

## **Evidence for public health management of invasive meningococcal disease**

**Composed by a quintet of the  
European Meningococcal Disease Society (EMGM)**

Wiebke Hellenbrand (Robert Koch Institute, Germany)  
Germaine Hanquet (Consultant Epidemiologist, Belgium)  
Pawel Stefanoff (National Public Health Institute, Poland)  
Sigrid Heuberger (Meningococcal Reference Laboratory, Austria)  
James Stuart (Conductor)

### **A story**

- A 35 year old man takes a plane from London to Chicago (8hr flight) on a business trip returning 2 days later.
- On the return flight, he sits in Seat 27B between 2 other passengers whom he does not know. He has a brief conversation with each of them during mealtimes. He feels a bit unwell during the flight.
- The next day he collapses and is admitted to hospital. He is in shock and has a florid haemorrhagic rash.

He has a clinical diagnosis of meningococcal septicaemia.  
His wife is pregnant.  
They have two sons aged 2 and 5 years.

For one million rupees...  
Do you arrange antibiotic prophylaxis now for

1. His wife only
2. Their children only
3. His wife and children
4. No-one

As the public health team arrange prophylaxis for close contacts, they learn that the 2 year old son has just been admitted to hospital with a presumptive diagnosis of meningococcal disease.

The son attends a day nursery with 70 other children. He usually attends Mondays and Wednesdays.

Do you arrange prophylaxis for

1. All children attending the nursery
2. Those who attend on the same days
3. Close contacts only
4. No-one

How about passengers on the plane?

Do you arrange prophylaxis for

1. Passengers in the same row.
2. Passengers in the row behind and in front.
3. The whole plane
4. No-one

PCR result on blood samples from both father and son confirm meningococcal infection, group W135

Do you offer ACYW135 quadrivalent vaccine to close contacts?

1. Yes
2. No

## Background

- Survey of public health management of meningococcal disease in European countries in 2007
- Variation in policy
- ECDC tender
  - Develop evidence-based guidance for good practice
  - Assist European countries in decisions on policy

M Hoek, et al. *Eurosurveillance* 13 (1-3):78-80, 2008.

## Methods

- Five consortium members
  - Defined research areas
  - Systematically reviewed and graded evidence
  - Developed recommendations

By

- E-mail (473 mails in project folder!)
- Telephone conferences
- 2 Face-to-face meetings
- 6 months

Dear all, ....

Dear fantastic team, ....

Dear exhausted team, ...

Where is James ?....

Dear slaves,....

Interesting that reading the abstract makes you change the recommendation, after all this time!

## PICO – T

- Cochrane approach to defining research questions and search strategies
  - **P**articipants
  - **I**nterventions
  - **C**omparisons
  - **O**utcomes
  - Definition of study **T**ypes
    - Experimental studies
    - Observational studies
    - Case series > 10 cases
    - Exclusion if
      - no comparison groups
      - case series ≤ 10 cases

## Search strategy

- Databases
  - Cochrane, Medline, Embase, Global Health
- Search period 1990 to 2008
  - If systematic review, only abstracts published after performance date of review screened
  - If no review found, all abstracts screened
  - Any European language
  - Searched reference lists of identified key papers
  - Citation search in Google Scholar

## Grading the quality of the evidence

- According to GRADE methodology<sup>1-3</sup> based on
  - Study design and limitations
  - Consistency
  - Directness
  - Precision of estimate
- Four categories of evidence
  - High
  - Moderate
  - Low
  - Very low

1. Atkins D, et al. BMJ. 2004; 328(7454):1490. 2. Schunemann HJ et al. PLoS Med. 2007 May;4(5):e119.  
3. Schunemann HJ et al. Lancet Infect Dis. 2007 Jan;7(1):21-31.

## Making recommendations

- Based on
  - Quality of evidence
  - Potential benefit, harm, values, burdens, costs
- GRADE classification
  - Strong
    - Most individuals should receive intervention
    - Most well informed individuals would want intervention
    - Intervention unequivocally used in policy making
  - Weak
    - Most would want intervention, but significant minority would not
    - Values/preferences likely to vary widely
    - Extensive debate, many stakeholders in policy making

## The Questions

- A. Which antibiotic regimes are most effective in eradicating carriage among adults, children and pregnant women?
- B. What is the effectiveness of chemoprophylaxis to contacts of a case in preventing further cases in defined settings?
- C. What is the effectiveness of chemoprophylaxis to a case before discharge from hospital in preventing further cases?
- D. How effective is vaccination of contacts in addition to chemoprophylaxis in preventing further cases?
- E. What are the most sensitive and specific microbiological laboratory tests to confirm the diagnosis?

## A. Antibiotic regimens recommended for chemoprophylaxis

- Direct evidence from randomised controlled trials:

Antibiotic	Total dose (mg)	No. days	Eradication	Versus Placebo	Versus other regimen
1. Rifampicin*	1200-3000	2-5	81-98%	> placebo (6 RCT)	== 2,3,5,6; < 4
2. Ciprofloxacin	750-5000	1-5	91-100%	> placebo (2 RCT)	==1 (2 RCT)
3. Minocycline	700-1100	3-5	44-90%	> placebo (2 RCT)	==1 (2 RCT)
4. Ceftriaxone**	250 (i.m.)	1	97-98%	No data	>1 (1 RCT)
5. Azithromycin	500	1	93%	No data	==1 (1 RCT)
6. Cefixime	400	2	95%	No data	==1 (1 RCT)
7. Cephalexin	6000	10	6%	== placebo	No data
8. Ampicillin or	15/13.8	10	30%	== placebo	? No data

\* 1 trial in children only \*\* highly effective in non-controlled trial in pregnant and lactating women

## **Antibiotic regimens recommended for chemoprophylaxis**

- Development of antibiotic resistance
  - In three rifampicin RCTs, resistance in 10-27% of initial carriers
  - Cases with rifampicin-resistant strains in contacts after chemoprophylaxis
- Adverse effects
  - Mild and transient (19 RCT, 3 non-controlled studies)
  - Vestibular toxicity after minocycline (up to 78% of recipients)
  - Risk of osteo-articular side effects in children no higher with ciprofloxacin than with other antibiotics

## **Antibiotic regimens recommended for chemoprophylaxis**

- Quality of evidence: High or moderate
- Benefit, harm, burden, costs, values
  - High effectiveness at meningococcal eradication
  - Level of side effects acceptable (apart from minocycline)
  - Painful (ceftriaxone)
  - Risk of resistance (rifampicin)
  - Low cost
  - Contacts often desire intervention



## Antibiotic regimens recommended for chemoprophylaxis

- Recommendations
  - STRONG: Rifampicin, ciprofloxacin, ceftriaxone, azithromycin, cefixime can be advised for chemoprophylaxis in adults and children
  - WEAK: Ceftriaxone, azithromycin, cefixime preferred in pregnancy
- Implications for practice
  - Rifampicin currently drug of choice in Europe, change feasible
  - Regimen dosage not always evidence based (ciprofloxacin )
  - Antibiotic resistance monitoring vital

## B. Chemoprophylaxis of contacts in households

Direct evidence:

- Meta-analysis of studies in one systematic review<sup>1</sup> plus one additional study<sup>2</sup> (all observational)
- Comparing incidence in treated and untreated contacts
  - Pooled Risk Ratio 0.14 (95% CI 0.02-0.58)
  - Number Needed to Treat (NNT) to prevent one case  
= 304 (95% CI 89-564)

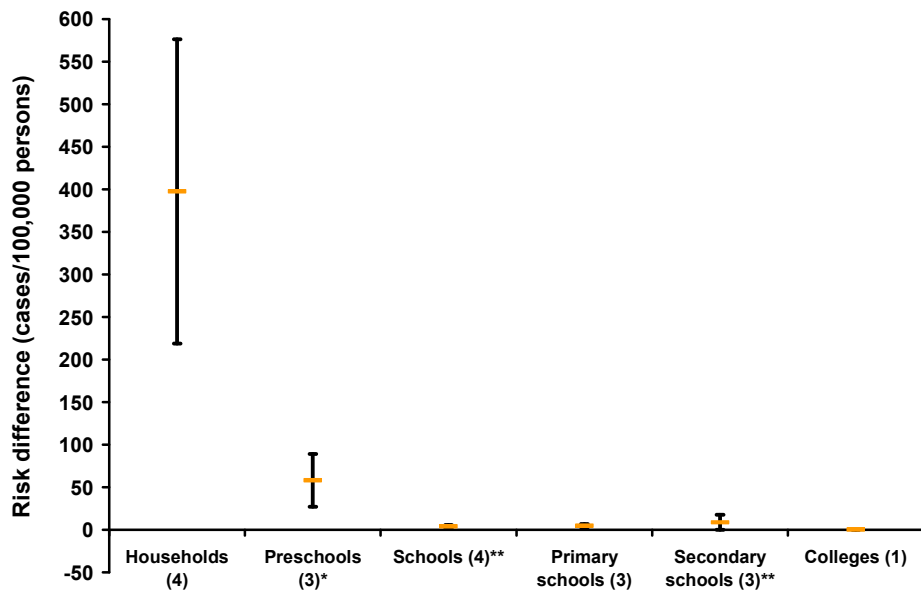
1. B. Purcell, et al. *BMJ* 328 (7452):1339-1340, 2004. 2. Stefanoff, M. et al. *Eurosurveillance* 13 (1-3):44-46, 2008.

## Chemoprophylaxis of contacts in educational settings

- Direct evidence: none
- Indirect evidence:
  - Ecological study across Europe<sup>1</sup> Lower incidence of clusters in pre-schools in countries with policy of giving chemoprophylaxis to preschool contacts
  - Observational studies of risk

Boccia D et al. *Epidemiol.Infect.* 134 (4):872-877,

### Pooled risk differences in household & educational settings (incidence in contacts – incidence of sporadic disease)



## Chemoprophylaxis of “salivary” or drink sharing contacts

- Direct evidence: None
- Indirect evidence
  - No data on risk
  - Sharing drinks not associated with meningococcal acquisition<sup>1</sup>
  - Meningococci found in only 1 /258 (0.4%) salivary samples from students with 32% prevalence of nasopharyngeal carriage<sup>2</sup>

1. Neal et al. BMJ 2000; 320:846-9. 2. Orr et al. EID 2003; 9:131

## Chemoprophylaxis of contacts on same transport vehicle

- Direct evidence: None
- Indirect evidence
  - Clusters on same transport vehicle (3 papers)
    - N=5 regular passengers of same school bus
    - N=2 regular passengers of same school bus
    - N=2 passengers on TransPacific flight seated 12 rows apart, disease onset 2 and 5 days after flight, identical strain
  - 25 sporadic cases described in literature without known occurrence of subsequent cases

## Chemoprophylaxis of contacts of a case in specific settings (summary)

- Recommendations
  - STRONG: Chemoprophylaxis indicated for household contacts
  - WEAK: Attending same pre-school as a case is an indication for chemoprophylaxis, depending on duration/closeness of contact and similarity to household setting
  - WEAK: Attending same school/college (incl. same class), sharing drinks/cigarettes, sharing the same transport vehicle with a case *not* by themselves an indication for chemoprophylaxis

## C. Chemoprophylaxis before hospital discharge

- Direct evidence: none
- Indirect evidence
  - 2.6% of 160 patients treated with “non-eradicating” antibiotics (penicillin, chloramphenicol) had persistent carriage
  - Further cases in households in which contacts but not index cases received chemoprophylaxis<sup>2</sup>
- Recommendation

STRONG: Chemoprophylaxis indicated for cases before leaving hospital if not treated with “eradicating” antibiotics

NB Does cefotaxime eradicate carriage?

1. Purcell B *et al.* *BMJ* 2004;**328** (7452):1339-0. 2. Cooke RP *et al.* *British Medical Journal* 1989;**298**:555-8.

## D. Postexposure vaccination

- Direct evidence: none
- Indirect evidence
  - Incidence in unvaccinated contacts 14-365 days after contact with index case = 1.1/1000 contacts (95% CI 0.7-1.7)
  - Estimated 600-1700 persons need to be vaccinated to prevent one subsequent case
- Recommendation
  - STRONG:** Household contacts of cases caused by vaccine-preventable strain should receive a course of vaccine in addition to chemoprophylaxis if previously unvaccinated

1. Hoek M, *et al. Epidemiology and Infection* 2008;**136** (11):1441-7

## E. Laboratory diagnosis

Laboratory method	Studies (N)	Sensitivity (range)	Specificity (range)
<b>Culture (blood/CSF)</b>	9	17-97%	100%
<b>PCR (blood/CSF)</b>	8	73-100%	98-100%
<b>Gram stain (CSF)</b>	2	64-68%	100%
<b>Antigen detection</b>			
Blood	1	14%	82%
CSF	1	61%	N/A
<b>Skin biopsy</b>			
Culture	2	15-36%	100%
PCR	1	100%	N/A

## Laboratory diagnosis

- **Recommendations**
  - **STRONG:** All microbiological laboratories performing IMD diagnosis should have access to PCR testing
  - **WEAK:** PCR testing of skin lesions recommended particularly if antimicrobial therapy already begun

## Further research

- **Antibiotic regimens**
  - Further RCTs to assess effectiveness of azithromycin and 3rd generation cephalosporins at eradicating carriage
  - Optimal dosage for children and regimens for pregnant women
  - Risk of resistance with all antibiotics used
- **Chemoprophylaxis of contacts in specific settings**
  - Further studies on risk of transmission and further cases as well as effectiveness of chemoprophylaxis in pre-schools
  - Attitudes to value of prevention and use of antibiotics

## Acknowledgements

- This work was made possible by grant from ECDC
- We thank the following colleagues for their expert input
  - Stine Nielsen, EPIET Fellow, RKI, Germany
  - Hannah Christensen, University of Bristol
  - Pierluigi Lopalco and Helena de Carvalho Gomes (ECDC)
  - All colleagues who gave feedback

**Thank you for your attention!**

