (15)	17 (6)	3·4 (1·3, 9·1)

Data expressed as numbers (percent).
* Likelihood ratio statistic (LRS) 9·31 (2 D.F.), $P = 0{\cdot}001$.
† LRS 4·93 (1 D.F.), $P = 0{\cdot}026$.
‡ Number of persons in household/number of bedrooms; LRS 3·4 (1 D.F.), $P = 0{\cdot}06$.
§ LRS 6·43 (2 D.F.), $P = 0{\cdot}04$.

minding was analysed together with crèche attendance as 'day-care'.

Household characteristics

Cases were more likely than controls to live in households with a higher number of adults (18 years and older). There was a linear increase in risk of MD as the number of adults in the household increased (Table 3). When analysed as continuous variables, for each additional adult, the odds ratio increased by a factor of 1·5 (95% CI 1·1–2·0).

Cases were less likely to live in households with two or more children under the age of 6 years (OR 0·5, 95% CI 0·3–0·9), while the number of school-age siblings or the total number of siblings was not related to risk of illness (Table 3).

To assess if household crowding was a risk factor for MD, a crowding index was calculated as the ratio of the number of people in the home to the number of bedrooms. Cases were more likely than controls to live in households with a crowding index ⩾ 2 (OR 1·8, 95% CI 1·0–3·4). Other indices (number of adults and adolescents/number of bedrooms or total rooms) showed weaker associations while no associations were found for the absolute number of living rooms, bedrooms or total number of rooms (Table 3). Effect modification of household variables by age, gender or SEC was not present.

In 71% of case households and 66% of control households at least one person was a smoker (OR 1·4, 95% CI 0·8–2·5). Cases were more likely to come from households with three or more smokers than controls (OR 3·4, 95% CI 1·3–9·1) (Table 3).

Multivariate analysis

Conditional logistic regression was carried out with the following dichotomous variables: day-care, ⩾ 2 children under 6 years of age in household, crowding index ⩾ 2, and household smoking. The average number of adults was included as a continuous variable, as there was no threshold effect when the variable was categorized.

After adjustment, day-care (OR 0·3, 95% CI 0·1–0·7) and two or more young children in the household remained protective factors, and the number of adults and household crowding remained risk factors. After allowing for these variables, household

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press

Table 4. *Conditional logistic regression comparing MD cases and controls; ERHA, Dublin 1997–8*

	β(S.E.)*	OR (95% CI)†
Day-care (yes/no)	−1·23 (0·47)	0·3 (0·1, 0·7)
Number of children under 6 in home (⩾ 2 / < 2)	−0·86 (0·33)	0·4 (0·2, 0·8)
Number of adults in home (continuous)	0·32 (0·18)	1·4 (1·0, 1·9)
Crowding index (⩾ 2/ < 2)‡	0·51 (0·40)	2·2 (1·0, 4·1)
Household smoking (yes/no)	0·13 (0·31)	1·1 (0·6, 2·1)

Likelihood ratio statistic (5 D.F.) = 22·1, $P < 0·001$.
* Estimated coefficients (β) and standard errors (S.E.).
† Matched odds ratios (OR) adjusted for all other variables in table and age, sex and socio-economic class, and 95% confidence intervals (95% CI).
‡ Number of persons in household/number of bedrooms.

smoking was no longer associated with illness at the 95% confidence level (Table 4).

Interactions were investigated for all variables in the multivariate model but did not change the interpretation of the results.

A separate multivariate analysis for serogroup B disease showed similar results to those obtained from the entire study population. An analysis by serogroup C disease was not feasible because of the small numbers of pairs.

DISCUSSION

Our results suggest that there is no increased risk of MD for children attending day-care. In fact, we found that children attending crèche were at a lower risk than non-attenders and that the more time children spent in day-care, the more marked was this protection. Size of a day-care facility or the number of children in a playgroup were not associated with illness.

A limitation of our study was the retrospective design. Given a study period of 2 years, recall bias is likely to be present. Particularly the public concern about the safety of day-care may have led to a more accurate recall of day-care exposures among parents of cases than of controls. This would strengthen rather than weaken our finding of day-care being protective. Conversely, by enquiring about day-care attendance over a 1-month period for controls and a 1-week period for cases we may have overestimated the protective effect. While unable to quantify this effect, we believe that it was small, as crèche attendance is unlikely to change over a 3-week period – particularly in view of the great demand for scarce places in Dublin and the large number of families with both parents working.

Underestimation of the protective effect of day-care may have been introduced by excluding controls who had received meningococcal vaccine in the past as vaccinated children may have been more likely to be in day-care than unvaccinated children. However, we assume this underestimation to be small as only 8 of 390 controls had to be replaced because of prior vaccination.

Our findings are plausible in light of current knowledge about transmission of meningococcal disease. It is generally accepted that asymptomatic carriers of *N. meningitidis* are the main source of transmission and that adults have much higher carriage rates (5–25%) than infants and young children [15,16]. To effect transmission, contact with a carrier generally needs to be close and prolonged, as usually found in members of the same household. Strains indistinguishable from index cases are often documented among family members, suggesting that most infants and young children acquire their invasive strain from close contact within the family [17]. Removing children from such contact – as would occur through regular attendance at day-care – may put them at a lower risk than when staying among adults at home. This hypothesis is supported by our findings and that of other studies showing that the number of adults and crowding in the household are independent risk factors for illness [17–19].

Unlike several other studies we did not demonstrate a link between passive smoking and MD [8,17,18]. Given the high prevalence of household smoking (68%) in our study population, our finding may reflect a lack of statistical power rather than a true lack of effect.

In conclusion, we found no evidence that day-care attendance puts children at higher risk of MD while we confirmed the importance of household risk factors that have been described previously.

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press

ACKNOWLEDGEMENTS

We wish to thank all persons in the Republic of Ireland who contributed to the study and supplied data on cases and controls; Dr Alain Moren and Dr Mike Rowland for their helpful advice in reviewing the manuscript; and the parents of all children who agreed to provide data on their children. The authors also thank the Department of Public Health in the Eastern Health Board in Dublin for financial support.

REFERENCES

1. Noah N, Henderson B. Surveillance of bacterial meningitis in Europe 1998–1999. London: PHLS Communicable Disease Surveillance Centre, 2000.
2. National Disease Surveillance Center. Epidemiology of meningococcal disease in Ireland. Epi-Insight 2000; 1: September 2000. Available at URL: http://www.ndsci.ie.
3. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory infections: to what degree is incidence affected by day-care attendance? Pediatrics 1987; **79**: 55–60.
4. Cody A, Makintube S, Istre GR. Day-care attendance and other risk factors for invasive *Haemophilus influenzae* type b disease. Am J Epidemiol 1993; **138**: 333–40.
5. Istre GR, Conner JS, Broome CV. Risk factors for primary invasive *Haemophilus influenzae* disease: increased risk from day-care attendance and school aged household members. J Paediatr 1985; **106**: 190–5.
6. Fogarty J, Moloney AC, Newell JB. The epidemiology of *Haemophilus influenzae* type b in the Republic of Ireland. Epidemiol Infect 1995; **114**: 451–63.
7. De Wals P, Hertoghe L, Borlée-Grimée I, et al. Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. J Infect 1981; **3** (suppl 1): 53–61.
8. Fischer M, Hedberg K, Cardosi P, et al. Tobacco smoke as a risk factor for meningococcal disease. Paediafr lnfecf Dis J 1997; **16**: 979–83.
9. Jacobsen JA, Filice GA, Holloway JT. Meningococcal disease in day-care centers. Pediatrics 1977; **59**: 299–309.
10. Kaiser AB, Hennekens CH, Saslaw MS, Hayes PS, Bennet JV. Sero-epidemiology and chemoprophylaxis of disease due to sulphonamide resistant Neisseria meningitidis in a civilian population. J infect Dis 1974; **130**: 217–24.
11. Rosenstein N, Levine O, Taylor JP, et al. Efficacy of meningococcal vaccine and barriers to vaccination. JAMA 1998; **279**: 435–9.
12. Johnson Z, Lyons R. Socioeconomic factors and mortality in small areas. Ir Med J 1993; **86**: 60–2.
13. Dean AG, Dean JA, Coulombier D, et al. Epi Info, Version 6.04: a wordprocessing, database, and statistics program for epidemiology on micro-computers. Centers for Disease Control and Prevention, Atlanta, Georgia, USA, 1996.
14. Egret for Windows, Version 2.02. Cytel software corporation, 1985–1999. Cambridge, Mass, USA.
15. Cartwright, K. Meningococcal carriage and disease. In: Cartwright K, ed. Meningococcal disease. Chichester: John Wiley, 1995: 115–55.
16. Broome CV. The carrier state: *Neisseria meningitidis*. J Antimicrob Chemother 1986; **18** (suppl A): 25–34.
17. 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**: 315–28.
18. Stuart JM, Cartwright KAV, Dawson JA, Rickard J, Noah ND. Risk factors for meningococcal disease: a case control study in south west England. Commun Med 1988; **10**: 139–46.
19. Baker M, McNicholas A, Garrett N, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J 2000; **19**: 983–90.

https://doi.org/10.1017/S0950268801005817 Published online by Cambridge University Press