

Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review

Bernadette Purcell, Susanne Samuelsson, Susan J M Hahné, Ingrid Ehrhard, Sigrid Heuberger, Ivonne Camaroni, André Charlett, James M Stuart

Abstract

Objective To summarise the evidence for the role of antibiotics in preventing further cases of meningococcal disease through chemoprophylaxis given to the index patient, household contacts, and children in day care settings after a single case.

Design Systematic review.

Methods Studies were identified by searching Embase (1983-2003), Medline (1965-2003), and CAB Health (1973-2003) and by contacting the World Health Organization and the European meningococcal disease surveillance network and examining references of identified papers. The review included all studies with at least 10 cases in which outcomes were compared between treated and untreated groups.

Main outcome measure Subsequent cases of meningococcal disease 1-30 days after onset of disease in the index patient.

Results Four observational studies and one small trial met the inclusion criteria. Meta-analysis of studies on chemoprophylaxis given to household contacts showed a significant reduction in risk (risk ratio 0.11, 95% confidence interval 0.02 to 0.58). The number needed to treat to prevent a case was estimated as 218 (121 to 1135). Primary outcome data were not available in studies of chemoprophylaxis given to the index patient: when prophylaxis had not been given, rate of carriage after discharge from hospital was estimated as 3% (0 to 6), probably an underestimate of the true rate. No studies of chemoprophylaxis in day care settings were identified that met the inclusion criteria.

Conclusion There have been no high quality experimental trials looking at control policies for meningococcal disease. The best available evidence is from retrospective studies. The risk of meningococcal disease in household contacts of a patient can be reduced by an estimated 89% if they take antibiotics known to eradicate meningococcal carriage. Chemoprophylaxis should be recommended for the index patient and all household contacts.

Introduction

The severity of meningococcal disease and its tendency to cause clusters, mainly among household contacts of an index patient, means strategies to reduce the risk of further cases are of high priority. However, the lack of evidence for strategies to control meningococcal disease is a well recognised obstacle in the development of coherent policies¹ and is reflected in the variation in approach across Europe.²

Chemoprophylactic treatment to eradicate nasopharyngeal carriage and to interrupt further transmission has been a key

approach to control for more than 50 years.³ Most European countries recommend a short course of rifampicin or ciprofloxacin for all household contacts—taken here to mean those people living in the same household or having an equivalent degree of contact with the index patient. This approach is biologically plausible. The effect of rifampicin in preventing subsequent cases of meningitis caused by *Haemophilus influenzae* has, indeed, been demonstrated in a randomised placebo-controlled trial.⁴ However, the effectiveness of chemoprophylaxis for meningococcal disease has never been demonstrated in experimental research, and evidence cited in support has been limited to one observational study.⁵ Failures of this approach have been reported,⁶⁻⁸ and there is evidence of overprescribing.⁹ A different policy is recommended in Norway, where household members below 15 years of age are treated as though they have early meningococcal disease. They are kept at home and given oral penicillin for seven days, the period of maximum risk.

Some national policies also recommend chemoprophylaxis to the index case before discharge from hospital, on the premise that the pathogenic strain may otherwise be reintroduced by the index patient into the household. However, contradictory findings regarding carriage of the pathogenic meningococcal strain after full antibiotic treatment of the index patient are reflected in different recommendations. For example, policy in Denmark, Norway, and Sweden does not recommend prophylaxis for the index patient, whereas it is recommended in the United Kingdom, Canada, the United States, Spain, and Germany.

There are no uniform recommendations as to how contacts should be managed in day care settings (children aged 0-6 years). The national control policies of the United Kingdom and Denmark recommend chemoprophylaxis only after the second case in a day care setting, whereas other countries such as Ireland, Sweden, Spain, and Germany recommend chemoprophylaxis after a single case.

There is a new impetus to improve coordination of infectious disease control across countries in the European Union.¹⁰ A prerequisite for better coordination is a shared understanding of the evidence on which recommendations for disease prevention and control are based. To further this aim the European Monitoring Group on Meningococci formed a working group to conduct a systematic review of interventions for meningococcal disease where there was greatest variation between countries. Here we have evaluated the effectiveness of giving chemoprophylaxis to the index patient and to contacts in households and childcare settings.

Methods

Study inclusion and characteristics

We included all studies that had clear intervention and non-intervention groups, including experimental (randomised and non-randomised trials), observational studies, and case series with a minimum of 10 cases. We excluded case reports and opinions of authorities or committees. We did not restrict by date, country, or language of publication. We included in the intervention group those people who were given prophylactic antibiotic regimens considered effective in eradicating meningococcal carriage (for example, for adults, rifampicin 600 mg orally twice a day for two days, ciprofloxacin 500 mg orally single dose, ceftriaxone 250 mg intramuscular single dose). Those not given prophylactic antibiotics or given antibiotics considered ineffective at eradicating carriage (for example, penicillin) were included in the non-intervention group.

The primary outcome was specified a priori as the rate of subsequent cases 1-30 days after an index case, where a subsequent case was defined as another case among household contacts of the index patient (or for the day care analysis as another case in the same day care setting). We included only those studies that described at least one month of follow up after the index case. The other main outcome of interest was the rate of nasopharyngeal carriage of the pathogenic organism in the index patient on discharge from hospital.

Search strategy

We searched the Cochrane register of trials and systematic reviews, the database of abstracts of reviews of effectiveness, the health technology assessment and the national research register in England and Wales, Medline 1966-2003, Embase 1983-2003, and CAB Health 1973-2003. The text word terms and MESH headings used were: meningococcal infections, *Neisseria meningitidis*, chemoprevention, prophylaxis, chemoprophylaxis, antibiotics, drug therapy, primary health care, patient care management, community health services, communicable disease control, disease outbreaks, disease transmission, cluster, outbreak, carrier state, cases, household. We checked bibliographies of existing reviews and the identified studies. We contacted the Cochrane Acute Respiratory Infections group, the World Health Organization, and the European Monitoring Group on Meningococci.

Data extraction and synthesis

The full texts of all potentially relevant articles were obtained and two reviewers independently checked the data. If more than one paper with the same data was identified only that which contained the definitive data was included. A third reviewer from the group was available to resolve any disagreements.

Statistical methods

The meta-analyses were performed with the "meta" command in Stata (StataCorp, College Station, TX).¹¹ Combined estimates of the risk ratio and the absolute risk reduction (or risk difference) were obtained by assuming that the treatment effects from the different studies had a distribution (random effect) rather than a common treatment effect (fixed effect). In those studies where there were no cases in either the treated or untreated groups we added 0.5 to all four cells. When there were no cases in the intervention and control groups, we did not estimate risk ratios and the study was excluded from the pooled risk ratio. We used the DerSimonian and Laird approach, in which an estimate of variation within studies is combined with an estimate of variation between studies.

To estimate the pooled relative risk we used the natural logarithm and back transformed results to obtain an estimated relative risk. The number needed to treat was the reciprocal of the estimated absolute risk reduction. We used a fixed effect approach with an inverse variance method to pool the carriage rates. The effects were pooled in the same manner in the two groups. We tested statistical heterogeneity with χ^2 tests, with pre-specified potential sources of heterogeneity.

Results

The search identified 2606 papers. After reviewing titles and abstracts we retrieved 102 as potentially relevant. Of these, five studies met the criteria for this review. Of the excluded reports, many were descriptive accounts of outbreaks and case reports, some addressed a different set of questions or did not evaluate an intervention, and others did not report the outcomes of primary interest or had no comparison group. We did not identify any studies of day care and nursery schools that met our criteria.

Evidence of benefit from chemoprophylaxis to household contacts

Five studies satisfied our inclusion criteria, four retrospective cohort studies and one small trial.^{5 12-15} In total they involved 1249 sporadic cases of meningococcal disease and about 4271 household contacts. The only experimental study was a small randomised trial within a larger seroepidemiological survey.¹² Fifty four contacts from 11 affected households were randomised to receive rifampicin (35) or no treatment (19). No subsequent cases occurred in either group after nine months (table 1).

The largest and most frequently cited study used enhanced surveillance of a case series in 27 US states between 1973 and 1974.⁵ This paper partly duplicated earlier findings.¹⁶ They found an attack rate of 4.2/1000 among untreated household contacts and no cases among treated contacts (table 2). This difference suggests that chemoprophylaxis is effective (relative risk 0.15, 95% confidence interval 0.01 to 2.79) but not significant.

In a survey of meningococcal disease in the Netherlands from April 1989-May 1990,¹⁴ a secondary objective was to assess the attack rate among household contacts and document the uptake of chemoprophylaxis. Although it was not official policy to give chemoprophylaxis in the Netherlands during the study period, 55% (627 people from 220 families) of close contacts had received antibiotics. There were 502 primary cases reported during the study period. Information was available on 1130 household contacts in 75% (378) of these cases, and on antibiotics for 98% (1102) of these contacts. In the 30 day period after occurrence of the index case, there were four subsequent cases among 826 contacts that did not receive adequate chemoprophylaxis (including two in people who received penicillin) and no cases among 276 who had "optimal" treatment (0.33, 0.02 to 6.14, table 2).

In a study to evaluate the efficiency of the implementation of prophylactic measures in Denmark,¹⁵ there were no cases among 724 treated contacts and two among 72 who were not treated (0.02, 0.00 to 0.42, table 2). The two subsequent cases were in friends of the index patients who had slept in the same room as their respective index case. No further information was available on 56% of cases (table 1).

Kristiansen's study, among the 165 000 inhabitants of Telemark in Norway, examined whether a policy of targeted prophylaxis with rifampicin for contacts carrying the meningococcal strain that caused the disease could limit the spread of infection more efficiently than treatment with penicillin alone to

Table 1 Effectiveness of antibiotics to contacts after case of meningococcal disease: study characteristics

	Kaiser 1974 ¹²	MDSG 1976 ⁵	Kristiansen 1992 ¹³	Scholten 1993 ¹⁴	Samuelsson 2000 ¹⁵
Was primary goal to determine effect of prophylaxis on subsequent cases?	No (effect on eliminating carriage)	Yes	Yes (compared effectiveness of targeted rifampicin and penicillin to all <15 years)	No (assessed subsequent attack rate and described use of chemoprophylaxis)	No (assessed whether different target groups were offered chemoprophylaxis)
Study design	Experimental; small RCT	Observational; enhanced surveillance of case series	Observational. Enhanced surveillance of cases with time series comparison	Observational national survey	Observational; cross sectional with retrospective review
Setting	Two communities in Dade county, Florida; low social status; predominantly black	USA (27 states and district of Columbia)	Telemark, Norway	Netherlands, whole population	Denmark, whole population
Period of study	Apr 1970	Nov 1973-Mar 1974	Nov 1987-Dec 1989	Apr 1989-May 1990 (excluding Jul-Sep 1989)	Oct 1995-Apr 1997
Follow up time for subsequent cases	9 months	1-30 days after admission of index case to hospital	7-31 months (1976 study); 12 months (1974 study)	1 month	>24 hours (at least 2 months' surveillance for 1 year)
Household contact definition	"Frequently slept and ate in same dwelling"	"Member of patient's household"	Wide definition for children (see text)	"Slept in household of index case 1 week before"	Slept in household or "kissing" <10 days before index case
Case ascertainment	Health authority notifications	Health authority notifications	Hospital admissions. Cross checking with laboratory	Ref lab or notifications. Visits (x2) and questioning households of cases	Notification to national system
No of primary cases	11 households	512 cases (324 serogrouped)	52 cases	502 cases	172 cases (out of 394 total for period)
Intervention strategy (household contacts)	Rifampicin	Minocycline (27%); rifampicin (8%); sulfonamide (18%)	Penicillin <15 years (1984-87); rifampicin (carriers only) (1987-89)	Rifampicin or minocycline	Ciprofloxacin
Comparison group	Untreated "controls" (no placebo specified)	Untreated households (penicillin, 34%)	Penicillin to HHC <15 years only	Insufficient/no treatment	No treatment
No of contacts treated	35/54 (65%)	693/1872 (37%)	14/441 (3%) (1987-89)*	276/1102 (24%)	724/802 (90%) (79% <1/7)
Loss to follow up/no information	NR	4% (12 out of 311 households) 1974 NR 1976	NR	25% (124 out of 502 households)	56% (222 out of 394 notified cases)
Index case prophylaxis	NR	NR	NR	6% (29)	Not recommended in Denmark
Background incidence	13/100 000 (in 2 communities); 2.4/100 000 (Dade county) Epidemic (observed/expected incidence=30/16 × 10 ⁴ Aug 1969-Apr 1970)	0.23/100 000; non-epidemic	Norway: 6.7/100 000 (1986); 4.2/100 000 (1989). Telemark: 9.4/100 000 (1986); 1.8/100 000 (1989); non-epidemic	4/100 000; non-epidemic	3-4/100 000; non-epidemic
Serogroup of cases	C	5A; 89B; 66C; 36Y; other	8B, 4C, 1Y	4B, 1C	B; 15; P1.7, 16

*In addition, eight household members <15 years treated with penicillin.
NR = not recorded.

Table 2 Estimate of effect of chemoprophylaxis given to household contacts after sporadic case of meningococcal disease

Study	Primary cases	Contacts	Attack rate		Risk ratio (random 95% CI)	Risk difference × 10 ⁴ (random 95% CI)
			Treated group	Untreated group		
Kaiser 1974 ¹²	11 households	54	0/35	0/19	—	0 (−784 to 784)
MDSG 1976 ⁵	512	1872	0/693 (177 households)	5/1179 (297 households)	0.15 (0.01 to 2.79)	−42 (−86 to 1)
Scholten 1993 ¹⁴	502 (including 2 co-primary cases)	1130	0/276	4/826	0.33 (0.02 to 6.14)	−48 (−119 to 22)
Samuelsson 2000 ¹⁵	172	802	0/724	2/72	0.02 (0.00 to 0.42)	−278 (−695 to 140)

household members aged under 15 years.¹³ No subsequent cases occurred among 441 potential contacts screened and treated with rifampicin compared with 15 (11 confirmed) cases in 1984-87, when only penicillin was given. Although this study suggests benefit from the targeted intervention, we could not measure risk reduction as the number of contacts was not available for the earlier time period. The follow up period was much longer and the contact definitions were much broader than the definitions used for our review.

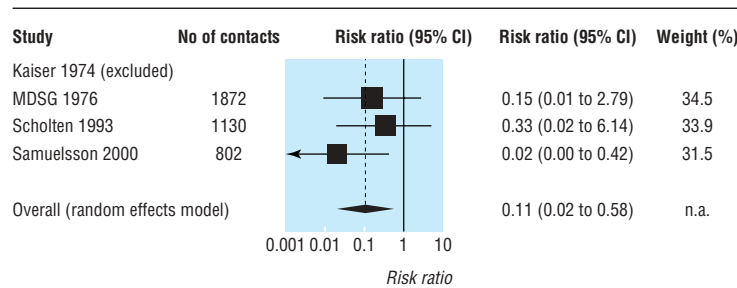
Summary effect estimates for chemoprophylaxis versus no treatment

Three studies, in the United States, Denmark, and the Netherlands, had sufficiently similar characteristics (clinical homogeneity) for inclusion in the meta-analysis.^{5 14 15} We did not include Kaiser's study¹² as there were no events in treatment or intervention group.

The summary risk ratio was 0.11 (0.02 to 0.58; figure). This implies that chemoprophylaxis given to household contacts after a case of meningococcal disease reduces the risk of subsequent cases by 89%. Results of tests for heterogeneity were not significant ($P=0.39$). The pooled absolute risk reduction was 46/10 000 (9/10 000 to 83/10 000), and the number needed to treat to prevent a case was estimated as 218 (121 to 1135).

Evidence for use of chemoprophylaxis in index patients before discharge from hospital

We found no studies comparing index patients given chemoprophylaxis with those who were not. Four studies assessed persistent meningococcal carriage on discharge from hospital in patients who had not received chemoprophylaxis. Alvez et al showed that three of 48 children (aged 3 months to 13 years) who were treated with 300 000 units/kg/day of penicillin G sodium intravenously for at least 10 days were carriers of *Neis-*



Effect of chemoprophylaxis given to household contacts after a case of meningococcal disease on risk of subsequent cases: pooled risk ratio

seria meningitidis on discharge.¹⁷ In the study of Abramson and Spika meningococci were cultured from the upper respiratory tract in one of 14 patients discharged after completion of intravenous therapy, initially with ampicillin or chloramphenicol then benzyl penicillin.¹⁸ Four patients had positive cultures one week after the end of treatment. The household contacts of the patients, but not the patients themselves, had received chemoprophylaxis with rifampicin. Barroso found two of 51 patients had positive nasopharyngeal swabs after the end of their treatment,¹⁹ though the exact timing of the swabs in relation to hospital discharge (eight hours after the end of treatment to six days after discharge) is not clear. The patients had been treated with ampicillin, penicillin, or chloramphenicol. Weis found no carriers among 47 patients on discharge.²⁰ Although this study did not specify the antibiotic treatment used, benzyl penicillin was then the standard treatment for meningococcal disease in Denmark (S Samuelsson, personal communication).

The four studies were included in meta-analysis. Results of tests for heterogeneity were not significant ($P = 0.35$). The pooled estimate from these studies was calculated as 0.03 (0.00 to 0.06, table 3).

Discussion

We found that if household contacts of a patient with meningococcal disease are given prophylaxis with antibiotics that eradicate meningococcal carriage there are fewer subsequent cases. The reduction in risk is considerable. We estimate that about 200 household contacts need to be treated to prevent a subsequent case during the first month. This applies to a strategy of giving chemoprophylaxis to a network of household contacts but provides no evidence to support indiscriminate prescribing of antibiotic prophylaxis to people outside this group.

The main difficulty in interpreting the findings is that they are obtained from retrospective observational studies. Risk factors for meningococcal disease, such as young age, male sex, passive smoking, and lower socioeconomic status, are all potential confounding factors.²¹⁻²² None of the studies took account of these factors in their analysis. There is evidence that people of lower socioeconomic status are less likely to receive preventive

interventions.²³ If this were the case for meningococcal disease, these observational studies would overestimate the true benefit of treatment. On the other hand, adults have a lower baseline risk of disease and if children were more likely to get prophylaxis than adults this would underestimate the true effect. The studies gave no baseline comparisons of age distribution between treated and untreated groups. If efforts to achieve follow up had differed in some way between treated and untreated groups, this would only dilute the observed effect of treatment, unless the investigators had somehow applied different stringency of criteria (for instance, for case definitions) between groups. The risk to untreated household contacts is highest in the first week after the index case and declines rapidly thereafter.²⁴ A one month period to measure risk reduction is therefore reasonable but does not assess whether chemoprophylaxis could prevent subsequent cases beyond this period.²⁵

Previous studies have suggested that subsequent cases may be caused by reintroduction of the virulent strain to the household by the index patient.²⁶ We estimate that about 3% of index patients treated with penicillin and who have not received chemoprophylaxis will still be carrying the virulent strain on discharge from hospital. As carriage may be suppressed but not eradicated by penicillin treatment so that carriage is less easily detected on completion of treatment,¹⁸ this figure is likely to underestimate the true carriage rate among index patients. Giving chemoprophylaxis to the index patient before discharge from hospital should also be supported, unless they have already been treated with an antibiotic such as ceftriaxone, which is known to eradicate carriage.

Studies to estimate the effect of chemoprophylaxis in day care settings are needed, and the current variation in policy across European countries is therefore not surprising. As clusters are unusual in this setting and as policies vary by country, a multinational study may be needed to provide evidence on benefit.

This is the first systematic review of evidence for control policies for meningococcal disease and supports giving a short course of antibiotics that eradicate carriage to household contacts and index patients. The consistency of the study findings, the size of the risk ratio, and the biological plausibility of this approach lend further weight to our conclusions. We believe that such a policy should be applied across Europe and other industrialised countries.

Table 3 Estimated carriage rate on discharge from hospital in index patients not treated with chemoprophylaxis. Meta-analysis results

Study	Carriage on day of discharge from hospital	% carriage rate (95% CI)	Weight
Alvez ¹⁷	3/48	6.3 (1.3 to 17.2)	819.20
Abramson ¹⁸	1/14	7.1 (0.2 to 33.9)	211.08
Barroso ¹⁹	2/51	3.9 (0.5 to 13.5)	1353.58
Weis ²⁰	0/47	0.0 (0.0 to 7.5)	2257.02*
Pooled effect	—	2.6 (0.0 to 5.5)	—

*Assuming carriage rate of 1/47.

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Contributors: JMS conceived the study. All authors except AC contributed to the design of the study, carried out searches, and extracted data. AC performed the meta-analyses. BP wrote the first draft. All authors were involved in the writing of the final draft. JMS is guarantor for this study.

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What is already known on this topic

A lack of evidence for strategies to control meningococcal disease has resulted in a variation in approach among countries in Europe

Most countries recommend a short course of rifampicin or ciprofloxacin for all household contacts but evidence to support this has previously been limited to one observational study

There are no uniform recommendations for giving chemoprophylaxis to the index patient or to contacts in childcare settings

What this study adds

Evidence from three studies supports the use of chemoprophylaxis to prevent further cases of meningococcal disease

The risk of further cases during the first month is reduced by 89%, and to prevent one case about 200 household contacts need to be treated

After treatment of disease with penicillin and without giving chemoprophylaxis, at least 3% of index patients will be carrying the virulent meningococcal strain on discharge from hospital

There are insufficient studies to estimate the effect of chemoprophylaxis in childcare settings

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Communicable Disease Surveillance Centre South West, Gloucester GL10 3RF
Bernadette Purcell *specialist registrar*
James M Stuart *consultant epidemiologist*

Statens Serum Institut, Copenhagen, Denmark 2300
Susanne Samuelsson *consultant epidemiologist*

Communicable Disease Surveillance Centre, Cardiff, Wales CF4 3QX
Susan J M Hahné *European Programme for Intervention Epidemiology training fellow*
Ivonne Camaroni *European Programme for Intervention Epidemiology training fellow*
Landesuntersuchungsanstalt für das Gesundheits und Veterinärwesen, Dresden, Germany 01099

Ingrid Ehrhard *consultant microbiologist*

National Reference Centre for Meningococci, Graz, Austria A-8010
Sigrid Heuberger *consultant microbiologist*

Public Health Laboratory Service Statistics Unit, Colindale, London NW9 5EQ
André Charlet *head*

Correspondence to: J Stuart
james.stuart@hpa.org.uk