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REVIEW ARTICLE
Effectiveness of vaccinating household contacts in addition to chemoprophylaxis after a case of meningococcal disease: a systematic review

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SUMMARY

We performed a systematic review to estimate the effectiveness of vaccination, in addition to chemoprophylaxis, in preventing meningococcal disease among household contacts. Medline, EMBASE, EMGM, and EUIBIS were used for data collection. Studies reporting on at least 100 primary cases and on subsequent cases in household settings with follow-up of more than 2 weeks after onset of disease in the primary case were reviewed. A meta-analysis was used to calculate the average attack rate in household contacts given chemoprophylaxis 14–365 days after onset of disease in the primary case. In total, 652 studies were identified, five studies and one unpublished report met the inclusion criteria. The weighted average attack rate was 1·1/1000 household contacts (95% CI 0·7–1·7). This review supports vaccination of household contacts in addition to chemoprophylaxis to reduce the risk of meningococcal disease among household contacts of a case caused by a vaccine-preventable serogroup.

INTRODUCTION

Meningococcal disease is a severe illness with high case fatality (5–10%) and frequent sequelae (10–20%) that require lifelong medical attention [1–3]. Long-term complications include headaches, skin scarring, limb amputation, deafness and learning difficulties. One well-defined risk factor for developing meningococcal disease is being a close contact of a primary case [4, 5]. Treatment with rifampicin, ceftriaxone, or ciprofloxacin is effective in the eradication of meningococcal carriage and reduces the number of subsequent cases in a household setting [6, 7]. However, subsequent cases still occur, and it has been suggested that chemoprophylaxis merely postpones the onset of disease in household members [8]. Some countries also recommend chemoprophylaxis for the primary case before discharge from hospital. Even so, eradication of carriage within households using chemoprophylaxis cannot be expected to eliminate the short-term risk of meningococcal disease among household members. Appropriate immunization of close contacts could add medium and longer term protection.

Two types of vaccines are currently licensed in Europe; polysaccharide vaccines against serogroups A, C, W135 and Y and newer protein-polysaccharide conjugate vaccines against serogroup C. A survey in 2007 found that 14 European countries recommended vaccination of household contacts in addition to chemoprophylaxis, and seven did not [9]. The lack of

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evidence for effectiveness of strategies used in public health management of meningococcal disease is a well-recognized obstacle in the development of coherent policies and is reflected in the variations in approach [10]. We systematically reviewed the risk of subsequent cases among household contacts who had already received effective chemoprophylaxis (rifampicin, ciprofloxacin, ceftriaxone) after diagnosis of meningococcal disease in the primary case.

METHODS

Systematic literature review

We identified studies by searching Medline (1 January 1966 to 31 March 2006) and EMBASE (1 January 1974 to 31 March 2006) and by examining the references of the papers that met the inclusion criteria. We used the following search terms: *Neisseria meningitidis or* meningococcal disease *and* subsequent cases *or* associated cases *or* household contacts *or* chemoprophylaxis *or* subsequent attack rate *or* secondary attack rate *or* close contacts. In addition, members of the European Monitoring Group for Meningococci (www.emgm.eu) and members of the European Union Invasive Bacterial Infection Surveillance network (www.euibis.org) were contacted and asked to inform us of any relevant published or unpublished data.

Inclusion and exclusion criteria

Abstracts were reviewed by M.H., and initially selected on title and abstract alone. The remaining papers were reviewed by M.H. and J.S., and further selected based upon the full text. Studies reporting on at least 100 sporadic cases and on subsequent cases in household contacts after effective chemoprophylaxis with a follow-up period of more than 2 weeks after onset of disease in the index case were included in the meta-analysis. Effective chemoprophylaxis was taken to be a short course of rifampicin, or one dose of ceftriaxone or ciprofloxacin [7]. Papers reporting specifically on outbreaks were excluded to avoid bias from unusually high attack rates.

Case definitions

A primary case was defined as the first case of invasive disease due to *N. meningitidis* in a household setting. A household contact was defined as any person living in the same house or sharing the same sleeping quarters as the primary case in the 10 days prior to the onset of disease in the index case. A subsequent case of potentially vaccine-preventable disease was defined as a case of *N. meningitidis* in a household contact 14–365 days after onset of disease in the primary case.

Assumptions

The minimum interval of 14 days was the sum of the period between onset of meningococcal disease in the primary case and vaccination of household contacts (estimate 7 days) and the period between vaccination and development of immunity (estimate 7 days). Where data on some variables was incomplete, e.g. size of households in primary cases, proportion of contacts given prophylaxis, we made an estimate based on data from similar settings in other studies. In one paper [11] where only aggregated data on times of subsequent cases was available, we assumed an equal time distribution of subsequent cases within each given time period. Vaccine efficacy of 85–95% and case fatality of 5–10% were used in the meta-analysis [1, 12, 13].

Analysis

The attack rates in household contacts in the included studies were tested for heterogeneity using a Cochran Q test. A Poisson model was used to calculate the weighted average attack rate in the meta-analysis using Stata 9.2 software (Stata Corporation, College Station, TX, USA). The number of household contacts needed to vaccinate to prevent one case of vaccine-preventable meningococcal disease among household contacts given chemoprophylaxis was calculated using the following formula:

$$\frac{(1000/\text{attack rate per 1000 household contacts})}{\text{vaccine efficacy}}.$$

Similarly, the formula for the number to prevent one death was:

$$\left(\frac{1000 \Big/ \dfrac{\text{attack rate per 1000}}{\text{household contacts}}}{\text{vaccine efficacy}}\right) \Big/ \text{case fatality}.$$

We undertook a sensitivity analysis on these estimates.

RESULTS

The literature search identified 652 abstracts, of which 173 were duplicates. After review of the abstracts 447

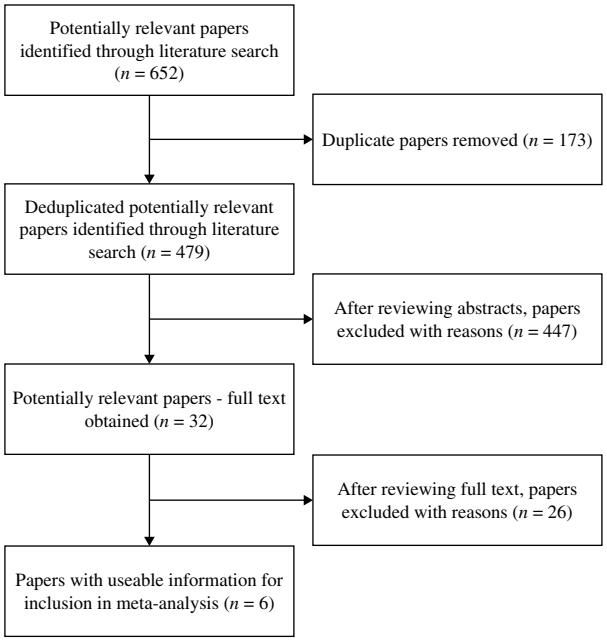

Fig. 1. Progress through the stages of the literature review.

were excluded. After review of the full text of 32 papers by two authors, six were included in the meta-analysis [11, 14–18] (Fig. 1). The main reasons for exclusion were reports of small outbreaks (<10 cases), reports on cases outside the household setting, or administration of ineffective chemoprophylaxis to contacts.

All were observational studies that measured attack rates in household contacts of primary cases. Three studies were prospective (data collected as clusters occurred) and three retrospective. We found no randomized controlled trials or observational studies that compared attack rates in vaccinated and unvaccinated groups after chemoprophylaxis. The six studies reported on a total of 4630 primary cases and 30 household clusters with 40 subsequent cases (Table 1).

Meningococcal disease attack rates among household contacts (those receiving effective chemoprophylaxis) in the six studies were statistically homogeneous ($Q = 1{\cdot}469$, $P = 0{\cdot}689$). Therefore a fixed-effect Poisson model was used for the meta-analysis. The attack rate derived from this model was 1·08/1000 contacts (95% CI 0·7–1·7) (Table 2) in the time period 14–365 days after disease onset in the primary case. After a case of meningococcal disease due to a vaccine-preventable serogroup, our best estimate of the number of household contacts needing vaccination (in addition to chemoprophylaxis) to prevent one case ranged between 638 and 1678.

Duration of follow-up was at least 31 days in all studies. Two studies had no follow-up beyond 31 days [15, 17] and the end point was not well defined in three studies [11, 16, 18]. In one study [11] the time interval between the primary and the subsequent case was reported as aggregated data (individual cluster data not available from authors) without precise dates of subsequent cases among household contacts. No studies reported on subsequent cases beyond a 1-year period.

In one study [14] 93% of contacts in household clusters had received chemoprophylaxis. In another study [11], covering an earlier period in the same country, no information was available on this proportion. For analysis we assumed that 95% of household contacts of primary cases were given effective chemoprophylaxis in both these studies. Proportions of contacts given effective prophylaxis in the other studies varied between 25% and 90% (Table 1).

All studies included laboratory-confirmed and clinically diagnosed cases. Of the clusters in households given chemoprophylaxis, all the cases in household contacts were microbiologically confirmed in three studies [11, 16, 18] and none had a different serogroup to that of the primary case. In two studies there were no cases in these contacts [15, 17], and in one study [14] it was reported that 67% of cases in clusters were confirmed and that cases within all household clusters were caused by the same or possibly the same serogroup.

DISCUSSION

Meningococcal disease is a severe illness with high attack rates in household contacts. Our best estimate of the attack rate among household contacts who received chemoprophylaxis with an antibiotic capable of eradicating meningococcal carriage (108/100 000) was 11 times higher than the CDC threshold for mass vaccination in outbreaks (10/100 000) [18]. Using existing data on vaccine efficacy, we estimated that between 640 and 1680 contacts need vaccinating to prevent a case. This is less or similar to equivalent figures in vaccination programmes that have been implemented in developed countries and that are considered cost effective, such as seasonal influenza and routine pneumococcal immunization [20, 21]. Cost-effectiveness of a meningococcal vaccination policy for contacts would depend on the costs of vaccination and the health-care costs of case management, both varying by type of vaccine used (conjugate or

Table 1. *Characteristics of studies investigating subsequent cases of meningococcal disease in household contacts used in this review*

Paper	Hastings, 1997 [14]	Sholten, 1993 [16]	Samuelsson, 2000 [17]	Cooke, 1989 [11]	CDC, 1976 [15]	Stefanoff, 2008 [18]
Country	England and Wales	Netherlands	Denmark	England and Wales	USA	Poland
Study period	1 Jan. 1993–31 Mar. 1995	1 Apr. 1989–30 Apr. 1990 (but not July–Sept. 1989)	20 Oct. 1995–30 Apr. 1997	1 Jan. 1984–31 Dec. 1987	Nov. 1973–Mar. 1974 & Jan. 1975–Apr. 1975	1 Jan. 2003–31 Dec. 2006
Follow-up period after the primary case in days	365 days	>1 month	31 days	>1 month	31 days	>1 month
Study design: all observational	Retrospective	Prospective	Prospective	Retrospective	Prospective	Retrospective
Case definition	Clinically diagnosed and/or laboratory confirmed					
Total number of primary cases	2809	502	172	3239	512	635
Number of clusters	11	7	2	16	5	5
Total number of subsequent cases	20	7	2	17	6	5
Serogroup of clusters	B, 70%; C, 30% of clusters	B, 4; B†, 1; C, 1	Not specified	A, 2; B, 13; C, 2‡	B, 2; Y, 3	B, 1; C, 1; Unknown, 3
Percentage of HHC correctly treated with CHP	95%*	25%	90%	95%*	37%	33%
Total number of HHC	8428	1506	802	9717	1510	1905
Number of HHC correctly treated	8007	381	722	9231	559	629
Number of HHC not or incorrect treated	421	1125	80	486	951	1276
Average household size	4·0	4·0	5·7	4	3·9	4·0
With correct CHP						
Subsequent cases 0–13 days	0	0	0	2*	0	0
Subsequent cases 14–30 days	6	0	0	3*	0	0
Subsequent cases 31–365 days	1	1	n.a.	9*	n.a.	1
SAR (per 1000 HHC) with CHP 0–13 days	0·0	0·0	0·0	0·2	0·0	0·0
SAR (per 1000 HHC) with CHP 14–30 days	0·7	0·0	0·0	0·3	0·0	0·0
SAR (per 1000 HHC) with CHP 31–365 days	0·9	2·6	n.a.	1·0	n.a.	1·6
Time interval primary-subsequent case	6, 18–28 days; 1, 92 days	35 days	n.a.	3, <8 days; 5, 8–34 days; 3, 35–90 days; 6, >90 days§	n.a.	42 days

Table 2. *Sensitivity analysis – number needed to vaccinate (NNV) to prevent one case, or one death*

	Minimum	Mean	Maximum
SAR per 1000 HHC	1·6	1·1	0·7
Vaccine efficacy (%)	95	90	85
Case-fatality rate (%)	10	7·5	5
NNV to prevent one case	638	1033	1678
NNV to prevent one death	6382	13777	33560

SAR, subsequent attack rate; HHC, household contact.

Case definition	Clinically diagnosed and/or laboratory confirmed					
Without/incorrect CHP						
Subsequent cases 0–13 days	12	6	2	3*	4	4
Subsequent cases 14–30 days	0	0	0	0	2	0
Subsequent cases 31–365 days	1	0	0	0	0	0
SAR (per 1000 HHC) with CHP 0–13 days	28·5	5·3	24·9	6·2	4·2	3·1
SAR (per 1000 HHC) with CHP 14–30 days	0·0	0·0	0·0	0·0	2·1	0·0
SAR (per 1000 HHC) with CHP 31–365 days	2·4	0·0	n.a.	0·0	n.a.	0·0
Time interval primary-subsequent case	10, <1 day; 2, 1–6 days and 1, 96 days	2, <1 day; 2 days; 2, 4 days and 13 days	2 and 3 days	3, <8 days; 5, 8–34 days; 3, 35–90 days; 6, >90 days§	0, 10, 11, 12, 14, and 27 days	0, 6, 7 and 8 days

HHC, Household contacts; CHP, chemoprophylaxis; SAR, subsequent attack rate; n.a., not available.
* Estimate.
† At least one case in the cluster diagnosed with serogroup B, the other case in the cluster diagnosed on clinical grounds only.
‡ Two subsequent cases occurred in a HHC who had received CHP, but not all HHC had received CHP.
§ Time interval of all subsequent cases among HHC regardless of whether or not they received CHP.

polysaccharide) and by country. There would also be high additional costs to the family and society of death and disability.

The potential impact of routine vaccination of household contacts on the attack rate among household contacts is shown in Danish surveillance data [22]. In Denmark, vaccination of household contacts has been recommended to the same group of persons as for those who receive chemoprophylaxis when the primary case is due to a vaccine-preventable serogroup since 1992. Between 1980 and 1992, before the introduction of this policy, seven serogroup C clusters were reported in household settings, with eight subsequent cases of which four occurred more than 15 days after hospitalization of the primary case. Between 1992 and 1996, after introduction of the vaccination policy, five serogroup C clusters were recorded in a household setting, all subsequent cases in these clusters occurring within the first 6 days after hospitalization of the primary case. The absence of late cases suggests benefit from vaccination.

The estimates of risk of meningococcal disease among household contacts in the six studies were consistent. All studies had limitations of data quality from incomplete data or follow-up. However, most of these limitations would have led to an underestimate of the risk in household contacts, resulting in an overestimate of the number needed to vaccinate to prevent a case. First, only one of the six studies had a follow-up period of 365 days, and only two detected subsequent cases beyond a 6-week interval. The longer the interval between the primary case and any subsequent case, the more likely that the subsequent case would be reported as a primary case. The inability to link subsequent cases that occur more than 1 month after the primary case to the primary case, results in an underestimation of the subsequent attack rate. Second, the probable overestimate of the

proportion of household contacts given effective chemoprophylaxis in two studies would have led to an underestimate of the attack rate in this group. Third, the assumption of equal time distribution is not likely to be correct. Cases in persons given effective chemoprophylaxis occur later than in those not or incorrectly treated. Fourth, the minimum period of 14 days assumed necessary for a vaccination strategy to become effective may be too long. Protective levels of antibodies can be detected 5 days after vaccination [23, 24] and, if there is more rapid diagnosis and vaccine administration, the estimated 7-day interval between diagnosis and vaccination [17] could be reduced. Therefore, countries with rapid diagnostic capacities and efficient systems for vaccine administration may be able to prevent more subsequent cases among household contacts. Fifth, some contacts of primary cases due to vaccine-preventable serogroups may have actually been given meningococcal polysaccharide vaccines in addition to chemoprophylaxis; this information was not available in most studies.

One possible reason for overestimating risk would be that some cases in clusters were clinically diagnosed, so that some may not have been true cases or may have been due to a different serogroup. However, in all but one study the cases in household contacts were microbiologically confirmed and no clusters were identified where the cases were due to different serogroups. To calculate the number of household contacts of a primary case caused by a vaccine-preventable serogroup needed to vaccinate to prevent one secondary case we assumed a similar subsequent attack rate for all serogroups including B. This assumption is supported by data on clusters in educational settings [25]. Serogroup B clusters would not be currently preventable by vaccination. Another possibility is that the cases themselves may not have been treated with antibiotics that eradicated carriage [11] such that chemoprophylaxis of the household was not optimal. Whatever drug regime is used it is clear that chemoprophylaxis cannot be 100% effective in eradicating carriage in the household or in preventing virulent strains from re-entering the family. Family members among household contacts may also be at increased risk due to genetic susceptibility.

Without the evidence of a randomized controlled trial, the findings of this review support vaccination of household contacts of meningococcal disease cases in developed countries. We do not consider that the data are strong enough to give point estimates of risk and benefit, but the true values of attack rate and number needed to vaccinate are likely to lie within or below the range of estimates given. The effectiveness of giving serogroup A vaccines in a setting where antibiotics are not used for household contacts has been shown [24]. We believe that in developed countries, household contacts of a case should be given chemoprophylaxis and, if the primary case is caused by a vaccine-preventable serogroup that contacts should also receive an appropriate vaccine. Such a policy would have a low impact on disease burden when the incidence of disease due to such strains is low and as most cases are sporadic [14, 26]. Conversely this public health measure would also have a low cost and our estimates suggest that it is cost effective. Some countries have recently seen a dramatic fall in incidence following the introduction of meningococcal serogroup C conjugate vaccines into childhood vaccination programmes [27]. Household contacts of cases due to serogroup C and who have already received C conjugate vaccine are expected to have long-term protection. Moreover, although polysaccharide vaccines are less effective in young children, quadrivalent conjugate vaccines are licensed in North America [28], and may soon be available in Europe. Therefore our recommendation should apply to those contacts of cases caused by A, C, W135 and Y strains who have not received an appropriate conjugate vaccine, and potentially in the future to contacts of cases due to B serogroups when new vaccines become available.

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DECLARATION OF INTEREST

None.

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