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

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## 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 policies[1] 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.

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.[4] Failures of this approach have been reported,[5–7] and there is evidence of overprescribing.[8] 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.

ELPS *This is an abridged version; the full version is on bmj.com*

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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. 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 the rate of subsequent cases 1-30 days after an 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 (see also bmj.com). We contacted the Cochrane Acute Respiratory Infections group, the World Health Organization, and the European Monitoring Group on Meningococci.

## 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. We did not identify any studies of day care and nursery schools that met our criteria.

### Evidence of benefit from chemoprophylaxis to household contacts

We included four retrospective cohort studies and one small trial (see bmj.com).[4 9–12] In total they involved 1249 sporadic cases of meningococcal disease and about 4271 household contacts (tables 1 and 2).

Three studies, in the United States, Denmark, and the Netherlands, had sufficiently similar characteristics

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

| | Kaiser 1974[9] | MDSG 1976[4] | Kristiansen 1992[10] | Scholten 1993[11] | Samuelsson 2000[12] |
|---|---|---|---|---|---|
| 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 (×2) 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×10⁴ (random 95% CI) |
|---|---|---|---|---|---|---|
| | | | Treated group | Untreated group | | |
| Kaiser 1974[9] | 11 households | 54 | 0/35 | 0/19 | — | 0 (–784 to 784) |
| MDSG 1976[4] | 512 | 1872 | 0/693 (177 households) | 5/1179 (297 households) | 0.15 (0.01 to 2.79) | –42 (–86 to 1) |
| Scholten 1993[11] | 502 (including 2 co-primary cases) | 1130 | 0/276 | 4/826 | 0.33 (0.02 to 6.14) | –48 (–119 to 22) |
| Samuelsson 2000[12] | 172 | 802 | 0/724 | 2/72 | 0.02 (0.00 to 0.42) | –278 (–695 to 140) |

**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[13] | 3/48 | 6.3 (1.3 to 17.2) | 819.20 |
| Abramson[14] | 1/14 | 7.1 (0.2 to 33.9) | 211.08 |
| Barroso[15] | 2/51 | 3.9 (0.5 to 13.5) | 1353.58 |
| Weis[16] | 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.

(clinical homogeneity) for inclusion in the meta-analysis.[4 11 12] We did not include Kaiser's study[9] 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 meningogcoccal carriage on discharge from hospital in patients who had not received chemoprophylaxis (table 3). Patients were treated with 300 000 units/kg/day of penicillin G sodium intravenously for at least 10 days,[13] intravenous therapy, initially with ampicillin or chloramphenicol then benzyl penicillin,[14] with ampicillin, penicillin, or chloramphenicol.[15] One study did not specify which antibiotic treatment was used[16], but benzyl penicillin was then the standard treatment for meningococcal disease in Denmark (S Samuelsson, personal communication).

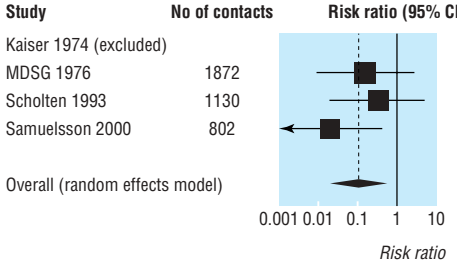
Results of tests for heterogeneity were not significant (P = 0.35). The pooled estimate from these studies was calculated as 0.03 (0.00 to 0.06, table 3).

## 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.[17 18] 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.[19] 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.[20] A one month period to measure risk reduction is therefore reasonable but does not assess whether chemoprophylaxis could prevent subsequent cases beyond this period.[21]

Previous studies have suggested that subsequent cases may be caused by reintroduction of the virulent strain to the household by the index patient.[22] We estimate that about 3% of index patients treated with peni-




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

## 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

cillin 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,[14] 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.

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*Endpiece*

### When to discharge a patient

It is not always an easy matter for a physician to judge, with precision, when a patient ought to be discharged from the hospital. It sometimes happens that patients, whose circumstances at home are necessitous, and their lives laborious, wish to loiter in the house as patients, and being cured of real diseases, would amuse the physician with fictitious feelings, of which he cannot constitute himself a judge, as pain in the stomach or the bowels, general or local rheumatisms, and a variety of similar complaints.

*The history and statutes of the Royal Infirmary of Edinburgh.*
Edinburgh: E Balfour and Smellie, 1778:86

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