ECDC **GUIDANCE**

Public health management of sporadic cases of invasive meningococcal disease and their contacts

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Contents

Abbreviations

CSF	Cerebrospinal fluid
ECDC	European Centre for Disease Prevention and Control
EMGM	European Monitoring Group for Meningococci
EU	European Union
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
IMD	Invasive meningococcal disease
ISC	Incidence of sporadic cases
PCR	Polymerase chain reaction
RR	Risk ratio
RD	Risk difference
SAR	Subsequent attack rate
WHO	The World Health Organization

Executive summary

Neisseria meningitidis is a common commensal bacterium of the human pharyngeal mucosa. This organism can cause severe invasive meningococcal disease (IMD) usually presenting as meningitis, septicaemia or both. Unfortunately, public health management of sporadic IMD varies widely in Europe and this can be partly attributed to uncertainty surrounding the effectiveness of preventive measures.

The purpose of this document is to provide evidence-based guidance for good practice in public health management of sporadic cases of meningococcal disease and their contacts. It has the additional aim of assisting countries across Europe in making decisions about appropriate measures to control and prevent meningococcal disease at national and sub-national levels. This guidance document should assist European countries in reviewing their own policies on public health management and microbiological diagnosis of meningococcal disease. While the results presented here do not include guidance for management of exposed healthcare workers nor of community outbreaks, it will cover the following relevant areas:

- Laboratory tests to confirm the diagnosis of IMD.
- Use of antibiotics at discharge from hospital.
- Chemoprophylaxis for close contacts considering different settings.
- Choice of antibiotic for chemoprophylaxis for different groups (adults, children, pregnant women).
- Use of meningococcal vaccine in addition to chemoprophylaxis.

In addition to the quality of scientific evidence, the conclusions take into account potential benefit and harm, values, burdens and costs.

Results

Conclusions are based on the systematic review and critical assessment of the current, best available evidence. For a more comprehensive overview, please refer to the main body of the document.

1. What laboratory tests are advised to make an accurate (sensitive, specific) and rapid diagnosis of IMD?
Research question: What are the most sensitive and specific laboratory tests to confirm the diagnosis of IMD?

- Based on evidence of moderate quality, polymerase chain reaction (PCR) and culture should be the diagnostic tests of preference. If logistically and economically feasible, microbiology laboratories that undertake diagnosis of meningococcal disease should have access to PCR testing. In cases where antimicrobial treatment has already started, PCR testing of skin biopsy/aspirate as a supplementary sample to blood/cerebrospinal fluid (CSF) could—based on evidence of low quality—increase the sensitivity of diagnosis in patients with skin lesions.

2. Should antibiotics, apart from those used in clinical treatment, be given to a case of IMD on discharge from hospital?
Research question: Is administration of antibiotics effective in eradicating carriage to a case of IMD in order to prevent secondary cases on discharge from hospital, compared to no antibiotics administered on discharge?

- The quality of evidence for or against the administration of antibiotics to a case of IMD at hospital discharge is very low. However, due to the moderate quality evidence for the effectiveness of chemoprophylaxis when given to close contacts, and given the relatively low cost of the intervention, antibiotics that eradicate carriage should be offered if not already used in treatment.

3. Should chemoprophylaxis be given to people who shared the same household or equivalent level of contact with a case of IMD?
Research question: What is the effectiveness of chemoprophylaxis given to those who had household contact with a case of IMD in preventing further cases among those contacts?

- Based on moderate quality evidence from observational studies, household contacts of a case of IMD should be offered chemoprophylaxis with an antibiotic regimen that eradicates carriage.

4. Should chemoprophylaxis be given to children or students who attend the same pre-school, school or college as a case of IMD?
Research question: What is the effectiveness of chemoprophylaxis given to contacts of a case of IMD in pre-school, school and college settings in preventing further cases?

- Based on low quality evidence, those attending the same pre-school as a case of IMD should be offered chemoprophylaxis, depending on risk assessment. Attending the same school/college as a case of IMD should not in itself be an indication for chemoprophylaxis.

5. Should chemoprophylaxis be given to people who have shared drinks with a case of IMD?
Research question: What is the effectiveness of chemoprophylaxis given to those who have shared drinks (or had similar contact, e.g., shared the same cigarette, shared eating utensils) with a case of IMD in preventing further cases among those contacts?

- Based on low quality evidence, sharing drinks, cigarettes or similar contact with a case of IMD should not, in itself, be an indication for chemoprophylaxis.

6. Should chemoprophylaxis be given to people who share the same transport vehicle (e.g., plane, boat, bus, car) as a case of IMD?
Research question: What is the effectiveness of chemoprophylaxis given to contacts who shared the same transport vehicle as a case of IMD in preventing further cases among those contacts?

- The current available evidence is of very low quality. Based on this evidence, the risk of transmission in different transport settings cannot be quantified. No secondary cases have been confirmed in this setting. Sharing the same transport vehicle as a case of IMD should therefore not, in itself, be an indication for chemoprophylaxis.

7. Which antibiotic regimes should be advised for chemoprophylaxis among adults, children and pregnant women?
Research question: Which antibiotic regimes are most effective in eradicating carriage among adults, children and pregnant women?

- Based on moderate to high quality evidence, rifampicin, ciprofloxacin, ceftriaxone, azithromycin and cefixime can be used for prophylaxis in adults and children. No regimen seems to be superior, but ciprofloxacin, azithromycin and ceftriaxone can be given as single dose. Resistance development has been reported after rifampicin use.

8. Should contacts of a case of IMD who receive chemoprophylaxis also be offered a meningococcal vaccine, if appropriate?
Research question: What is the effectiveness of vaccination, in addition to chemoprophylaxis, among household contacts of a case of IMD in preventing further cases among those contacts?

- The quality of the current available evidence is very low and the following conclusions are based on indirect evidence. If a case of meningococcal disease is caused by a strain that is preventable by an available licensed vaccine, vaccination in addition to chemoprophylaxis should be offered to household contacts unless considered to be already immune.

Introduction

Background

Public health management of sporadic IMD varies in Europe. A European survey published in 2007 compared national policies on public health management of IMD cases and their contacts. It found wide variation in definitions of cases and close contacts, and in the application of chemoprophylaxis and vaccination. This was partly attributed to uncertainty surrounding the effectiveness of preventive measures.

Purpose and target audience

The purpose of this document is to provide evidence-based guidance for good practice in public health management of sporadic cases of meningococcal disease and their contacts. It has the additional aim of assisting countries across Europe in making decisions about appropriate measures to control and prevent meningococcal disease at national and sub-national levels. This guidance document should assist countries across Europe in reviewing their own policies on public health management and microbiological diagnosis of meningococcal disease.

Methodology

The systematic summary of the current, best available evidence was outsourced by ECDC to a consortium of five external experts. The external working group followed a three step approach:

1) Formulation of clear questions, a systematic literature search, critical appraisal and summary of the current, best available evidence.
2) Assessment of potential risks, benefits and areas of uncertainty based on the summarised evidence. Additionally, the group drafted the guidance document and assessed the strength of the guidance/recommendation following the principles suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.
3) Review of the guidance document by European meningococcal disease experts and ECDC, and revision of the document.

Epidemiology and surveillance in Europe

Neisseria meningitidis is a common commensal bacterium of the human pharyngeal mucosa. This organism can cause severe IMD usually presenting as meningitis, septicaemia or both. Peaks of incidence are seen in children younger than five years of age and, to a lesser extent, teenagers. Invasive meningococcal disease remains rare in Europe and overall incidence decreased over the last 10 years from around 2 per 100 000 population in 1999 to around 1 per 100 000 in 2007. Most IMD cases in Europe are caused by serogroups B and C. Vaccination with serogroup C conjugate vaccines (MenC) has contributed to a decrease in incidence of the disease in European countries over the last ten years (1). In countries using MenC, the incidence of serogroup C-caused IMD was lower in the age groups targeted by the vaccination in comparison with countries without vaccine (2). The case fatality rate remains around 5–15%, clusters and outbreaks generate significant amounts of anxiety, and even a single case can sometimes have important public health implications (3,4).

A standard European case definition is available (5) but variations in truly used case definitions and completeness of reporting make comparisons between countries nevertheless difficult.

The relationship between carriage and disease is complex. Symptomless carriage is common among European populations, with prevalence of carriage varying from <5% in young children to a peak of 20–30% in young adults (6,7). Most episodes of carriage are symptomless, last for months and build up immunity against meningococcal disease (8). If carriage leads to invasive disease, this usually happens within a few days of acquisition and before generation of antibodies (9,10). Organisms vary in their virulence and in their propensity to invade according to clonal complex (11).

Public health management of sporadic disease in Europe

Invasive meningococcal disease cases are mainly sporadic in that they have no identified connection with another case (12). This is not surprising, given the large numbers of symptomless carriers. Clusters and outbreaks are, however, well documented in households, schools and wider communities (13). The relative risk for the occurrence of a subsequent case in the household compared to background incidence is high (14).

Public health management after a case relies largely on raising awareness and arranging prophylaxis for close contacts. In 2007, a European survey (15) compared national policies on public health management of meningococcal disease and their contacts. Important differences were found in definitions of cases and close contacts and in the application of chemoprophylaxis and vaccination, attributed in part to uncertainty about the effectiveness of preventive measures. There was no common approach to policy development.

Topics covered by the guidance

The following guidance should assist countries across Europe in reviewing their own policies on public health management and microbiological diagnosis of meningococcal disease in the following relevant areas:

1) Laboratory tests to confirm the diagnosis of IMD.
2) Use of antibiotics at discharge from hospital.
3) Chemoprophylaxis for close contacts considering different settings.
4) Chemoprophylaxis for different groups (adults, children, pregnant women).
5) Use of meningococcal vaccine in addition to chemoprophylaxis.

The guidance presented here does not include guidance for healthcare workers of IMD cases in healthcare settings.

Synopsis

The upcoming sections contain the complete assessment performed by the external working group. The outline chosen by the external working group has not been changed by ECDC. For each individual question addressed, a more thorough assessment covering the following aspects will ensue:

- research question;
- specific background;
- specific methods applied for searching and selecting the evidence;
- evidence review:
  - direct evidence
  - indirect evidence
  - quality of evidence
- assessment of potential benefits, harms and costs;
- recommendations;
- implications for practice; and
- further research needs

The provided quality level of evidence and strength of recommendation in these sections follow the wording suggested by the GRADE working group (www.gradeworkinggroup.org). The general methodology applied by the external working group is summarised in Annex 2.

1. What laboratory tests are advised to make an accurate (sensitive, specific) and rapid diagnosis of invasive meningococcal disease?

1.1 Research question

What are the most sensitive and specific laboratory tests to confirm the diagnosis of IMD?

1.2 Specific background

The rapid and precise detection of *Neisseria meningitidis* in samples from cases of invasive bacterial disease is essential for prompt and effective clinical and public health interventions. Diagnostic procedures that can increase the proportion of microbiologically confirmed cases of meningococcal infection and give faster results are therefore of great importance. In the case definition for IMD set out by Commission Decision 28/IV/2008, the following laboratory criteria are specified for case confirmation:

(i) isolation of *Neisseria meningitidis*; or

(ii) detection of *Neisseria meningitidis* nucleic acid from a normally sterile site, including purpuric skin lesions;

(iii) detection of *Neisseria meningitidis* antigen in cerebrospinal fluid (CSF); and

(iv) detection of Gram negative diplococci in CSF.

1.3 Specific methods

The following search string was used to search for relevant papers: (neisseria meningitidis OR meningococc?) AND diagnosis AND (?culture OR latex agglutination OR pcr or polymerase chain reaction OR gram stain OR microscop?) AND (sensitivity or specificity).

Date of publication was restricted to the period since 1999 in view of recent and continuing developments in nucleic acid detection methods.

Although culture has long been accepted as the bacteriological gold standard of IMD diagnosis, its sensitivity may not be high, especially if the sample is collected after starting antimicrobial treatment. In recent years, nucleic acid detection has developed as a supplementary reference test. Its value has been documented through inter-laboratory surveys, especially in terms of fast and sensitive genogrouping of meningococcal infections (17). In this report, the gold standard for the purpose of microbiological performance evaluation was positive culture of *N. meningitidis* and/or positive PCR for meningococcal DNA.

1.4 Evidence review

Two hundred and seventy-five abstracts were identified through the search strategy (143 through MEDLINE, 110 through Embase and 22 through Global Health), and 14 full papers were assessed. Eleven papers met the requirements (18–28).

1.4.1 Direct evidence

Nine papers compared performance of nucleic acid detection, culture, Gram stain, and/or antigen detection (19–26,28). The necessary numbers were extracted to compute sensitivity and specificity (Table 1). Culture was 100% specific, but showed a large range in sensitivity (17–97%). The various PCR methods used in these studies had a high sensitivity (73–100%) and specificity (98–100%). In two studies evaluating Gram stain, the sensitivity of Gram stain was higher than culture and lower than PCR. Antigen test detection had a low sensitivity and moderate specificity.

Another two studies evaluated the use of samples from skin lesions compared to CSF or blood samples (Table 2). In the first study (18), culture from skin biopsy had a lower sensitivity than blood culture. In the second study (27), PCR on skin biopsy was positive in all 34 cases compared with 15% for skin culture and 59% for blood PCR.

1.4.2 Quality of evidence

Polymerase chain reaction and culture: Moderate.

Nine studies consistently showed a higher sensitivity for PCR than for culture. From the data available it was not possible to evaluate blood against CSF specimens, the effect of prior antibiotics, nor the different PCR techniques used. Having two gold standards allowed for the comparison of their relative sensitivity, but evidence on specificity was difficult to assess as discordant results (e.g., positive culture for *N. meningitidis*, positive PCR for a different organism) were rarely recorded. One study of PCR on skin lesion biopsy showed 100% sensitivity.

Gram stain: Low.

Only two studies evaluated Gram stain in this review.

Antigen detection: Very low.

Only two studies evaluated antigen tests. As several antigen detection kits are available, it is not possible from this data to make a general statement on their relative value.

1.5 Assessment of potential benefits, harms and costs

Polymerase chain reaction and culture of blood or CSF are regarded as the gold standard; however, the sensitivity of culture is lower than PCR.

Polymerase chain reaction and culture need trained staff and a microbiological laboratory with sophisticated equipment. The widespread use of PCR may be hindered by costs and logistics.

Venepuncture is simple and safe. A 2 mm punch biopsy of the skin can be carried out under local anaesthetic without complications (27). Lumbar puncture carries the most serious risk—that of cerebellar herniation—and is contra-indicated in the presence of raised intracranial pressure or septicaemic shock (29).

Isolation of meningococci was previously the only method that allowed the organism to be serotyped and serosubtyped, which provided the necessary information for effective intervention. Polymerase chain reaction is the first non-culture method that can provide equivalent information.

No evidence comparing the timelines of the methods was available from this review. From current experience working in a national reference laboratory (S. Heuberger), approximate time intervals from specimen receipt to result (i.e. excluding time for transport to the laboratory) are 15–20 minutes for Gram stain, 30 minutes for antigen detection, 2.5–6 hours for PCR detection, and 16 hours to several days for culture. If PCR testing is only available in reference laboratories, additional time is required for transport of specimens from peripheral laboratories.

Gram stain has a similar sensitivity to culture. It is the fastest method but can only confirm meningococcal disease in CSF. For all other information (serogroup, serotype, serosubtype) another test is necessary.

Antigen detection can also provide more rapid results than PCR or culture, but the sensitivity is low and specificity uncertain. The serogroup discrimination is low; only serogroup B or non-B is possible.

Polymerase chain reaction testing of skin biopsy/aspirate as a supplementary sample to blood/CSF could increase the sensitivity in patients with skin lesions after antimicrobial treatment. Skin biopsy cultures obtained up to 13 hours after the start of antibiotic therapy can still be positive and PCR testing was positive up to four days on antibiotics (27).

1.6 Recommendations

1. PCR and culture should be the diagnostic tests of preference. If logistically and economically feasible, microbiology laboratories that undertake diagnosis of meningococcal disease should have access to PCR testing (Strong).
2. PCR testing of skin lesion samples is recommended, especially after antimicrobial treatment has started (Weak).

1.7 Implications for practice

Facilities for PCR testing are already available and used for diagnosis of IMD in most national reference laboratories in Europe (22 out of 28 laboratories in 2007, EMGM survey). If PCR is used as the sole diagnostic method, further strain characterisation to determine serogroup is essential for making vaccination recommendations for close contacts. Further genogrouping (PorA variable regions) should be undertaken for epidemiological purposes. If performed in peripheral laboratories, PCR positive and culture negative samples should also be sent to the national reference laboratories for further characterisation. In outbreaks, parallel specimens for PCR diagnosis should be sent to national reference laboratories. Physicians may need education on punch biopsy of skin lesions if unfamiliar with this procedure.

1.8 Further research needs

Further studies to evaluate the use of PCR testing in skin lesion biopsy are recommended. The sensitivity and specificity of antigen testing in CSF compared to PCR and culture is urgently needed to assess the place of this test among the recommended confirmatory tests for IMD.

A comparison of recommended methods from different sterile sites using a quality assurance distribution to all reference laboratories, particularly to examine specificity, would increase confidence in the relative value of current tests. Also, the reliability and efficiency of genogrouping in prediction of serogroup should be evaluated as a tool in the microbiological diagnostics of *N. meningitidis*.

Table 1: Comparison of microbiological confirmatory tests. The gold standard reference test was either positive culture of N. meningitidis or positive PCR test result

	Gold standard (+)		Gold standard (-)		SE (95% CI)	SP (95% CI)
	Test (+)	Test (-)	Test (+)	Test (-)		
Antigen detection						
Hackett 2002 (5) **(Blood)**	12	72	2	9	14 (8-24)	82 (48-98)
Rebelo 2006 (8) **(CSF)**	73	47	-	-	61 (52-70)	-
Gram stain (CSF)						
Richardson 2003 (9)	25	14	0	280	64 (47-79)	100 (99-100)
Rebelo 2006 (8)	82	38	-	-	68 (59-77)	-
PCR (CSF,blood)						
Carrol 2000 (4)	82	20	0	64	80 (71-88)	100 (94-100)
Hackett 2002 (5)	84	0	0	11	100 (96-100)	100 (71-100)
Pollard 2002 (7)	15	1	0	16	94 (70-100)	100 (80-100)
Richardson 2003 (9)	39	0	0	280	100 (91-100)	100 (99-100)
Tzanakaki 2003 (11)	383	1	4	163	99 (98-100)	98 (94-99)
Bryant 2004 (3)	23	1	0	94	96 (79-100)	100 (96-100)
Rebelo 2006 (8)	120	0	-	-	100 (97-100)	-
Munoz-Almagro 2009 (6)	85	32	0	51	73 (64-80)	100 (93-100)
Culture (CSF, blood)						
Carrol 2000 (4)	57	45	0	64	56 (46-66)	100 (94-100)
Hackett 2002 (5)	32	52	0	11	38 (28-49)	100 (71-100)
Pollard 2002 (7)	5	11	0	16	31 (11-59)	100 (79-100)
Tzanakaki 2003 (11)	66	318	0	167	17 (13-21)	100 (98-100)
Richardson 2003 (9)	21	18	0	280	54 (37-70)	100 (99-100)
Baethgen 2003 (2)	60	2	0	40	97 (89-100)	100 (91-100)
Bryant 2004 (3)	15	9	0	88	63 (41-81)	100 (96-100)
Rebelo 2006 (8)	55	65	-	-	46 (37-55)	-
Munoz-Almagro 2009 (6)	45	72	0	51	39 (30-48)	100 (93-100)

Table 2: Evaluation of skin biopsy as microbiological test

	Gold standard	Evaluated test	Gold standard (+)		Gold standard (-)		SE (95% CI)	SP (95% CI)
			Test (+)	Test (-)	Test (+)	Test (-)		
Arend 2006 (1)	Culture positive from any specimen	culture from skin biopsy	9	16	0	6	36 (18-57)	100 (54-100)
Staquet 2006 (10)	Culture or PCR positive from any specimen	culture from skin biopsy	5	29	-	-	15 (5-31)	-
Staquet 2006 (10)	Culture or PCR positive from any specimen	PCR from skin biopsy	34	0	-	-	100 (90-100)	-

2. Should antibiotics, apart from those used in clinical treatment, be given to a case of IMD on discharge from hospital?

2.1 Research question

Is administration of antibiotics effective in eradicating carriage to a case of IMD in order to prevent secondary cases on discharge from hospital, compared to no antibiotics administered on discharge?

2.2 Specific background

Some antibiotic regimens used in the treatment of IMD may not efficiently eradicate nasopharyngeal carriage in the case (Section 7). Since an increased risk of disease among household contacts of cases persists for several months (30), the convalescent case who is still a carrier of a pathogenic strain may represent a risk for their close contacts. According to a recent survey across Europe (31), 12 out of 21 countries recommended administration of chemoprophylaxis to index IMD cases if they do not receive an antibiotic regimen effective at eradicating carriage during hospital treatment.

2.3 Specific methods

The following search string was used to search for relevant papers: (neisseria meningitidis OR meningococc?) AND (carriage OR carrier? OR coloni? OR nasopharyn?) AND (eradicat? OR eliminat? OR antibiotic? OR ?prophyla?) AND (discharge? OR hospital? or treat? or ?therapy).

2.4 Evidence review

Three hundred and forty-nine papers were identified through the search strategy. A systematic review performed in 2003 was identified (32). The review of abstracts was therefore limited to 2003–2008. Thirty-two abstracts were reviewed; three potentially addressed the research question, but were excluded after the review of full papers. The four papers identified in the review by Purcell were assessed (33–36).

2.4.1 Direct evidence

No papers were identified that compared incidence of cases among contacts of patients who received chemoprophylaxis at discharge compared to incidence of secondary cases in those who did not receive chemoprophylaxis at discharge.

2.4.2 Indirect evidence

In the systematic review, four papers were identified that assessed persistent meningococcal carriage on discharge from hospital in patients who had not received chemoprophylaxis (Table 3). These papers are difficult to compare because different antibiotic regimens were used during hospital treatment, and the nasopharyngeal swabs were collected at different times following discharge. Nonetheless, statistical testing for heterogeneity was not significant ($p=0.35$), and the point estimate from the pooled studies was that 2.6% of cases still carried meningococci after treatment of disease with penicillin and/or chloramphenicol.

Although no direct evidence was found of reduction of risk by carriage eradication in the case, it seems reasonable to suppose that continued carriage in the case may pose a continuing risk to close contacts. Indeed, the risk to household contacts, even if given chemoprophylaxis, appears to be raised when the index case has not been given chemoprophylaxis (37). According to this paper, based on review of records of 3256 IMD cases from England and Wales from 1984 to 1987, secondary cases occurred in seven households where close contacts—but not the index patients—were given chemoprophylaxis. The limitations of this paper are that records were based on strains sent to a reference laboratory, and that no direct comparison of different groups of secondary cases was possible as denominator data are missing.

2.4.3 Quality of evidence

- No studies addressed the research question.

- Available evidence providing estimates of carriage following hospital treatment support a risk of carriage. However the studies used problematic methodology, diverse outcome measurements, and included small groups of patients.

2.5 Assessment of potential benefits, harms and costs

The quality of evidence to support (or not support) a recommendation is very low. However, there is high potential benefit in reducing the disease burden among close contacts, given the evidence for effectiveness of chemoprophylaxis when given to close contacts of IMD cases (Section 4). The cost of the intervention and the risk of harm are low.

2.6 Recommendation

Chemoprophylaxis is recommended for patients with IMD on discharge from hospital unless an antibiotic regimen effective in eradicating carriage was used during hospital treatment (Strong).

2.7 Implications for practice

Over half of the countries in Europe already recommend administration of chemoprophylaxis to index cases of IMD (31). The remaining countries could consider implementation of this straightforward routine.

The recommendation to give chemoprophylaxis should apply to all cases of IMD unless they have already been treated with an antibiotic (such as ceftriaxone or cefixime) that eradicates carriage (Section 7). However, in situations when other third generation cephalosporins are administered to inpatients, the recommendation may be considered as weak. Cephalosporins were probably not used in any of the five studies quoted (33–37), and it is plausible that this group of antibiotics is generally effective in eradicating carriage.

2.8 Further research needs

A trial to assess the effectiveness of administering chemoprophylaxis to cases in hospital in preventing further cases among household contacts could improve the evidence base, but may not be feasible. Nonetheless, for cephalosporins such as cefotaxime, which are often used in case treatment, it would be useful to evaluate their effectiveness in carriage eradication.

Table 3: Estimated carriage rate on discharge from hospital index patients not given chemoprophylaxis (32)

	Carriage on discharge	Carriage rate (%) (95% CI)	Antibiotics at hospital	Time after discharge
Abramson 1985	1/14	7.1 (0.2 – 33.9)	ampicillin /chloramphenicol + penicillin	7 days
Alvez 1991	3/48	6.3 (1.3 – 17.2)	Penicillin	on discharge
Weis 1994	0/47	0.0 (0.0 – 7.5)	not specified	on discharge
Barroso 1999	2/51	3.9 (0.5 – 13.5)	ampicillin /chloramphenicol / penicillin	8 hrs – 6 days
Pooled effect	-	2.6 (0.0 – 5.5)	-	-

3. Should chemoprophylaxis be given to people who shared the same household or equivalent level of contact with a case of IMD?

3.1 Research question

What is the effectiveness of chemoprophylaxis given to those who had household contact with a case of IMD in preventing further cases among those contacts?

3.2 Specific background

The absolute and relative risk of IMD among household contacts of a case is high (38). Chemoprophylaxis is recommended across Europe (39) for such contacts to reduce this risk. The rationale behind this line of thought is to eradicate carriage from the following cases:

- asymptomatic carriers who may be a potential source of further cases; and
- those who have just acquired the organism and may themselves be at risk.

An alternative approach to chemoprophylaxis, used in a small minority of countries, is to give a course of oral penicillin as treatment for possible incubating disease.

3.3 Specific methods

The following search string was used to search for relevant papers: (meningococc? OR neisseria meningitidis) AND (chemoprevention OR ?prophylaxis OR antibiotic?) AND (contact tracing OR transmission OR contact? OR cluster? OR outbreak?) AND (household? OR kiss? OR saliva OR transport? OR travel?).

3.4 Evidence review

One hundred and three abstracts were identified through the search strategy (46 through MEDLINE, 40 through Embase, 16 through Global Health and one through the Cochrane database of systematic reviews). Five full papers were assessed.

3.4.1 Direct evidence

One systematic review (40) in 2003 identified three papers suitable for meta-analysis that compared incidence rates among household contacts given and not given chemoprophylaxis (41–43). In those given antibiotics shown to be effective in eradicating carriage (Section 7), there was a statistically significant reduction in risk (risk ratio (RR) 0.11, 95% CI [0.02, 0.58]). One additional paper (44) was identified in this project through a search from 2003 to 2008. Combining this paper in a new meta-analysis (Table 4) gave a pooled RR of 0.14, 95% CI 0.03, 0.59. The studies were statistically homogeneous. The best estimate of the number needed to treat in order to prevent a case was 284, 95% CI 156 to 1515.

3.4.2 Quality of evidence

Although no randomised trials were identified, direct evidence was available from four observational studies. The main weakness in all of these studies was the lack of data on potential confounding variables such as socio-economic status and age. Nonetheless, a reduction in risk after chemoprophylaxis is plausible. The results of the four studies were statistically homogeneous and the strength of association was high (the upper limit of the 95% confidence interval was well below a value of no effect). The consistency of results after the addition of data from a new study adds weight to this conclusion.

3.5 Assessment of potential benefit, harm and costs

The risk of subsequent cases of meningococcal disease among household contacts is relatively high. Direct evidence (classified as of moderate quality) on the impact of chemoprophylaxis suggests a large risk reduction. The costs of follow-up and antibiotic administration are low, and side effects from chemoprophylaxis are mild (Section 7). Treatment is widely accepted.

3.6 Recommendation

Chemoprophylaxis with an antibiotic regime that eradicates carriage is recommended for household contacts of a case of IMD (Strong).

3.7 Implications for practice

Chemoprophylaxis for household contacts is already routine practice across most of Europe. The recommendation supports this policy. Recommendations on antibiotic regimens are given in Section 7.

In the few countries that currently recommend penicillin for contacts, implementing the working group's recommendation would require a change of policy. Treating with oral penicillin would be expected to reduce risk but no studies were found that evaluated risk reduction. Carriage among contacts may persist after penicillin treatment, such that there is a theoretically higher residual risk of further cases than in contacts given chemoprophylaxis. One obstacle to overcome may be concern about use of rifampicin leading to resistance. These issues are discussed in Section 7. Alternative antibiotics are available.

3.8 Further research needs

Randomised controlled trials are unlikely to be conducted. Additional observational studies may help to further refine the estimates of risk reduction but are not likely to change policy.

Table 4: Estimate of effect chemoprophylaxis to household contacts following a sporadic case of meningococcal disease

Study	Number of Primary cases	Number of Contacts	Antibiotics used	Attack rate Treated group	Attack rate Untreated group	Risk Ratio [95% CI random]	Risk Difference x 10^4 [95% CI random]
MDSG, 1976	512	1872	Minocycline or Rifampicin or Sulphonamides	0/693 (177 households)	5/1179 (297 households)	0.15 [0.01, 2.79]	-42 [-86, 1]
Scholten, 1993	502 (including 2 co-primary cases)	1130	Rifampicin or Minocycline	0/276	4/826	0.33 [0.02, 6.14]	-48 [-119, 22]
Samuelsson, 2000	172	802	Ciprofloxacin	0/724	2/72	0.02 [0.00, 0.42]	-278 [-695,140]
Stefanoff, 2008	635	1905	Rifampicin	0/629	3/1276	0.29 [0.01, 5.60]	-24 [-60, 13]

Pooled RR = 0.135 [0.031, 0.59]
Heterogeneity chi-squared = 2.2 (d.f. = 3) p = 0.5
RD -0.0035 95% CI -0.0064 to -0.00066

4. Should chemoprophylaxis be given to children or students who attend the same pre-school, school or college as a case of IMD?

4.1 Research question

What is the effectiveness of chemoprophylaxis given to contacts of a case of IMD in pre-school, school and college settings in preventing further cases of IMD?

4.2 Specific background

For the most part, IMD cases in Europe occur sporadically. Epidemiologically linked subsequent cases generally comprise <5% of all cases, with higher proportions occasionally reported in high-incidence settings (45–47). While observational studies have shown that chemoprophylaxis of household contacts of IMD cases reduces the risk of subsequent cases among those contacts (48) (Section 4), this has not been shown for contacts in other settings. Nevertheless, there are numerous reports on the occurrence of secondary cases in pre-school (45,47,49–55), school (45–47,50,52,55,57–68), and college settings (52,69–72). Asymptomatic transmission of the index strain has also been shown in these settings, although to a lesser extent than in household settings (49,56,73,74). In a recent survey, 16 out of 28 European countries defined contacts in pre-school settings as close contacts for whom chemoprophylaxis is recommended. Of these, three recommended chemoprophylaxis for the entire institution and 10 for contacts in the group or class of the index patient (M Hoek, unpublished data) and three others did not further define close contacts.

4.3 Specific methods

The following search string was used to search for relevant papers: (meningoc? OR neisseria meningit?) AND (chemoprev? OR ?prophyla? OR antibiotic?) AND (transmission OR contact? OR second? OR attack OR cluster? OR outbreak?) AND (?school? OR day care OR nurser? OR child care OR college? OR universit? OR dormitor?).

4.4 Evidence review

After removal of duplicates, 280 articles were found (215 through MEDLINE, 50 through Embase, 15 through Global Health).

Six key papers fulfilled the inclusion criteria of being observational studies with data on disease status in contacts of at least 10 primary cases in each educational setting. Another key paper was found in literature cited in retrieved papers (Table 5). In addition, papers on the risk of subsequent IMD in household contacts of sporadic cases that allowed for comparison with risk in educational settings were identified from the literature search in Section 4. An additional study compared the risk of IMD clusters in countries with and without a policy of giving chemoprophylaxis to contacts in pre-schools.

4.4.1 Direct evidence

No papers were found that compared the incidence of subsequent cases among contacts given and not given chemoprophylaxis in the above settings.

4.4.2 Indirect evidence

In a retrospective ecological study in Europe, Boccia et al. (75) found that countries with a policy of giving chemoprophylaxis only to close contacts after a single case of IMD in a nursery school had 3.8 times the risk of clusters than countries with a policy of giving chemoprophylaxis to all children in a nursery. The difference was not statistically significant. There was a lack of accurate national statistics on the size and number of nursery schools. Co-primary cases were not excluded.

The incidence of subsequent cases 1–30 days after contact with the index case (subsequent attack rate (SAR)) was extracted or calculated (or a period as close to this as possible) in seven retrieved studies for each educational setting and compared this to the background, age-specific incidence of sporadic cases (ISC) in the same time period by calculating the RR and risk difference (RD). Pooled risk estimates were calculated using the 'metan' command in STATA[i].

4.4.3 Risk of subsequent cases in educational settings

Pre-school setting

Five studies permitted estimation of risk in pre-school settings (Table 5). In the two studies in which chemoprophylaxis was recommended by public health authorities for contacts in the same pre-school as the case of IMD, no subsequent cases were observed (52,55). In the three other studies where chemoprophylaxis was not generally recommended, the risk of subsequent cases in contacts was significantly higher than the background IMD incidence (Table 8). The pooled estimate of RR and RD from these studies, which fulfilled criteria for homogeneity, were 22.3 (95% CI: 12.1-40.9) and 58.2/105 (27.3-89.0), respectively, using a random effects model and weighting based on inverse variance. For comparison in the four household studies (Table 8), the pooled RR and RD were 1381 (95% CI: 924-2064) and 397.6/105 (95%CI: 218.8-576.3), respectively.

School setting

Five studies permitted calculation of SAR, RR and RD in various school settings (Table 6). Chemoprophylaxis was not recommended for school contacts in these settings, with the exception of close contacts among classmates in France (55). The SAR was generally lower than in pre-school settings with the exception of the Brazilian study which was, however, undertaken in a high incidence setting. The RR was significantly elevated in all studies, with a wide range that overlapped with that in pre-school settings. The RD was, however, consistently lower than in pre-school settings, with a pooled estimate of 4.1/105 (95% CI: 2.3-5.8) from the one US and three European studies, but with significant heterogeneity between these studies (Chi2 for heterogeneity p=0,002), making interpretation difficult. When only data from primary school children are pooled (possible in three studies) (50,52,55), heterogeneity was no longer significant for the RD estimate, which was 4.9/105 (95% CI: 2.9-6.9). When only data from secondary school children from these studies were pooled, heterogeneity remained significant (p Chi2=0,004) with an RD estimate of 8.8/105 (-0.046–17.7). In the one study that included both pre-school and school settings without chemoprophylaxis (50), both RR and RD were markedly lower among school than nursery contacts. In school settings, RR and RD were highest when analyses were restricted to contacts in classrooms (46,55) (Table 6).

College setting

Only one study (50) provided data on risk of secondary cases in the college setting (Table 7). The size of the contact group was very large (>5000) and the SAR was non-significantly elevated. Defining smaller contact groups might have led to higher estimates of SAR. The extremely large denominator populations would probably have led to underreporting of any further cases.

Timing and exact setting of subsequent cases within institutions

Exact data on the time interval between occurrence of the primary and subsequent cases were not available in all studies and not specifically provided for the particular settings in any study. Available data suggested that about 70% of subsequent cases occurred within one week and 90–100% within three weeks. Davison et al. (50) reported that 57% of all subsequent cases occurred in the same grade or class in pre-school and school settings combined, and Zangwill et al. (58) reported that 55% of subsequent cases were in a different grade than the index case.

[i] More details on methods are available upon request

4.4.4 Quality of evidence

No studies directly addressed the research question by comparing the incidence of subsequent cases among treated and untreated contacts. The studies on risk by setting all had some of the following limitations: retrospective data collection; lack of data on potential confounding variables; inclusion of co-primary cases (not in pre-school settings); variable duration of follow up; imprecise estimates of numbers of contacts; sparse data for SAR estimates; and a lack of data on whether contacts obtained chemoprophylaxis. Nonetheless, there was a consistently significantly increased risk of subsequent IMD cases compared to the background incidence when chemoprophylaxis was not generally recommended. The risk difference was much higher in pre-school settings than in school settings. The absence of cases in pre-school settings when prophylaxis was recommended is also consistent with the benefit from chemoprophylaxis. The studies applied directly to the populations of interest although the background incidence was variable.

4.5 Assessment of potential benefits, harms and costs

Risk of subsequent IMD after occurrence of a primary case in a pre-school setting is higher than in a school setting. Both are higher than the risk of sporadic IMD and both lower than the risk to household contacts. Chemoprophylaxis is effective at reducing risk among household contacts (Section 4) and may well be effective among other groups of contacts at risk, but there is no direct evidence to support this. It may take longer to arrange for all contacts to receive antibiotics so that early cases are not preventable.

Side effects of recommended chemoprophylaxis regimens are minimal; however, development of resistance has been described (48,76) (Section 7) and is more likely as the number of treated contacts increases. Theoretically, another negative effect of chemoprophylaxis is the eradication of *N. lactamica* from the nasopharynx. Colonisation of *N. lactamica* is associated with the induction of cross-protective immunity to *N. meningitides* (79,80). Carriage of *N. lactamica* is highest in nursery-aged children (79,81) and prior antibiotic therapy has been shown to decrease carriage (81).

Invasive meningococcal disease is associated with a high risk of complications and death. If chemoprophylaxis in educational settings was as effective in risk reduction as in households, the number of contacts that would need to be treated to prevent one subsequent case based on the studies analysed in this review would vary from 1930 (95%CI 1262-4116) in pre-school settings to 27 405 (95%CI 19372–48851) in school settings, compared to a pooled estimate of 304 in household settings (95%CI 89-564)[i].The burden of taking short-term antibiotics is considered low (Section 7). However, depending on the number of contacts that would need to be treated when a case occurs in an educational setting, the cost and logistical efforts could be substantial.

Because IMD generates a high degree of anxiety and is associated with severe disease, it is believed that contacts would want chemoprophylaxis even if the evidence for benefit is weak, as direct harmful effects are minimal and further risks only theoretical. This is in keeping with comments from The Meningitis Trust—a non-governmental organisation in the UK with a public helpline—that it is difficult to convince parents of children attending the same nursery/playgroup as a case that prophylaxis is not needed.

The provision of prophylactic antibiotics in educational settings after a single case would have higher costs than for households.

4.6 Recommendations

1. Attending the same pre-school as a case of IMD is an indication for chemoprophylaxis, depending on risk assessment (Weak). (See **Implications for practice**).
2. Attending the same school/college (including the same class) as a case of IMD is not in itself an indication for chemoprophylaxis (Weak).

4.7 Implications for practice

Although most countries follow these recommendations, there is a wide variation in pre-school settings in European countries so that some variation in policy is not surprising. Implementing a change to start administering chemoprophylaxis in pre-school settings would have resource implications. It is suggested that recommendations regarding use of chemoprophylaxis should be reviewed by the appropriate public health authorities in each country. A risk assessment in the pre-school setting that takes into account duration and closeness of contact may assist decision making. The risk of further cases is considered higher in settings similar

[i] This estimate is slightly higher than that in Section 4 as the calculation compares incidence in contacts with back ground incidence and not incidence in treated versus untreated contacts, as well as including different studies.

to households, where there would be a higher risk of exposure to respiratory droplets. Children in the same group as the index case who have spent long periods of time in the same room (e.g., full-time attendance, sharing meals, napping together) are likely to be at higher risk than children in a different group or with contact to the index case that is less direct (e.g., free play versus fixed seating) or of shorter duration (e.g., part-time attendance).

4.8 Further research needs

Further prospective studies on the risk of subsequent cases and the transmission of disease-causing strains in educational settings are needed. Prospective studies on the risk of subsequent cases among contacts that receive or do not receive chemoprophylaxis may be feasible as an initiative involving several countries with divergent public health policies.

Table 5: Subsequent attack rate (SAR) among contacts in defined time interval after occurrence of a case of IMD in pre-school settings and estimation of relative risk (RR) and risk difference (RD) compared to background incidence in same time interval from seven published studies

Study	Chemoprophylaxis of contacts in study settings	Age group	Primary cases	Number of contacts/ primary case	Interval for occurrence of subsequent cases (days)	Subsequent attack rate (cases/100,000 contacts) (no. subsequent cases/contacts)	Incidence sporadic IMD (cases/100,000 inhabitants) (no. sporadic cases/population)	RR (95% CI)	Risk difference (cases/100.000 persons)
Hastings 1997(8)	Not recommended	2-3 years	281	40	1-30	0 (0/11250)	1.2 (10/853702)	0 (0-40)	-
Olivares 1992 (11)	Not recommended	0-2 years	17	57.4	1-120	0 (0/976)	1.8 (3/166667)	0 (0-302)	-
Olivares 1992 (11)	Not recommended	3-5 years	51	118	1-120	0 (0/6018)	0.7 (9/1285714)	0 (0-120)	-
Davison 2004(6)	Not recommended	2-4 years	1046	27	2-28	40.4* (8/19814)	1.4 (9/665074)	29.8 (11.5-77.3)	39.0 (11.0-67.0)
De Wals 1981 (1)	Not recommended	1-2 years	28	35.4	1-60	302.7 (3*/991)	5.7 (1/17500)	53.0 (5.5-508.8)	297.0 (45.2-639.2)
De Wals 1981 (1)	Not recommended	3-5 years	227	80.0	1-60	55.1 (10**/18160)	3.5 (8/227000)	15.6 (6.2-39.6)	51.5 (17.3-85.7)
Favorova, 1975 (36)	Not recommended	0-6 years	-		1-30	99.5 16/16080	6.2 ##1/16080	16.0 (2.1-120.6)	93.3 (43.1-143.5)

*lower than published figure presumably due to rounding errors
**estimated 30% of co-primary cases subtracted from no. in study
Incidence in contacts in period 2-12 months after index case (9 cases) as a for true background incidence

Table 6: Subsequent attack rate (SAR) among contacts in defined time interval after occurrence of a case of IMD in school settings and estimation of relative risk (RR) and risk difference (RD) compared to background incidence in same time interval from seven published studies

Study	Chemoprophylaxis of contacts	Age group	Primary cases	Number of contacts/ primary case	Interval for occurrence of subsequent cases (days)	Subsequent attack rate (no. subsequent cases/contacts)	Incidence sporadic IMD (no. sporadic cases/population)	RR (95% CI)	Risk difference (cases/100.000 persons)
Hastings 1997(8)	Not recommended	4-10 years	342	208	0-30	7.0 (5/71136)	0.3 (12/4259629)	25.0 (8.8-70.8)	6.7 (0.6-12.9)
Hastings 1997 (8)	Not recommended	11-15 years	137	808	0-30	10.8 (12/110898)	0.2 (5/3119504)	67.5 (23.8-191.6)	10.7 (4.5-16.8)
Davison 2004 (6)	Not recommended	4-10 years	7477	237	0-30	5.2 (23/443500)	0.5 (26/4754337)	9.4 5.4-16.6)	4.6 (2.5-6.8)
Davison 2004 (6)	Not recommended	11-16 years	2195	862	0-30	3.2 (33/1016197)	0.5 (16/3274674)	6.6 (3.7-12.1)	2.8 (1.6-3.9)
Olivares 1992 (11) *	Recommended for close contacts only	6-11 years	78	22	1-120	58.3 (1/1716)	0.3 (4/1333333)	198 (3-1099)	58.0 (10.0-329.1)
Olivares 1992 (11)**	Recommended for close contacts only	6-11 years	78	90	1-120	22.9 (2/8736**)	0.3 (4/1333333)	76.3 (14.0-416.6)	22.6 (-9.1-54.3)
Olivares 1992 (11)*	Recommended for close contacts only	12-18 years	97	24	1-120	43.0 (1/2328*)	0.3 (5/1666667)	141 (2-787)	42.7 (7.3-242.6)
Olivares 1992 (11)**	Recommended for close contacts only	12-18 years	97	190	1-120	28.9 (6/20758**)	0.3 (5/1666667)	96.3 (29.4-315.7)	28.6 (5.5-51.7)
Zangwill 1997 (14)	Not recommended	5-18 years	2288	516	1-30	2.5 (30/1180608)	0.1 (34/38535037)	28.8 (17.6-47.1)	2.5 (1.5-3.4
Jacobson 1976 (2)	Not recommended	5-14 years	40	29	1-30	431.0 (5/1160)	58.8 (10/17012)	7.3 (2.5-21.4	372.3 (6.5-751.0)

*contacts in classrooms and **entire school

Table 7: Subsequent attack rate (SAR) among contacts in defined time interval after occurrence of a case of IMD in college settings and estimation of relative risk (RR) and risk difference (RD) compared to background incidence in same time interval from seven published studies

Study	Chemoprophylaxis of contacts	Age group	Primary cases	Number of contacts/ primary case	Interval for occurrence of subsequent cases (days)	Subsequent attack rate (no. subsequent cases/contacts)	Incidence sporadic IMD (no. sporadic cases/population)	RR (95% CI)	Risk difference (cases/100.000 persons)
Hastings 1997 (8)	Not recommended	16-22 years	326	5030 (colleges) 7850 (universities)	0-30	0.6 (11/1894838)	0.3 (12/3745240)	1.8 (0.8-4.1)	0.3 (0.1-0.7)

Tables 8: Subsequent attack rate (SAR) among contacts in defined time interval after occurrence of a case of IMD in household settings and estimation of relative risk (RR) and risk difference (RD) compared to background incidence in same time interval from seven published studies

Study	Chemoprophylaxis of contacts	Age group	Primary cases	Number of contacts/ primary case	Interval for occurrence of subsequent cases (days)	Subsequent attack rate (no. subsequent cases/contacts)	Incidence sporadic IMD (no. sporadic cases/population)	RR (95% CI)	Risk difference (cases/100.000 persons)
De Wals 1981 (1)	~1% of contacts received adequate chemoprophylaxis		1665	1.7	1-60	469.5 (24*/5112)	0.5 (46/8409090)	858.2 (524.3-1404.8)	468.9 (281.5-656.3)
Scholten 1993 (37)	No		502	3	1-30	484.3 (4/826)	0.3 (38/12550000)	1599.3 (572.1-4470.9)	484.0 (10.5-957.4)
Samuelsson 2000 (38)	No		172	Not stated	1-30	2777.8 (2/72)	0.4 (21/5251027**)	6945.8 (1659.1-29079.3)	2777.4 (-1018.5-657.3)
Stefanoff 2008 (39)	No		635	Not stated	1-30	235.1 (3/1276)	0,03 (13/38,635,000**)	6987.3 (1993.5-24490.2)	235.1 (30.7-500.8)

*estimated 30% of co-primary cases subtracted from number in study ** estimated from published national statistics

5. Should chemoprophylaxis be given to people who have shared drinks with a case of IMD?

5.1 Research question

What is the effectiveness of chemoprophylaxis given to those who have shared drinks (or had similar contact, e.g., shared the same cigarette, shared eating utensils[i]) with a case of IMD in preventing further cases among those contacts?

5.2 Specific background

Guidelines for prophylaxis among contacts who shared drinks or had similar contact with a case of IMD vary across Europe. In a 2007 survey (84), prophylaxis was recommended for such contacts in nine out of 23 countries. One standard textbook on control of communicable diseases (85) has, over many editions, included a recommendation that those 'socially close enough to have shared eating utensils' should be given prophylaxis. This may simply be a proxy measure for a higher risk of respiratory droplet transmission. The rationale for this recommendation is not given.

5.3 Specific methods

The following search strings were used to search for relevant papers:

1. (meningococc? OR neisseria meningitidis) AND (chemoprevention OR ?prophylaxis OR antibiotic?) AND (contact tracing OR transmission OR contact? or cluster? or outbreak?) AND (household? OR kiss? OR saliva OR transport? OR travel?).
2. (meningococc? OR neisseria meningitidis) AND (saliva OR (shar? AND (drink? OR eating utensil? OR glass? OR pacifier? OR soother? OR dumm? OR cigarette?)).

5.4 Evidence review

One hundred and sixty-four abstracts were identified through the search strategy and nine full papers were assessed.

5.4.1 Direct evidence

No papers were identified that specifically compared incidence among drink-sharing contacts given and not given chemoprophylaxis.

5.4.2 Indirect evidence

No papers assessed the risk of sharing drinks with a case.

One study of college students found no association between rates of meningococcal acquisition and sharing drink glasses or cigarettes (86). Another study found a slightly higher risk of disease linked to sharing food, drink or pacifiers (87), but the association was of marginal statistical significance. It is difficult to separate the risk of this behaviour from the risk of close respiratory contact which may confound the relationship. If sharing drinks is a risk factor, then the likely route of transmission would be through saliva residue on a cup or glass. One anecdote reports a security guard who developed meningococcal conjunctivitis three days after having someone spit in his face (88). *Neisseria meningitidis* can survive at low rates in artificial media (not saliva) on environmental surfaces for 24 hours (89), but are meningococci found in saliva? In one study that was designed to address this question, 258 students in an English college were each swabbed from the nasopharynx, tonsils and front of mouth (90). The cultures were examined blind by the national reference laboratory. Students had a high prevalence of

[i] The research question initially included kissing contact. It was later changed to be more specific to contact with salivary and not respiratory secretions. See below.

nasopharyngeal carriage (32%), but only one out of 258 (0.4%) had a positive culture from the front of the mouth (0.4%, p<0.001). Saliva has long been shown to inhibit the growth of *Neisseria meningitidis* (91).

In risk assessments, it is important to distinguish between salivary contact and respiratory droplet contact. *Neisseria meningitidis* colonises the posterior pharyngeal wall and is transmitted through respiratory droplets. In practice, some contact activities may involve both. For example, activities such as intimate (mouth-to-mouth) kissing are likely to involve both an important exchange of saliva and also an important exchange of respiratory droplets, and have been linked to increased risk of carriage (92) and disease (93). However, activities such as sharing drinks and cigarettes may occur in the absence of close contact. Using questions about these activities to define contacts for prophylaxis may generate false perceptions of the mode of transmission.

5.4.3 Quality of evidence

No studies addressed the research question directly. That sharing drinks is unlikely to pose a risk of acquisition is supported by studies that do not show an independent risk from such contact, as well as by laboratory evidence that transmission by saliva via this route is very unlikely.

5.5 Assessment of potential benefits, harms and costs

If saliva does not harbour meningococci, it is hard to argue that sharing drinks is a risk factor. In the absence of any studies that suggest an independent risk from drink sharing, it is not possible to quantify potential benefit from giving chemoprophylaxis to such contacts. On the other hand the cost of intervention is low, as is the potential for harm from antibiotics, and chemoprophylaxis is likely to be accepted if offered.

5.6 Recommendation

Sharing drinks or cigarettes or similar contact[i] with a case of IMD is not in itself an indication for chemoprophylaxis (Weak).

5.7 Implications for practice

Many countries already follow this recommendation. In other countries, a change in policy not to give chemoprophylaxis routinely to contacts who share drinks with a case should not be difficult.

5.8 Further research needs

A question addressed in one paper (87) that came up in discussions surrounded the risk of sharing 'oral pacifiers' in young children. The quantity of oral fluid exchange may be much higher compared with sharing drinks. It would be interesting to sample pacifiers for Neisseria species in a day nursery setting.

[i] Implying a low level of salivary contact.

6. Should chemoprophylaxis be given to contacts who have shared the same transport vehicle (e.g. plane, boat, bus, car) as a case of IMD?

6.1 Research question

What is the effectiveness of chemoprophylaxis given to contacts who have shared the same transport vehicle as a case of IMD in preventing further cases among those contacts?

6.2 Specific background

Guidelines for prophylaxis of contacts of meningococcal disease cases on aeroplanes and other public transportation vary widely across Europe (94). Depending on the country, chemoprophylaxis is recommended for plane passengers who are seated adjacent to, in the same row, or the row in front or behind an IMD case for periods varying between four and 10 hours. Some countries do not recommend any chemoprophylaxis. US guidelines recommend that chemoprophylaxis be considered for passengers seated directly next to an index case on an aircraft for at least eight hours (95).

6.3 Specific methods

The following search string was used to search for relevant papers: (meningococc? OR neisseria meningitidis) AND (chemoprevention OR ?prophylaxis OR antibiotic?) AND (contact tracing OR transmission OR contact? OR cluster? OR outbreak?) AND (household? OR kiss? OR saliva OR transport? OR travel?).

6.4 Evidence review

One hundred and three abstracts were identified through the search strategy (46 through MEDLINE, 40 through Embase, 16 through Global Health and one through the Cochrane database of systematic reviews), and 10 full papers were assessed.

6.4.1 Direct evidence

No papers were identified that compared IMD incidence among public transport contacts given and not given chemoprophylaxis.

6.4.2 Indirect evidence

Data on risk were examined. A review article found three papers on clusters of meningococcal disease linked by contact on the same transport vehicle (96). Two of the three clusters (n=5, n=2) occurred among regular passengers of the same school bus (97,98). Two cases in the third cluster had dates of onset two and five days after travelling on the same international flight from USA to Australia (99). They had been seated 12 rows apart. The strains isolated from cases within each of these three clusters were indistinguishable by genotyping. The range of dates of onset within each cluster did not exceed three days. None of the cases in the clusters had received chemoprophylaxis before onset.

Reports of 25 sporadic cases linked to air travel were found in the same review article (96). These occurred among passengers of long duration flights and without any known occurrence of secondary cases. Most of these cases are described in a paper from the US Center for Disease Control and Prevention (CDC) (100). Some cases were symptomatic on the flight while others became ill after the flight. Information on completeness of chemoprophylaxis and follow up was variable.

It was not possible to quantify the risk of transmission from transient contact on public transport not only because of few data on denominators, but also because there was no clear evidence of secondary transmission. The cases in the three clusters could equally be explained by exposure to unidentified asymptomatic carriers. In two of the clusters, cases were in regular contact with other children on the same school transport. In the third cluster, the cases did not appear to have any contact with each other apart from being on the same plane.

6.4.3 Quality of evidence

No studies addressed the research question. Data on risk was very limited. No studies were found that established secondary transmission.

6.5 Assessment of potential benefits, harms and costs

The quality of evidence for or against giving chemoprophylaxis was very low. The lack of clusters in the published literature suggests that the risk to contacts of cases sharing the same transport as cases is very low.

It is likely that contacts would willingly accept an offer of antibiotics, even if there was very low risk and uncertain benefit due to the perceived harm from meningitis (meningococcal disease). There is a low risk of harm from chemoprophylaxis. The costs of treatment are low, but in this setting the cost of contact tracing (i.e., identifying and locating fellow passengers on the same aeroplane as a case) can be considerable and may not be feasible.

Consistency of policy is important for the credibility of public health institutions. The working group considered the analogy of policy after a single case in a school. Despite evidence for an increased risk, which is lacking in the travel setting, chemoprophylaxis is not normally recommended for all pupils in the same class despite sharing the same classroom day after day. The working group had difficulty recommending prophylaxis to fellow passengers, even on a flight of long duration, without evidence of risk.

6.6 Recommendation

Sharing the same transport vehicle as a case of IMD is not, in itself, an indication for chemoprophylaxis (Weak).

6.7 Implications for practice

Although the recommendation not to give chemoprophylaxis to fellow passengers on the same transport is graded as weak, various follow-up policies in different countries have a high risk of causing confusion among professionals and the public. A consistent European policy is highly desirable, but achieving consensus may not be easy.

7. Which antibiotic regimen should be advised for chemoprophylaxis among adults, children and pregnant women?

7.1 Research question

Which antibiotic regimes are most effective in eradicating carriage among adults, children and pregnant women?

7.2 Specific background

Type and dosage of antibiotics recommended for meningococcal prophylaxis vary across Europe (101). The most frequently recommended antibiotics include rifampicin, ciprofloxacin, ceftriaxone and azithromycin. Due to concern about safety, some of these antibiotics are not recommended for children and pregnant women; however, recommendations are usually based on manufacturers' indications rather than evidence. The epidemiology of meningococcal antibiotic resistance may differ per country and needs to be taken into account for recommendations.

7.3 Specific methods

The following search string was used to search for relevant papers: (neisseria meningitidis OR meningococc*) AND (carriage OR carrier* OR coloni* OR nasopharyn*) AND (eradicat* OR eliminat* or antibiotic* OR *prophyla*).

Since chemoprophylaxis using antibiotics that eradicate carriage has been shown to be effective in reducing the risk of further cases in household contacts (see 3.1), carriage of *N. meningitidis* was used as the main outcome in this evidence review.

As emergence of strains resistant to antibiotics may develop after prophylaxis and decrease the effectiveness of some antibiotic regimens, emergence of non-susceptible strains after prophylaxis was also considered as an outcome.

Because the risk of disease is highest one week following exposure to a case, effectiveness was defined as eradication at ≥ 7 days of follow-up (102).

7.4 Evidence review

One Cochrane systematic review was identified, covering 24 studies up to June 2006. The search strategy identified 67 additional abstracts in the period following the review. According to the stated criteria, three studies were found eligible and retrieved. Nine additional studies included in the Cochrane review were also retrieved for further analysis of data, as well as one non-indexed randomised controlled trial (RCT) referred to in a study from the Cochrane review. In total, 14 full papers were assessed.

7.4.1 Direct evidence

Effectiveness of antibiotics in eradicating carriage at ≥ 7 days of follow-up

Rifampicin and ciprofloxacin were shown to be more effective than placebo in six and two RCTs respectively (103). Rifampicin continued to be effective compared to placebo for up to four weeks of follow-up in two studies. Ciprofloxacin and rifampicin showed non-significant differences in effectiveness in two RCTs. Minocycline was more effective than placebo in two RCTs and was as effective as rifampicin in two RCTs (104–106)[i]. None of the trials evaluated ceftriaxone, azithromycin or cefixime compared to placebo. In single studies, ceftriaxone was more effective than rifampicin, and cefixime and azithromycin were as effective as rifampicin (107–109). Ceftriaxone and cefixime also showed high effectiveness (95–100%) in non-controlled studies (110,111) and ceftriaxone showed 98% effectiveness at six days of follow up in another RCT (110). Penicillin, ampicillin and cephalexin were not more effective than placebo at 1–2 weeks of follow up in single RCTs (113,114). A single dose of ofloxacin (400 mg) showed 95% effectiveness in an open study (115). The effectiveness of antibiotics in specific groups (i.e., children, pregnant and lactating women) has been poorly studied. Only one RCT involved children exclusively

[i] The Cochrane review performed a meta-analysis of the two RCT comparing the effectiveness of minocycline to placebo, in spite of a high level of heterogeneity. Though the 2 RCTs showed a significantly higher efficacy, the meta-analysis concluded in non-significant difference in efficacy.

and showed that rifampicin 20 mg/kg was 93% effective, significantly higher than placebo (116). Four other RCTs included children and/or infants. All regimens were effective overall but the effectiveness in children was not separately analysed (106,107,111,117). One study, administering ceftriaxone 2 g to 176 pregnant and lactating women, showed very high effectiveness at two weeks (98%) but there were no separate analyses and no adequate comparison group (111). However, effectiveness is not likely to differ between the general adult population and pregnant or lactating women.

Effective dosage

There is no evidence on the optimal dosage for these antibiotics. No review or RCT compared the effectiveness of different dosages of the same antibiotic and Cochrane meta-analyses grouped studies using different dosages (Table 9). Evidence from individual RCTs suggests that all of the dosages included in Table 11 were effective. Evidence is stronger for the effectiveness of rifampicin 2400 mg and ciprofloxacin 750 mg single dose, as they were found to be significantly effective in at least three trials.

Development of antibiotic resistance

Development of resistance was only detected in trials using rifampicin. In three of the six RCTs assessing the resistance to rifampicin, resistance developed in 10–27% of initial carriers (Table 10) (104,106,118). Increases in minimal inhibitory concentration (MIC) to rifampicin were also described in these three studies. The highest resistance rate was observed with a low daily dose of rifampicin (600 mg). However, studies showed a lack of consensus on MIC breakpoints of rifampicin and ciprofloxacin.

7.4.2 Indirect evidence

Adverse events of antibiotic regimen

Nineteen RCTs provided data on adverse events, and all events were mild and transient. Side effects due to rifampicin (29%) were significantly more frequent than those due to ceftriaxone (21%) in one RCT (112). Two RCTs did not show any significant differences in the rates of adverse events due to rifampicin or ciprofloxacin (111,119). One RCT showed a higher frequency of side effects for minocycline than for rifampicin but the difference was not statistically significant (106). However, minocycline is known to be associated with vestibular toxicity in up to 78% of those receiving prophylaxis in an open study (120). A higher dosage (400 mg daily) resulted in a higher rate of side effects than a lower dosage (200 mg daily) (105,106). Symptoms disappeared after discontinuing use of the drug. This high rate of vestibular side effects has limited its use as a prophylactic agent.

Toxicity in children

In general rifampicin, ceftriaxone, cefixime and azithromycin are recommended for use in children. Minocycline is not recommended in children younger than eight years of age because abnormal bone formation and discoloration of teeth may occur. Ciprofloxacin is usually not recommended in children due to induced arthropathy in juvenile animals, but abundant evidence of lack of joint damage was found in young children given ciprofloxacin. In one RCT on carriage eradication, ciprofloxacin did not lead to a higher rate of side effects in 469 children aged 2–18 years compared to rifampicin (111). Multiple controlled prospective and retrospective studies, using higher doses of ciprofloxacin, showed that the rate of adverse events of ciprofloxacin in children was similar to that seen using other antibiotics, and that long-term cartilage damage was not seen in humans (120,121). In all studies, the risk of arthropathy due to ciprofloxacin was very low; arthralgia were transient and most were coincidental. A controlled study of 116 neonates receiving ciprofloxacin also showed similar clinical growth compared to 100 controls, even at one year of follow-up (123). The risk of tendon disorders in a large retrospective study involving 4531 children given ciprofloxacin was similarly low compared to children given azithromycin (0.8%) (124). In all studies, side effects resolved after cessation of therapy.

Toxicity in pregnant and lactating women

Safety of antibiotic regimens for chemoprophylaxis in pregnant and lactating women is poorly described. In general ceftriaxone, cefixime and azithromycin are not contra-indicated in pregnancy[i]. The only RCT involving 176 pregnant and lactating women administered ceftriaxone (2 g) via the intra-muscular route, and only five subjects reported mild side effects; however, there was no control group (111). Ciprofloxacin and rifampicin should preferably be avoided during pregnancy[ii]. Rifampicin teratogenicity has been demonstrated in high doses in animals, but epidemiological studies did not reveal any notable risk in humans when administered for tuberculosis

[i] Category B: Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

[ii] Category C (ciprofloxacin and rifampicin): Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

treatment (125). Ciprofloxacin is contra-indicated in pregnancy but short duration treatment for other indications appeared to be safe (126,127). Minocycline should not be used in pregnancy[i].

Safety of antibiotic regimen for the nursing infant is poorly studied, and a drug that is safe for use during pregnancy may not be safe for the infant. A systematic review of antibiotic use in lactation considered ciprofloxacin and rifampicin as compatible with breastfeeding; other antibiotics were not studied (128).

Development of antibiotic resistance in non controlled studies

Several non-controlled studies observed the emergence and spread of rifampicin resistant strains among carriers after prophylaxis (129–131). Cases due to rifampicin resistant meningococcal isolates have also been reported after prophylaxis (132–136).

7.4.3 Quality of evidence

There is high evidence that rifampicin, ciprofloxacin and minocycline eradicate carriage (>1 RCT, meta-analyses), and effectiveness values are very consistent across studies. Moderate evidence suggests that ceftriaxone, azithromycin and cefixime eradicate carriage (one RCT and open studies).

Moderate evidence suggests that there is no regimen (type of antibiotic, dosage, duration, route) superior to others in terms of effectiveness or rate of side effects. There is also moderate evidence that the same antibiotics are also effective in children, pregnant and lactating women.

High evidence exists that rifampicin resistance develops after prophylaxis and there is low evidence that resistant strains may lead to further cases.

Moderate evidence suggests that side effects following prophylaxis are mild and transient. Moderate evidence also suggests that minocycline leads to a high rate of vestibular side effects. There is moderate evidence that ciprofloxacin is associated with a low rate of osteoarticular side effects in children no higher than as has been seen with other prophylactic drugs.

7.5 Assessment of potential benefits, harms and costs

Evidence has shown high effectiveness of the six studied antibiotics in eradicating carriage. The three antibiotics administered as a single dose should result in higher compliance.

Evidence has also shown limited harm, as side effects are mild and transient. However, the emergence of rifampicin resistance is proven and relatively frequent, and rifampicin has interactions with other drugs (e.g. contraceptives). Minocycline has frequent vestibular side effects and cannot be used in children younger than eight years and in pregnant women. Safety in pregnancy and during lactation of other antibiotics is poorly known.

Evidence on the burden of the proposed intervention has not been studied. Longer durations of rifampicin, minocycline and cefixime regimens are probably less convenient—especially for subjects that are asymptomatic. Ceftriaxone cannot be given orally and requires an intra-muscular injection which is painful.

Preferences have not been assessed, but exposed persons often want an intervention. It is likely that intramuscular injections are less acceptable, at least among children and their parents. A single oral dose is likely to be preferred over a 2–5 day regimen.

Drug pricing varies between countries but costs of recommended regimens are unlikely to exceed 6€ per treated person. For normally recommended dosages rifampicin, ceftriaxone and minocycline rank highest with similar cost, followed by azithromycin and then ciprofloxacin (cheapest option, 2–3€)[ii].

7.6 Recommendations

Rifampicin, ciprofloxacin, ceftriaxone, azithromycin and cefixime can be advised for chemoprophylaxis (Strong). Ciprofloxacin, azithromycin and ceftriaxone are preferred (Weak)[iii]. In children, all these antibiotics can be advised (Strong). In pregnant women, ceftriaxone, azithromycin and cefixime can be advised (Weak).

[i] Category D (minocycline): There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

[ii] Based on 2009 retail prices in Belgium

[iii] Single dose, similar effectiveness, can be given to adults and children, low rate of side effects, low risk of resistance.

7.7 Implications for practice

Rifampicin is the drug of choice for meningococcal chemoprophylaxis in the majority of European Union (EU) countries (101). One advantage for prescribers is that it is licensed for chemoprophylaxis. However, as rifampicin is associated with rapid induction of resistance, inhibition of contraceptives and longer regime duration, the use of single dose ciprofloxacin, azithromycin or ceftriaxone is recommended by a Cochrane review (103) and has many advantages. This recommendation would require a change of practice but has high feasibility at similar or lower cost. Based on available evidence, effective dosages (Table 11) do not always correspond to current recommendations and formulations available in EU countries. For instance, ciprofloxacin is recommended in many countries as a 500 mg single dose but the effectiveness of this dosage has not been assessed for in a controlled trial; only a single dose (750 mg) has been shown to be highly effective in three RCT. However, a non-controlled study has suggested that 500 mg was effective in eradicating carriage in 96% of 126 carriers at 11 days of follow-up (137). Ceftriaxone is usually available in vials containing ≥500 mg and cefixime is no longer available in all countries since the expiration of its patent in 2003. There is a growing concern that the wide use of prophylaxis would favour resistance, especially against quinolones and macrolides. A small number of IMD cases due to ciprofloxacin resistant strains have been reported in Spain, France and the US (138–142). The US cases resulted in a change of prophylaxis regimens, and the subsequent carriage survey also found that 8% of isolates, though susceptible, had minimum inhibitory concentrations (MICs) for azithromycin at the upper limit of susceptibility. Therefore, surveillance of resistance to antibiotics used for prophylaxis is essential in all countries. Ofloxacine and spiramycine are recommended for prophylaxis in a few EU countries for specific groups (101), but this review did not identify any RCT that evaluated their effectiveness. Penicillin and ampicillin are also recommended in a few countries: RCTs showed that they were not effective at eradicating carriage after seven days.

7.8 Further research needs

The effectiveness of azithromycin and third-generation cephalosporins in carriage eradication should be studied in further RCTs. Optimal dosage for young children and safe regimens for pregnant and lactating women should be studied. The risk of development of resistance to the recommended antibiotics should be investigated, and a consensus on MIC breakpoints should be reached.

Note: As part of the review, the evidence in a Cochrane review (76) was assessed and sometimes different conclusions were reached. For example, sufficient evidence for the effectiveness of azithromycin in carriage eradication was found, and some errors in categorisation of RCT follow up and treatment doses were identified.

Table 9: Effectiveness of different antibiotics at 7–14 days of follow up, based on RCTs

Drug	Total dose	Duration, frequency	Author study	Eradication in %[1]	Compared to control group
Rifampicin					
Adults	1200 mg	2 days, BID	Deviatkina	96% (?)	More effective than placebo
Adults	2400 mg	2 days, BID	Deal[a]	93% (14/15)	More effective than placebo
Adults	2400 mg	2 days, BID	Devine (70)	82% (31/38)	More effective than placebo
Adults Children <66 lb.	2400 mg 1200 mg	2 days, BID	Kaiser	82% (9/11)	More effective than placebo
Children (2-15y)	20 mg/kg	2 days	Borgono	93% (89/96)	More effective than placebo
Adults and Children (2-18y)	2400 mg 80 mg/kg	2 days, BID	Cuevas	98% (86/88) at 2 weeks	As effective as ciprofloxacin
Adults	2400 mg	2 days, BID	Kaya	96% (24/25)	As effective as ciprofloxacin
Adults	2400 mg	2 days, BID	Munford	91% (61/67)	As effective as minocycline
Children (1-12y) (Infants 3m–1y)	40 mg/kg (20 mg/kg)				No carrier in children <1 year
Adults	2400 mg	2 days, BID	Girgis	91% (52/57)	As effective as azithromycin
Adults Children	2400 mg 40 mg/kg	2 days, BID	Schwartz	81% (22/27)	Less effective than ceftriaxone
Adults	3000 mg	5 days, daily	Guttler	89% (131/147)	More effective than placebo As effective as minocycline (1g)
Adults	2400mg	2 days, BID	Podgore	98% (92/94)	As effective as cefixime
Ciprofloxacin					
Adults	10x500mg	5 days, BID	Pugsley	100% (21/21)	More effective than placebo
Adults	750 mg	Single dose	Dworzack	96% (23/24)	More effective than placebo
Adults	750 mg	Single dose	Kaya	92% (24/26)	As effective as rifampicin
Adults and Children (2-18y)	750 mg 15 mg/kg	Single dose	Cuevas	91% (72/79)	As effective as rifampicin
Azithromycin					
Adults	500 mg	Single dose	Girgis	93% (53/57)	As effective as rifampicin
Ceftriaxone					
Adults Children	250 mg 125 mg	Single dose	Schwartz	97% (62/64)	More effective than rifampicin
Pregnant/lactating[2] Children <2 years[2]	2000 mg 50 mg/kg	Single dose	Cuevas	98% (40/41) at 2 weeks	No randomised control group
Minocycline					
Adults	1100 mg	5 days, BID	Devine (71)	44% (18/41)	More effective than placebo
Adults	1000 mg	5 days, BID	Guttler	90% (132/147)	More effective than placebo As effective as rifampicin (3g)
Adults Children/infants	700 mg 14 mg/kg	3 days, BID	Munford	90% (52/58)	As effective as rifampicin (2.4g)
Cefixime					
Adults	400 mg	2 days, daily	Podgore	95% (77/81)	As effective as rifampicin
Other (non effective) antibiotics					
Cephalexin	6000 mg	12 doses	Deal[b]	6% (1/15)	Not more effective than placebo
Ampicillin **Penicillin**	15g 13.8g	10 days, TID 10 days, TID	Dowd	30% (14/46)	Not more effective than placebo

BID: twice a day, TID: three times a day, QID: four times a day

SS: statistical significance

1: number of initial carriers with eradication / total initial carriers given prophylaxis and tested at 7-14 days

2: not randomised group, thus not included in Cochrane review

Table 10: Evidence on rifampicin resistance and MIC increase after prophylaxis, per dosage

Total dose	Study author	% resistant strains /initial carriers	Change in MIC
3000 mg (600mg daily)	Guttler	27% (17/62) of initial carriers 76% (57/75) of strains after prophylaxis: 20 MIC>100 µg/ml, 37 MIC 2-6 µg/ml	From 0.024 to 49.3 µg/ml, p<0.001
2400 mg (600mg BID)	Munford	10% (7/67) of initial carriers (MIC≥0.25 µg/ml). All 7 strains had MIC>16µg/ml	NA
2400 mg	Blakebrough	10% with MIC>3.2 µg/ml	In 4 isolates: from <0.1 to ≥3.2 µg/ml
2400 mg	Lepe*	None	Significant increase in median MIC (from 0.3 to 0.13 µg/ml)
2400 mg 40 mg/kg	Jackson*	12% (3/26) with MIC>8 µg/ml	

*: non-controlled study, comparison group are the same subjects before intervention

Table 11: Effective dosage, route and side effects of antibiotics, per specific group

	Dosage	Route	Main side effects / inconvenience
Adults			
Ciprofloxacin	750mg single dose (500mg probably effective)	Oral	Gastro-intestinal disorders, headache, transient arthralgia
Azithromycin	500mg single dose	Oral	Nausea, abdominal pain, headache
Ceftriaxone	250mg single dose	Intra-muscular	Injection painful, headache, gastro-intestinal disorders
Rifampicin	300 or 600mg BID for 2 days	Oral	Interaction with other drugs, gastro-intestinal disorders, coloration of urine, resistance
Cefixime	200mg daily for 2 days	Oral	Loose stools, abdominal pain, diarrhoea, headache
Minocycline	200mg loading dose, followed by 100mg BID for 3-5 days	Oral	Frequent vestibular effects: dizziness, nausea, vomiting, abdominal pain
Children			
Ciprofloxacin	15mg/kg single dose	Oral	No osteo-articular toxicity. Gastro-intestinal disorders, headache
Azithromycin	10mg/kg single dose (CDC)*	Oral	Nausea, abdominal pain, headache
Ceftriaxone	125mg single dose	Intra-muscular	Injection painful, headache. Should not be mixed with calcium-containing products
Rifampicin	5-20 mg/kg BID for 2 days (usually 10mg/kg)	Oral, suspension not always available	Gastro-intestinal disorders, coloration of urine, resistance rising
Minocycline	4mg/kg loading dose then 2mg/kg BID for 3-5 days	Oral	Not <8 years of age. Frequent vestibular side effects, dental staining.
Pregnant and lactating women			
Azithromycin	500mg single dose*	Oral	Gastro-intestinal disorders, headache
Ceftriaxone	250mg single dose	Intra-muscular	Injection painful, cannot be administered with lidocaine, gastro-intestinal disorders

*: not specifically tested for meningococcal meningitis in this group

Table 12: Evaluation of benefits, harms, burdens and values for each antibiotic

Antibiotic	Benefits	Harms	Burdens	Values
Rifampicin	Very effective Used for adults and children	Rapid resistance Hepatic toxicity Interactions with other drugs	4 doses, 2 days Inhibit contraceptives Suspension not always available	Coloured urine might disturb
Ciprofloxacin	Very effective High compliance	None, but fear of side effects in children Sporadic/rare resistance	None	Short - single dose regimen likely preferred
Ceftriaxone	Very effective High compliance Used for adults and children	Injection is painful	Intra-muscular administration, need logistics	Injection likely not valued by children and parents
Minocycline	Very effective	Frequent vestibular side effects. Contra-indicated in children and pregnancy	6-10 doses, 3-5 days	Long regimen not wanted
Azithromycin	Very effective High compliance Used for adults and children	Decreased susceptibility has been described	None	Short - single dose regimen likely preferred
Cefixime	Very effective Can be used for both adults and children	None known	Duration 2 days Not registered in several countries.	Short - single dose regimen likely preferred

8. Should contacts of a case of IMD, who have received chemoprophylaxis, also be offered a meningococcal vaccine, if appropriate?

8.1 Research question

What is the effectiveness of vaccination, in addition to chemoprophylaxis, among household contacts of a case of IMD in preventing further cases among those contacts?

8.2 Specific background

Chemoprophylaxis is recommended for household contacts of cases of meningococcal disease across Europe (141). In 2007, if a case was caused by a vaccine preventable strain, most (74%) EU/EFTA countries recommended an appropriate vaccine to household contacts. In the countries that did not, the risk of further cases after chemoprophylaxis were considered too low to be cost effective.

8.3 Specific methods

The following search string was used to search for relevant papers: (meningococc? OR neisseria meningitidis) AND (chemoprevention OR ?prophylaxis OR antibiotic? OR vaccin?) AND (contact tracing OR transmission OR contact? OR household?).

The search was performed from 2005 onwards as a systematic review (142) that covered prior publications. Papers on outbreaks or epidemics were an additional exclusion criterion for this search question.

8.4 Evidence review

One hundred and forty-nine abstracts were identified through the search strategy (57 through MEDLINE, 86 through Embase, four through Global Health and two through CDSR). Six full papers were assessed.

8.4.1 Direct evidence

One recent systematic review was identified (142), but this found no studies that compared incidence rates among household contacts given and not given vaccination in addition to chemoprophylaxis. No other such studies were identified when updating the search from 2005 to 2008.

8.4.2 Indirect evidence

In the above review, six papers were analysed (143–148). All were observational studies that allowed measurement of attack rates in household contacts given chemoprophylaxis. The weighted average attack rate from these six studies was 1.1 cases per 1000 household contacts (95% CI 0.7-1.7) in the 14–365 days after a case. Assuming a vaccine efficacy rate of 85–95% over this time period, between 600 and 1700 contacts would need vaccination to prevent one case of meningococcal disease due to a vaccine preventable serogroup.

8.4.3 Quality of evidence

No studies addressed the research question directly. The indirect evidence involved a number of assumptions that produced an approximate estimate of risk and potential benefit from vaccination.

8.5 Assessment of potential benefits, harms and costs

The quality of evidence is very low. However, the best estimate of risk suggests that this measure would be cost effective, and the overall cost is low given the relatively small number of cases in Europe to whom such a policy would be relevant. Vaccination is generally acceptable as a public health measure. Other measures shown to prevent another case in the household would be expected to have high acceptance and value among contacts.

8.6 Recommendation

If a case of meningococcal disease is caused by a strain that is preventable by an available licensed vaccine, an appropriate course of vaccination—in addition to chemoprophylaxis—is recommended for household contacts unless considered to be protected by previous vaccination (Strong).

8.7 Implications for practice

In practice, this recommendation should be applied both to household contacts and close contacts outside the household who have been given chemoprophylaxis. Contacts of cases caused by serogroup C strains and who have already received MenC conjugate vaccine would be expected to have an age and time dependent decline in protection. The recommendation of the working group should be applicable to contacts of cases caused by serogroups A, C, W135 and Y who are not considered to be protected by an appropriate conjugate vaccine. As most cases in Europe are currently caused by serogroup B strains (149), implementation of this policy would not require significant resources until such time as a serogroup B vaccine becomes available.

8.8 Further research needs

Further studies to measure the risk among household contacts given chemoprophylaxis would provide more confidence in the estimates of risk and benefit. Qualitative research into the views of families and the value placed on preventing another case in the household would inform assumptions about those values.

Annex 1. Acknowledgements

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- Germaine Hanquet, consultant epidemiologist (independent), Brussels, Belgium.
- Wiebke Hellenbrand, consultant epidemiologist, Robert Koch Institute, Berlin, Germany.
- Sigrid Heuberger, consultant microbiologist, Meningococcal Reference Laboratory, Austrian Agency for Food and Health Safety, Graz, Austria.
- Pawel Stefanoff, consultant epidemiologist, National Institute of Public Health–National Institute of Hygiene, Warsaw, Poland.
- James Stuart, consultant epidemiologist (independent), Ausseing, France.

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Annex 2. General methodology

Development of the document

The five consortium members developed protocols, areas of recommendation, scientific questions to be addressed, evidence assessments and draft reports by email, teleconference and face-to-face meetings. The report was reviewed after comments on the draft from meningococcal experts across Europe and from ECDC.

Box 1: Areas of recommendation

A) What laboratory tests are advised to make an accurate (sensitive, specific) and rapid diagnosis of invasive meningococcal disease (IMD)?

B) Should antibiotics for chemoprophylaxis, if different to those used for clinical treatment, be given to cases of IMD before discharge from hospital?

C) Should chemoprophylaxis be given to defined groups of contacts of a case of IMD to reduce the risk of further cases among the following groups:

   (i) household members?

   (ii) pre-school, school or college contacts?

   (iii) contacts who share drinks (salivary contacts)?

   (iv) contacts through public transport?

D) Which antibiotic regimes should be advised for chemoprophylaxis among adults, children, pregnant women?

E) Should defined groups of contacts of a case of IMD be advised to have a meningococcal vaccine in addition to chemoprophylaxis?

Assumptions

Rapid diagnosis reduces time to delivery of public health measures. Chemoprophylaxis was considered to be administration of antibiotic regimes that eradicate carriage of *N. meningitidis*. 'No chemoprophylaxis' was considered to include administration of antibiotic regimes that do not eradicate carriage of *N. meningitidis*.

Scientific questions were framed using the Population, Intervention, Comparison, Outcome approach (150) to define the search strategy and the evidence assessments for areas of recommendation (Box 1).

Box 2: Scientific questions

A) What are the most sensitive and specific microbiological laboratory tests to confirm the diagnosis of IMD?

B) What is the effectiveness of chemoprophylaxis to a case of IMD before discharge from hospital in preventing further cases of IMD

C) What is the effectiveness of chemoprophylaxis to contacts (in defined settings) of a case of IMD in preventing further cases in those settings?

D) Which antibiotic regimes are most effective in eradicating carriage among adults, children and pregnant women?

E) How effective is vaccination of contacts in addition to chemoprophylaxis in preventing IMD?

Obtaining the evidence

The search aimed for abstracts of systematic reviews relating to the questions from 1990 up to the end of 2008. Primary evidence abstracts were searched for (and other reviews) in MEDLINE, Embase, Global health, Cochrane database of systematic reviews and the Cochrane central register of controlled trials through the German Institute of Medical Documentation and Information (DIMDI). If no relevant review was identified, all abstracts published from 1990 to 2008 were screened. The search period was expanded for some of the topics if initial screening showed relevant research had taken place earlier. If a relevant review was identified, only abstracts published from date of search for last systematic review up to end 2008 were screened.

Papers were accepted in any European language. Abstracts were individually assessed for relevance to the question and reviewed full papers on relevant abstracts, and selected for inclusion in the evidence assessment using stated criteria (Box 3). Reference lists in these papers were examined for other relevant publications, and Google Scholar searched for citations of identified key papers.

The external working group identified epidemiologists and microbiologists with expertise in meningococcal disease across Europe from EU and European Monitoring Group for Meningococci (EMGM) contact lists, sent out the study protocol and asked for unpublished data that fit the selection criteria (Box 3).

Box 3: Inclusion and exclusion criteria

Inclusion criteria:

Experimental studies

Observational studies (analytical studies with a comparison group)

Case series >10 cases

Exclusion criteria:

No comparison groups
Case series ≤ 10 cases

Grading the evidence, recommendations and implications for practice

The evidence was assessed and the quality of evidence and strength of recommendation categorised based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (151). The group particularly referred to two World Health Organization (WHO) publications on rapid advice guidelines (152,153) and to the Cochrane 'systematic reviews of health promotion and public health interventions' (150). A template for evidence assessment was developed.

Quality of evidence for each outcome was based on study design, study limitations, consistency of evidence, directness of evidence, and precision of the estimate. Evidence was classified as high, moderate, low or very low depending on the type, quality, results of retrieved studies and an assessment as to whether further research was likely to change confidence in the estimate of effect.

Quality of evidence and definitions (155)

High quality – Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality – Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low quality – Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality – Any estimate of effect is very uncertain.

Recommendations took into account quality of evidence but also potential benefit, harm, values, burdens and costs. Recommendations were classified as strong or weak (152). A strong recommendation was one where most individuals should receive the intervention, nearly all well informed individuals would want the intervention and the intervention could unequivocally be used in policy making. A weak recommendation was one where most well informed individuals would want the intervention but an appreciable proportion would not, values and preferences

were likely to vary widely, and policy making would require extensive debate and involvement of many stakeholders. It was considered that recommendations should be appropriate to a European setting.

Strength of recommendations (156)

The strength of recommendation reflects the extent to which the working group can be confident that the desirable effects of an intervention outweigh undesirable effects. The GRADE classifies recommendations as strong or weak. Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use.

Process and product were checked using the criteria in the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument training manual (154). An external review was not conducted. All members signed a declaration of interest form on personal or non-personal interest in the pharmaceutical industry. Only one declared any interest. This was non-personal and not related to IMD (industry funding to measure the burden of pertussis).

Evidence assessments (See main document Sections 1–8)

The quality of evidence and strength of recommendations were concluded for the eight questions. Strong or moderate quality of evidence was available only for the areas of chemoprophylaxis to household contacts, antibiotic regimes and diagnostic tests. After considering evidence, harm, benefit, values, burdens and costs, strong recommendations were made in these three areas. The group also gave strong recommendations for chemoprophylaxis to the case prior to hospital discharge and for vaccination to household contacts, where the evidence was of low quality (Box 4). More substantive reviews were performed for two important areas: antibiotic regimes (a complex area with a broad range of strong and moderate evidence), and chemoprophylaxis for contacts in educational settings (a difficult area of policy without direct evidence but where it was possible to estimate risk).

Box 4: Recommendations

A) Laboratory tests. All microbiology laboratories that undertake diagnosis of meningococcal disease should have access to PCR testing (Strong). Polymerase chain reaction testing of skin lesion samples is recommended, especially after antimicrobial treatment has started (Weak).

B) Antibiotics effective at eradication of carriage to cases of IMD prior to discharge from hospital. Chemoprophylaxis is recommended for patients with IMD before discharge from hospital. Chemoprophylaxis is recommended for patients with IMD before discharge from hospital, unless an antibiotic regimen effective in eradicating carriage was used during hospital treatment (Strong).

C) Chemoprophylaxis to contacts of a case:

- **Household**. Chemoprophylaxis with an antibiotic regime that eradicates carriage is recommended for household contacts of a case of IMD (Strong).
- **Pre-school, school, college**. Attending the same pre-school as a case of IMD in a pre-school setting is an indication for chemoprophylaxis depending on the risk assessment (Weak). Attending the same school/college as a case of IMD (including the same class) is not, in itself, an indication for chemoprophylaxis (Weak).
- **Sharing drinks**. Sharing drinks, cigarettes or similar contact with a case of IMD is not, in itself, an indication for chemoprophylaxis (Weak).
- **Travel**. Sharing the same transport vehicle as a case of IMD is not, in itself, an indication for chemoprophylaxis (Weak).

D) Antibiotic regimes for chemoprophylaxis. Rifampicin, ciprofloxacin, ceftriaxone, azithromycin and cefixime can be advised for chemoprophylaxis (Strong). Ciprofloxacin, azithromycin and ceftriaxone are preferred (Weak). All of these antibiotics can be advised for children (Strong). In pregnant women ceftriaxone, azithromycin and cefixime can be advised.

Strengths and weaknesses

Strengths

The overall process of developing guidance worked efficiently, and the product was successfully completed within six months. Communication by email, teleconference and face-to-face meetings allowed ample opportunity for discussion and debate. The group appreciated the opportunity to take into account issues surrounding harm, benefit, values, burdens and costs in addition to quality of evidence in making recommendations. In classifying evidence, Schunemann (152) suggests a key criterion should be whether further research might change confidence in the estimate of effect. For example, high quality evidence implies that further research is highly unlikely to change the estimate. This connotes that it is feasible for further research to take place. However in some areas, for example, with regards to the estimation of chemoprophylaxis effectiveness to cases in hospital, it would not be likely, if even desirable, that the necessary research would be done for logistic or ethical reasons.

Most of the AGREE criteria had been met under the categories of scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, application, and editorial independence. As this document does not have the status of an official guideline but sets out evidence-based guidance/recommendations to assist countries in reviewing their own guidelines, neither tools for application nor audit criteria were included.

Several areas of uncertainty and research gaps were identified; further research may contribute to the evidence and reinforce or change current guidance and recommendations. Other areas of public health policy may be suitable for similar assessment.

Weaknesses

This report was completed within six months. Due to time and resources restrains, the reviews of each topic cannot be regarded as meeting the standards of a full systematic review (Cochrane). Nonetheless, the group believes that most published papers meeting the pre-defined selection criteria had been identified. Although the evidence was not assessed as rigorously as suggested in the GRADE methodology, the suggested process and criteria for assessing quality of evidence and forming recommendations was followed and used by the group. If readers believe that relevant research has been missed, whether such research might reinforce or contradict the conclusions reached, comments and suggestions for improvement of the guidance document are very welcome.

One major gap was the lack of information on the views and values of contacts in prevention and prophylaxis, although the group did receive comments from two non-governmental organisations who work with patients affected by meningitis.

Although each group member signed a declaration of financial interest form, it was recognised that current policy recommendations in the country of the individual working group members might influence their recommendations. The group members declared their confidence that these interests did not affect their final conclusions.

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