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Effectiveness of different policies in preventing meningococcal disease clusters following a single case in day-care and pre-school settings in Europe

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SUMMARY

National policies for chemoprophylaxis after single cases of meningococcal disease in day-care or nursery settings vary across Europe. We carried out a multi-national retrospective study to compare the effectiveness of different policies. Countries were divided into those recommending chemoprophylaxis only to close contacts (policy A, close) and those recommending chemoprophylaxis for all children in the same nursery (policy B, mass). Country-specific relative risk (RR) of a cluster was defined as the ratio of the number of clusters observed to the number of clusters expected by chance. In total, 37 clusters were identified between 1 January 1993 and 31 December 2002. After adjusting for marked heterogeneity in RR by country, the ratio of RR between countries suggested possible benefit from mass prophylaxis (RR ratio 3·8, 95% CI 0·7–22·0), although the difference was not statistically significant ($P = 0{\cdot}22$). The costs of this approach and the low risk of clustering need to be taken into account when deciding national policy.

INTRODUCTION

Clusters of meningococcal disease are rare in child-care or nursery schools [1], but cause high levels of public and professional concern. In 1995 an enhanced surveillance system was set up in England & Wales to detect clusters of meningococcal disease in pre-school and school settings through retrospective and prospective reporting of clusters at district level. In 6 years of observation this system detected 20 clusters in nursery schools. The relative risk of clusters in the 4 weeks after a single case in nursery schools compared to the age-specific background risk was 28 (95% CI 15–40), an absolute risk to an individual in a nursery school of $70/10^5$ [2]. Nearly 30% of cases occurred within 2 days after a single case, and 68% within the first 7 days. The risk of further cases and the short time-interval between cases underlines the need for rapid implementation of any control measures.

In 2000 the European Monitoring Group on Meningococci (EMGM) Public Health Policy Working Group reviewed the effectiveness of

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Table 1. *Definitions adopted for the purpose of the study*

Term	Definition		
Cluster	Two or more laboratory-confirmed cases of meningococcal disease within 4 weeks in children attending the same nursery school		
Nursery school	Kindergarten, nursery or day-care centre attended by children of pre-school age (0–6 years)		
Close contacts	Those living and/or sleeping in the same household-like setting		
Policy B	Effective chemoprophylaxis provided to all children in a nursery school after a single case of meningococcal disease		
Policy A	Effective prophylaxis only to close contacts after a single case of meningococcal disease occurs or adoption of ineffective chemoprophylaxis		
Effective chemoprophylaxis	Drug	Dosage	Duration and route of administration
	Rifampicin	10 mg/kg (children 1–12 years), 5 mg/kg (<12 months of age)	Twice daily for 2 days, orally
	Ceftriaxone	125 mg/kg (children <15 years)	Single dose, intramuscular
	Ciprofloxacin	20 mg/kg	Single dose, orally
Ineffective chemoprophylaxis	Penicillin, ampicillin, nalidixic acid, erythromycin, chloramphenicol		
Exposed	Those nursery schools where policy B is adopted after a single case of meningococcal disease		
Non-exposed	Those nursery schools where policy A is adopted after a single case of meningococcal disease		

chemoprophylaxis in preventing further cases of meningococcal disease. Chemoprophylaxis reduced the risk of further cases in household contacts by 90% during the first month after a case [3]. No studies were found that evaluated the effectiveness of such policies in nursery schools. This lack of evidence has led to two main approaches to policy across Europe once a single case occurs: giving chemoprophylaxis either to close contacts of the case only (policy A) or to all children attending the same nursery (policy B).

With the aim of improving coordination of infectious disease control and informing prevention policies in Europe, we carried out a study to assess the effectiveness of these two policies by comparing the incidence of clusters of meningococcal disease in European countries according to the policy used.

METHODS

All 38 countries in the EMGM and/or the European Invasive Bacterial Infections Surveillance Network were invited to participate in a retrospective cohort study. The cohort comprised those children in the study countries who attended 'nursery schools' (for definitions see Table 1) with at least one case of meningococcal disease between January 1993 and December 2002. The outcome of interest was the number of clusters in nursery schools for each country.

Data collection was run in two phases: Phase 1 was a feasibility survey by email to assess data availability and willingness to participate. Phase 2 involved the collection of the data. The minimum set of data required for Phase 2 included information about clusters in nursery schools, surveillance information on laboratory-confirmed cases of meningococcal disease (number of cases aged 0–6 years by year of age), numbers of children (0–6 years) by year of age in the population, number of nursery schools, and number or proportion of children attending nursery schools.

In Phase 2, these data were requested from each country for 1994, 1997 and 2001, but information on clusters were requested for the full 10-year period. Data on clusters of meningococcal disease included number of cases in the cluster, date of onset of each case, age of cases and serogroup of the causative strains. Countries were also asked for definitions of cases of meningococcal disease, close contacts and clusters. Data about prophylaxis policy adopted after a single case in a nursery school were also collected, including year of implementation, type and dosage of antibiotic administered, target group for prophylaxis,

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Table 2. *Formulas adopted to estimate relative risk of clusters by country and relative risk ratio by policy*

Expected number of cases in nurseries during the observation period (N_1)	$N_1 = \Sigma_A$ number of cases aged $A \times$ proportion of children aged A attending nursery
Expected number of cases in a single nursery during the observation period (N_2)	$N_2 = N_1$/number of nurseries
Probability of 2, 3 cases within a single nursery by chance (P_2, P_3) (Note: Probability of >3 cases negligible)	$P_2 = \exp(-N_2) \times N_2^2/2$, (calculated from the Poisson distribution with mean N_2) $P_3 = \exp(-N_2) \times N_2^3/6$
Probability of 2, 3 chance cases form a cluster of 2 cases within 4 weeks of one another (C_2, C_3)	$C_2 = 8$/total weeks of observation (8 derived from assigning a date to one case then the next case must be within ± 4 weeks of this date) $C_3 = C_2 + (1 - C_2) \times 16$/total weeks of observation (16 derived from assigning dates for the first two cases then the third case needs to be within ± 4 weeks of either of the first two)
Expected number of nurseries with a chance cluster (E)	$E =$ Number of nurseries $\times [(P_2 \times C_2) + (P_3 \times C_3)]$
Country-specific relative risk (RR) of cluster in a nursery	$RR = O/E$ ($O =$ no. observed clusters)
Relative risk ratio (RRR) of having a cluster by policy	$RRR = \frac{\Sigma \text{ clusters observed}/\Sigma \text{ clusters expected (for countries adopting policy A)}}{\Sigma \text{ clusters observed}/\Sigma \text{ clusters expected (for countries adopting policy B)}}$

and any use of vaccine. Ineffective prophylaxis (Table 1) was recorded as not given.

For each country the relative risk of a cluster was estimated as the ratio of the number of clusters observed over the number of clusters expected by chance (Table 2). The method allowed adjustment for the number of children in the population, age group of children attending nurseries and background incidence of meningococcal disease. The risk ratio of a cluster according to policy used was defined as the ratio of the relative risk of a cluster among countries adopting policy A to the relative risk of a cluster among countries adopting policy B (Table 2).

As data on nursery school size in several countries was not available, the analysis was carried out assuming that all countries had the same nursery size using the median value of those countries that were able to provide this data. Heterogeneity between relative risk in countries using policy A or policy B was examined by testing for evidence of over-dispersion in a Poisson regression model. The data were re-analysed after adjustment for heterogeneity by rescaling the variance in the model by the ratio of the deviance and residual degrees of freedom. As data from France indicated that mean size of 'maternelles' was 95 and as policy in France was to recommend prophylaxis only for the same class (mean size 27), the country was assigned to policy B and cluster definition was restricted to cases in the same class.

RESULTS

Among the 38 countries initially invited to participate, 22 returned the feasibility questionnaire. Of these, 12 were able to provide the minimum dataset and were therefore included in Phase 2 (Austria, Czech Republic, Denmark, France, Italy, Norway, Portugal, Republic of Ireland, Scotland, Spain, Sweden, England & Wales). Nine countries reported using policy A, and five policy B (England & Wales and Austria were counted twice as they changed policy during the study period) (Table 3). More than 8 million children were included in the cohort. The overall number of nurseries was ~237 000 and the median nursery size was 38 (range 22–74). The estimated annual rate of meningococcal disease per 1000 nurseries was quite low, ranging between 0·01 (Italy) and 1·29 (Portugal).

Thirty-seven clusters of meningococcal disease in nurseries were observed, 31 from countries using policy A and six from countries adopting policy B (Table 4). England & Wales was the country with the highest number of clusters reported. There was variability in country-specific relative risk of a cluster, ranging between 0 and 75·9 (Table 4, Fig.). The mean absolute risk of clusters was 0·9/100 primary cases in countries using policy A and 0·3/100 in those using policy B. The overall number of expected clusters was 1·53 and 1·12 for countries using policy A and B

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Table 3. *Chemoprophylaxis policy adopted by country*

Country	Year of implementation	Vaccination*	Drugs used†
Policy A	2000	Yes	Rif, Ctx, Cip
Austria	1993	Yes	Pen
Czech Republic	1992	Yes	Cip, Rif, Ctx
Denmark	1980	Yes	Rif, Ctx, Cip
Italy	1989	Yes	Pen
Norway	1995	Yes	Rif, Cip
Scotland	Not mentioned	Yes	Rif, Ctx, Cip
Spain	1993	Yes	Rif, Cip, Pen
Sweden	1995	Yes	Rif, Cip
England & Wales			
Policy B			
Austria	Not mentioned	Yes	Rif, Ctx, Cip
Ireland	1999	Yes	Rif, Ctx
Portugal	1998	No	Rif
France	1990	Yes	Rif
England & Wales	1993–1995	Yes	Rif

* Use of vaccine combined with chemoprophylaxis.
† Rif, Rifampicin; Ctx, ceftriaxone; Pen, penicillin; Cip, ciprofloxacin.

respectively, an overall risk ratio of 3·77. Testing for over-dispersion showed significant heterogeneity between countries adopting the same policy ($P<0{\cdot}001$ for both policy A and B). After adjusting for heterogeneity, the protective effect of policy B was not significant ($P=0{\cdot}22$).

DISCUSSION

This is the first study to assess the effectiveness of different chemoprophylaxis policies across Europe in preventing clusters of meningococcal disease in nursery schools. Although there was possible benefit after mass prophylaxis, the wide heterogeneity in risk of clusters did not allow us to draw a firm conclusion. Many factors can account for such heterogeneity including (*a*) different sensitivities in detection of primary cases, (*b*) different sensitivities in detecting clusters, (*c*) differences in data quality. The overall risk of clusters was low whatever the policy adopted.

One limitation of the study was the lack of accurate national statistics on nursery schools, including number of institutions, proportion of children attending them and the nursery size. The dynamics of meningococcal transmission in nursery-school settings are not known, but it seems reasonable to think that group size may well be one important determinant of risk of clusters. Because of the lack of reliable data we assumed all countries had the same nursery size group and identified this number as the median of the nursery size available. This assumption precluded assessment of how this parameter affects the country-specific relative risk.

A protective effect of widespread chemoprophylaxis is somehow intuitive and has been shown to be effective in household settings. A systematic review suggested that chemoprophylaxis to household contacts reduced by 90% the risk of meningococcal disease after a case occurred [3]. However, the likelihood and type of contact in nursery schools and risk of transmission may differ from those in the household. If mass chemoprophylaxis is protective in the nursery setting, other factors need to be considered before such a policy is advised in nursery schools. One factor is the actual risk of having a cluster after a single case [4] (less than 1% in our study), another is the economic cost of treating the whole nursery school after a case has occurred [5]. Due to the high concern about meningococcal disease, it is likely that the general public would accept substantial financial costs, but costs of widespread use of antibiotics are not only financial. The higher the numbers of children treated, the higher the risk of adverse events and development of antimicrobial resistance [6, 7]. Moreover, the widespread use of antibiotics would be expected to clear carriage of *Neisseria lactamica* in children, potentially interfering with natural development of immunity against meningococcal infection [8].

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Table 4. *Relative risk ratio of cluster of meningococcal disease in nursery schools in countries using policy A or B, 1993–2002*

Policy	Country	Estimated no. of primary cases	No. of clusters		RR*	95% CI
			Expected	Observed		
A	Austria†	22	0·0025	0	0·0	0·0–1489
	Czech Republic	119	0·0160	0	0·0	0·0–23
	Denmark	407	0·2399	7	29·2	11·7–60
	Italy	41	0·0007	0	0·0	0·0–5366
	Norway	119	0·0234	1	42·7	1·1–239
	Scotland	261	0·1256	0	0·0	0·0–29
	Spain	1702	0·8554	7	8·2	3·3–17
	Sweden	41	0·0013	0	0·0	0·0–2908
	England & Wales†	680	0·2660	16	60·1	34·2–92
	Total		1·530	31		
B	Austria	56	0·0063	0	0·0	0·0–583
	France	890	0·0741	0	0·0	0·0–50
	Ireland	588	0·9520	1	1·1	0·03–5·9
	Portugal	177	0·0527	4	75·9	20·9–193
	England & Wales	158	0·0325	1	30·8	0·8–172
	Total		1·117	6		
			Expected	Observed	RRR‡	95% CI
	Policy A		1·530	31	3·77	1·6–9·0
	Policy B		1·117	6		
	After adjusting for heterogeneity				3·77	0·7–22·0

* Relative risk of cluster by country.
† Included in policy A and B as changed policy during the observation period.
‡ RRR, Relative risk ratio.

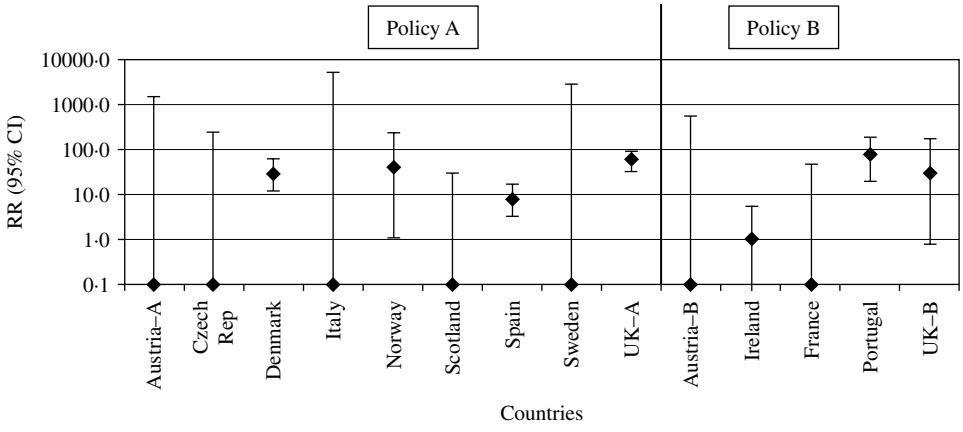

Fig. Relative risk (RR) of a cluster in nursery schools by country using policy A or policy B.

An alternative policy, as adopted in one country, would be to restrict prophylaxis to a subgroup of children of similar age sharing the same room within a nursery.

In conclusion, while our findings support possible benefit from mass chemoprophylaxis after a single case in nursery schools, marked heterogeneity of relative risk between countries does not provide clear evidence of benefit. The low risk of clustering in this setting and potential adverse effects from widespread antibiotic treatment should be considered when deciding policy on chemoprophylaxis.

Surveillance systems able to provide reliable and comparable data on cases and clusters of

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meningococcal disease in Europe are necessary to increase the validity of risk comparisons between countries.

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DECLARATION OF INTEREST

None.

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