

Sustained reduction in the carriage of *Neisseria meningitidis* as a result of a community meningococcal disease control programme

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SUMMARY

The effect of a community intervention programme of antibiotics and meningitis vaccine on pharyngeal carriage of *Neisseria meningitidis* was investigated. Carriage rates were determined in pupils at both secondary schools (ages 11–18 years) included in the community intervention programme and compared with two schools outside the area matched for socio-economic status. A total of 1869 pupils were studied 6 months after the programmes, and 2457 pupils after 11 months.

Six months after the programme was completed there was a 72% reduction in pharyngeal carriage of *Neisseria meningitidis* in pupils attending the schools in the intervention area compared with pupils in the control schools. After 11 months this difference persisted in the 11–14 age group but not in the 15–18 age group. No resistance to the antibiotics used in the programme was found.

A community intervention programme of antibiotics and vaccine for the control of meningococcal disease led to a long-term reduction in *Neisseria meningitidis* carriage in some age groups.

INTRODUCTION

Widespread outbreaks of invasive meningococcal disease due to serogroup C have become increasingly common [1]. During the winter of 1995–6 in the United Kingdom there were three community outbreaks of invasive serogroup C meningococcal disease (meningitis or septicaemia) for which community prophylaxis programmes were initiated [2, 3]. The largest of these was a combined exercise between Rotherham and North Nottinghamshire Health

Authorities in which 16000 children aged 2–18 years were vaccinated and received either rifampicin (ages 2–10 years) or ciprofloxacin (ages 11–18 years) [2]. Eight cases of invasive meningococcal disease occurred in the 6 weeks before the community programme was implemented (epidemic strain C:2b:P1.2, 1.5). A single further case due to the epidemic strain in a vaccine non-responder occurred 4 weeks after completion of the programme [4].

Objective evidence about optimal management of community outbreaks of serogroup C meningococcal disease is limited. Recently published guidelines in the UK [5] and USA [6] demonstrate significant differences; in particular, antibiotics are recommended in

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the UK but not the USA, the threshold number of cases for intervention differs, as does the use of age-specific rather than total population rates of disease.

Mass community intervention programmes are not without problems and most of the side-effects are probably due to the antibiotics used. These include allergic reactions, eradication of commensal flora, the removal of which could increase the risk of acquiring pathogenic meningococci strains [7] and the selection of antibiotic resistant strains that could impair the efficiency of future prophylaxis and also allow spread of resistance to other bacteria. A false sense of security may be engendered with people believing they have been protected against all types of meningitis after vaccination, rather than the limited spectrum covered by vaccination, leading to possible delays in referral and treatment. There are also significant logistical implications in delivering community intervention programmes and high vaccine coverage is needed for this to be an effective sole intervention [8].

The medium-term effect on meningococcal carriage of a large-scale community control programme has not been described in an urban setting. To determine this, we undertook a study of pharyngeal carriage of *Neisseria meningitidis* in school pupils at both secondary schools within an intervention area and two schools outside the intervention area but matched for socio-economic status.

METHODS

Populations

Two secondary schools (ages 11–18 years) were located in the area covered by the community control programme. The Jarman Underprivileged Area scores [9] for the electoral wards where each school were situated were obtained (+5.4 and –8.5). A list of secondary schools in Rotherham Metropolitan Borough Council was obtained from the Department of Education. The two schools in wards with Jarman scores closest to the intervention schools were identified (Jarman scores +4.8 and –9.2). After consultation with the education authority, each school was approached and all four agreed to participate. Approval was obtained from the ethics committees of Rotherham District Health Authority and the Public Health Laboratory Service (PHLS).

A letter explaining the study and requesting parents to allow their child to have pharyngeal swabs taken was distributed to each pupil by the school. This

included a consent section to be completed by the parent or guardian and returned by the pupil. Age, sex, school year and history of meningitis vaccination were obtained from each pupil before they had their pharyngeal swab. Pupils were swabbed in the summer (late June and early July) of 1996, 6 months after the community intervention and again in December 1996 (11 months). All pupils whose parents had consented, who were in school on the study day and were prepared to be tested were included. Response rates were calculated using the school roll, after adjusting for absent classes and authorized and unauthorized absences recorded on the study days. No adjustment for pupils absent on work experience sessions could be made.

Microbiology

Pharyngeal swabs were taken using cotton swabs and plated immediately on to New York City medium (Difco). Plates were incubated at 37 °C in air with 5% carbon dioxide (CO₂) and were examined at 24 and 48 h. A Gram film and an oxidase test were performed on colonies resembling *Neisseria* spp.

All oxidase positive Gram-negative diplococci were sent to the PHLS Meningococcal Reference Unit (Manchester Public Health Laboratory). These isolates were subcultured initially on to Difco GC base medium (Difco) with added Kellogg's supplement to encourage optimal expression of antigens used to characterize meningococci and grown overnight in air plus 5% CO₂ at 37 °C. Identity of single colony picks was provisionally established by Gram stain, oxidase test reaction and fermentation in CTA medium incorporating glucose, maltose, sucrose and lactose (Becton Dickinson).

Serogrouping was carried out by coagglutination of formalin-killed meningococci with a 10% staphylococcal suspension coated with rabbit antiserum agent raised against A, B, C, H, I, K, W135, X, Y and Z/29E polysaccharides [10]. Any isolate failing to serogroup was further tested for gammaglutamyl aminopeptidase activity to confirm its identity as *N. meningitidis* and for lactose fermenting activity by *ortho*-nitro-phenyl-glucosamine to distinguish strains of the closely related commensal organism *N. lactamica*.

Minimum inhibitory concentrations (MICs) of penicillin, sulphadiazine, rifampicin and ciprofloxacin were estimated by incorporation of antibiotic into blood agar plates and application of a standard

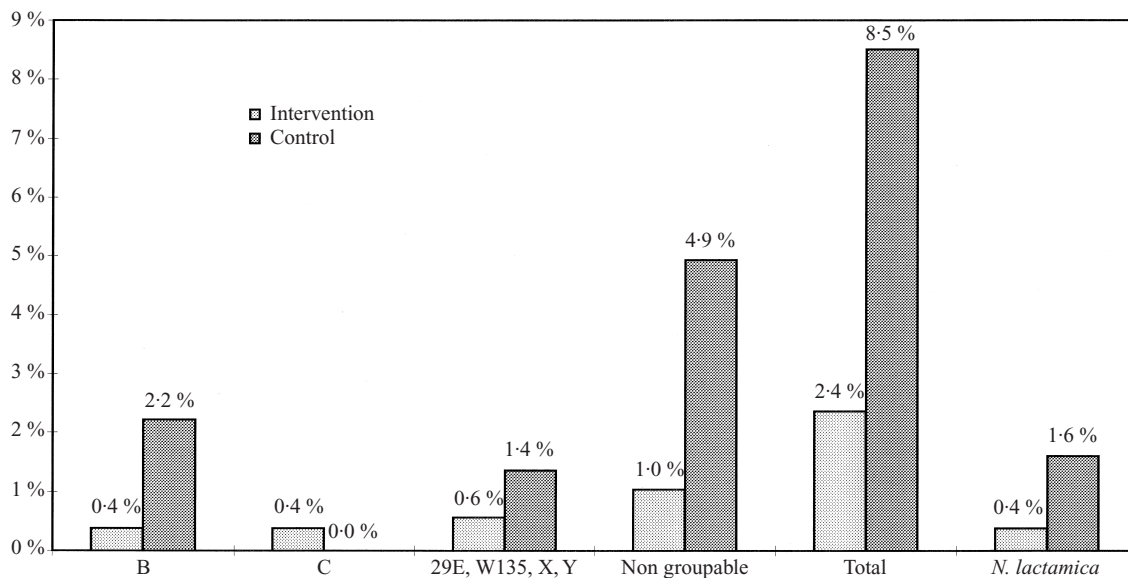


Fig. 1. Carriage rates of *N. meningitidis*, by group, and *N. lactamica* – summer 1996.

Table 1. Number of positive isolates, relative risk of carriage and 95% confidence intervals (CI) for *N. meningitidis* and *N. lactamica* in the summer 1996 period

	Intervention group (n = 1058)	Control group (n = 811)	Relative risk	95% CI	P value
All <i>N. meningitidis</i>	25	69	0.28	0.2–0.4	< 10 ⁻⁸
<i>N. meningitidis</i> group B	4	18	0.17	0.1–0.5	0.0006
<i>N. meningitidis</i> group C	4*	0	Undefined	Undefined	n.s.
<i>N. meningitidis</i> 29E, W135, X, Y	6	11	0.42	0.2–1.1	n.s.
Non groupable	11	40	0.21	0.1–0.4	< 10 ⁻⁷
<i>N. lactamica</i>	4	13	0.24	0.1–0.7	0.01

* C:2a:P1.5, P1.2 (2), C:NT:P1.5, 1.2, C:NT:P1.16.

suspension of organisms using a multipoint inoculator.

Statistics

Data were stored in Microsoft Access V2.0. Statistical analysis was performed using Epi-Info V6.04 for analysis of tables using χ^2 and Fisher's exact test and SPSS for Windows 6.1 for multiple logistic regression analyses with carriage as the dependent variable. Correction for multiple testing was done using the Bonferroni method [11]. The main analyses were done by community (intervention and control).

RESULTS

The carriage rates by community status for the summer 1996 swabbing exercise (6 months after antibiotics and vaccination) are shown in Fig. 1. The

relative risks for carriage of *N. meningitidis* and *N. lactamica* for the summer 1996 period are shown in Table 1 and for December 1996 in Table 2. Mean participation rates of pupils over both phases of the study were 90 and 63% in the intervention schools and 48 and 39% in the control schools. There were no significant differences in carriage rates comparing one intervention school with the other and similarly between the two control schools in both study periods.

Meningococcal carriage rates by school year are shown in Tables 3 and 4. (Year 7 is the first secondary school year, ages 11–12; school years 12–14 are the sixth form years, ages 16 and over). There were 19 pupils (1%) in the first round whose individual vaccination status was discordant with their community and 53 in the second (2%). Analyses by individual immunization status, or by excluding individuals whose vaccine status was discordant for

Table 2. Number of positive isolates, relative risk of carriage and 95% confidence intervals (CI) for *N. meningitidis* and *N. lactamica* in the December 1996 period

	Intervention group (n = 1296)	Control group (n = 1161)	Relative risk	95% CI	P value
All <i>N. meningitidis</i>	96	81	1.06	0.8–1.4	n.s.
<i>N. meningitidis</i> group B	14	22	0.56	0.3–1.1	n.s.
<i>N. meningitidis</i> group C	1*	0	Undefined	Undefined	n.s.
<i>N. meningitidis</i> 29E, W135, X, Y	20	18	0.99	0.5–1.9	n.s.
Non groupable	50	36	1.24	0.8–1.9	n.s.
<i>N. lactamica</i>	27	39	0.62	0.4–1.0	0.05

* C:NT:NT.

Table 3. Carriage rate of *N. meningitidis* (percent) by school year and community status in summer 1996

School year	Intervention	Control	Relative risk	95% CI	P value
7	5/281 (1.8)	22/303 (7.3)	0.25	0.1–0.6	0.003
8	6/313 (1.9)	17/255 (6.7)	0.29	0.1–0.7	0.008
9	8/212 (3.8)	21/156 (13.5)	0.28	0.1–0.6	0.001
10	6/197 (3.0)	6/76 (7.9)	0.39	0.1–1.2	n.s.
11	Not in school	Not in school			
12, 13, 14	0/55 (0)	3/21 (14.3)	0	0–0.9	0.02

Table 4. Carriage rate of *N. meningitidis* (percent) by school year and community status in December 1996

School year	Intervention	Control	Relative risk	95% CI	P value
7	5/214 (2.3)	31/352 (8.8)	0.27	0.1–0.7	0.004
8	5/144 (3.5)	44/316 (13.9)	0.25	0.1–0.6	0.001
9	8/185 (8.5)	19/204 (9.3)	0.46	0.2–1.0	0.08
10	22/258 (7.5)	12/164 (7.3)	1.09	0.6–2.0	n.s.
11	21/305 (6.9)	9/91 (9.9)	0.70	0.3–1.5	n.s.
12, 13, 14	26/190 (13.7)	2/34 (5.9)	2.33	0.6–9.4	n.s.

their community, did not alter the results. There were no significant differences in carriage rates between males and females.

No strains resistant to either ciprofloxacin or rifampicin were detected among the *N. meningitidis* or *N. lactamica* isolated.

DISCUSSION

Our results show clearly that 6 months after a mass community antibiotic and vaccination programme there was a reduction in the carriage of *N. meningitidis* and *N. lactamica* for ages 11–18 of 72 and 77% respectively. At 11 months the effect had altered so that the carriage rate in the 11–14 age group remained

low (85% reduction) whereas the rate in the 15–18 age group had reverted to the normal carriage rates seen in the control population.

Unfortunately the carriage rate could not be determined before the intervention programme was implemented as control measures had to be implemented quickly. However, there was no reason to expect the overall meningococcal carriage rate to be unexpectedly low during a community outbreak of serogroup C meningococcal disease. Carriage rates of serogroup C meningococci, even during outbreaks in open communities, are generally below one percent [12, 13]. Carriage rates of serogroup B and non-groupable meningococci in outbreak situations have been shown to be normal or increased [14–16], but not

low. The sudden cessation of new cases of invasive meningococcal disease after the intervention programme [2] could have happened naturally or have been a direct result of the marked community-wide reduction in carriage preventing acquisition by those at risk of disease and/or as a result of protection afforded by vaccination [8].

As the reduction in carriage rates at 6 months was seen in all serogroups of *N. meningitidis*, and also in *N. lactamica*, it was very likely that this widespread reduction was due to the mass use of antibiotics and not vaccination. The vaccine does not stimulate an immune response against serogroup B and polysaccharide vaccines are not thought to affect carriage of homologous strains [17]. Carriage rates were similar in both control schools and were comparable to data from other carriage studies [7, 15] so the results cannot be explained by a high prevalence in the control schools with a normal carriage rate in the intervention schools.

The reduction in carriage was seen equally in both intervention group schools and it is unlikely that the swabbing was performed less well in the intervention schools at 6 months compared with the control schools or in specific age groups only in the second round of swabbing. The age-specific differences in December 1996 (Table 4) are further evidence against differential swabbing efficacy.

One of the most important uses of the control group in our study was to validate the methodology of swabbing large numbers of pupils and the laboratory identification techniques. The results obtained in the control schools show that the methodology was satisfactory for the following reasons: similar results in both phases, results consistent with other carriage studies [7, 15] and the recovery of *N. lactamica*, a proxy for good swabbing technique. Therefore the low carriage rate in the intervention area was most likely due to a prolonged effect of antibiotics.

Importantly, the control schools did not differ from the intervention schools in any identifiable way. Firstly, the proportion of total pupils in each school year were similar. Secondly, although Jarman scores are a measure of general practitioner workload they have been widely used as a proxy for socio-economic status [18]. Although invasive meningococcal disease in young children is correlated with social deprivation this relationship is much weaker amongst the age groups in this study [19, 20]. The relationship between carriage of meningococci and socio-economic status is less clear [21, 22] and may be a confounder for

smoking and overcrowding. The selection of control schools using Jarman scores is the best method for controlling known or unknown socio-economic factors and our results cannot be explained by socio-economic or local area factors.

In summer 1996 fewer children were swabbed largely because years 11 and 13 had already finished school and a number of other classes were out of school on the study days. The study days were chosen by the school to minimize the disruption caused by our study. The higher participation rates in the intervention schools were not unexpected and in one intervention school in particular, participation was enhanced by enthusiasm for the study and better organisation. The correction for the authorized and unauthorized absence of pupils still underestimated the participation rates, as some classes were not in school or unable to attend for a variety of reasons. Although it cannot be excluded, it is highly unlikely that any systematic bias resulted from the absence of particular individuals or classes that could explain the difference in carriage rates between the two communities.

Although the participation rates were substantially lower in the control schools this would only be important if it introduced sufficient bias to alter the conclusions substantially. This is unlikely because firstly, despite differences in participation rates between the two intervention schools, carriage rates were similar in both schools for each phase of the study. The same also applied to the control schools suggesting that the participation rate did not affect the results. Secondly the carriage rates in the control area schools were similar to those reported in other published studies in children of this age [7, 15].

The degree of overlap of pupils between the two swabbing rounds could not be assessed as the ethics committee approval required all results to be anonymized. Even if the same pupils were largely swabbed twice, or they constituted different groups, the results still reflected the levels of meningococcal carriage within their respective communities. The high coverage rate of 90% in one of the intervention schools meant the majority of pupils were tested on both occasions. A number of pupils were certainly included only once, because years 7 and 12 in December 1996 year were not in school in July 1996.

The age-specific differences in carriage between the two study periods were also noteworthy (Tables 3 and 4). At 6 months all age groups showed similar reductions in carriage (Table 3). At 11 months there

were still large and highly significant differences between the two communities up to the age of 14 but above this age carriage rates were similar in both intervention and control populations. These persistently low carriage rates in children under the age of 14 support the contention that there is a low rate of acquisition in this age group within families [23].

Meningococcal carriage rates increase at around the age of 15 [15]. A number of factors that influence carriage alter at this age and the clear age difference in the carriage rates in our study at 11 months is likely to be associated with similar factors. These include smoking which is associated with an increased carriage rate of meningococci [24]. It was not possible to ask about smoking as the swabbing was carried out in public but as the schools were matched, differential smoking rates are unlikely to explain the difference in carriage rates between the two communities. Other possible factors are the increasing frequency of prolonged close contacts and intimate kissing that increases the risk of acquisition. Compared with younger children, those aged 15 years and over are more likely to mix socially with those over 18 years and with people outside the intervention area who were not included in the mass community programme and who would be expected to have maintained a normal carriage rate of meningococci.

Children in school year 7 (ages 11–12) in December 1996 had been given rifampicin, whereas all other groups reported in this study received ciprofloxacin. Both drugs are effective in the short term [25] and our findings show that this applies to periods up to 11 months.

Other studies of community chemoprophylaxis have shown a similar effect in reducing meningococcal carriage but have only included short follow-up periods: 9 weeks in an isolated Arctic community [26] and 3 weeks in Alabama [14]. The mass use of rifampicin and minocycline in Finnish army recruits led to an immediate decline in carriage but this recovered substantially to the pre-treatment prevalence at 4 weeks [27]. Rifampicin resistance was also detected, unlike in this study. There is only one published longer term follow-up study of a community intervention programme [28]. This was in an isolated Australian Aboriginal community with a population of 1250, including 509 children, and therefore not representative of any part of the UK. The use of meningococcal vaccine failed to stop the epidemic and overall meningococcal carriage rates were 8.4% when investigated 6 months later. The mass use of rif-

ampicin led to a 50% reduction in meningococcal carriage after a further 6 months. The confidence intervals of this and our study overlap but the Australian results reflect different living conditions, in particular with over-crowding [8]. There are many other examples of the use of meningitis vaccine without antibiotics failing to stop community outbreaks of serogroup C invasive meningococcal disease [1, 8].

The absence of any resistance to either drug is reassuring, particularly for ciprofloxacin which most of the study group had received. Although only five isolates came from children who had themselves been given rifampicin, there was no evidence of transmission of resistant organisms amongst the children studied.

In conclusion, 6 months after the use of a community meningococcal disease intervention programme there was a marked reduction in meningococcal carriage in children aged 11–18 years. This effect persisted at 11 months for children aged 11–14 years and was most likely to be due to the widespread use of antibiotics.

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REFERENCES

1. Jackson LA, Schuchat A, Reeves MW, Wenger JD. Serogroup C meningococcal outbreaks in the United States. An emerging threat. *JAMA* 1995; **273**: 383–9.
2. Irwin DJ, Miller JM, Milner PC, et al. Community immunisation programme in response to an outbreak of invasive *Neisseria meningitidis* serogroup C infection in the Trent region of England 1995–1996. *J Publ Hlth Med* 1997; **19**: 162–70.
3. Invasive meningococcal infections, England and Wales: laboratory reports, weeks 51/95–03/96. *CDR* 1996; **6** (4): 30–1.
4. Irwin DJ, Kaczmarek EB, Miller J. A case of invasive serogroup C meningococcal disease after a community vaccination programme in Rotherham, S. Yorks. *J Publ Hlth Med* 1998; **20**: 112–4.

5. Stuart JM, Monk PN, Lewis DA, Constantine C, Kaczmarek EB, Cartwright KAV on behalf of the PHLS Meningococcus Working Group and Public Health Medicine Environmental Group. Management of clusters of meningococcal disease. *CDR Rev* 1997; **7** (1): R3–5.
6. Control and prevention of serogroup C meningococcal disease: Evaluation and management of suspected outbreaks. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997; **46** (RR-5): 13–21.
7. Gold R, Golschneider I, Lepow ML, Draper TF, Randolph M. Carriage of *Neisseria meningitidis* and *Neisseria lactamica* in infants and children. *J Infect Dis* 1978; **137**: 112–21.
8. Rosentein N, Levine O, Taylor JP, et al. Efficacy of meningococcal vaccine and barriers to vaccination in a U.S. community. *JAMA* 1998; **279**: 435–9.
9. Jarman B. Identification of underprivileged area. *BMJ* 1983; **286**: 1705–8.
10. Eldridge J, Sutcliffe EM, Abbott JD. Serological grouping of meningococci and detection of antigen in cerebrospinal fluid by co-agglutination. *Med Lab Sci* 1978; **35**: 63–6.
11. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995; **310**: 170.
12. Le Saux N, Ashton F, Rahman M, et al. Carriage of *Neisseria* species in communities with different rates of meningococcal disease. *Can J Infect Dis* 1992; **3**: 60–4.
13. Rønne T, Berthelson L, Buhl LH, Lind I. Comparative studies on pharyngeal carriage of *Neisseria meningitidis* during a localised outbreak of serogroup C meningococcal disease. *Scand J Infect Dis* 1993; **25**: 331–9.
14. Jacobsen JA, Chester TJ, Fraser DW. An epidemic of disease due to serogroup B *Neisseria meningitidis* in Alabama: Report of an investigation and community-wide prophylaxis with a sulfonamide. *J Infect Dis* 1977; **136**: 104–8.
15. Cartwright KAV, Stuart JM, Jones DM, Noah ND. The Stonehouse survey: nasopharyngeal carriage of meningococci and *Neisseria lactamica*. *Epidemiol Infect* 1987; **99**: 591–601.
16. Davies AL, O'Flanagan D, Salmon RL, Coleman TJ. Risk factors for *Neisseria meningitidis* in a school during a community outbreak of meningococcal disease. *Epidemiol Infect* 1996; **117**: 259–66.
17. Hassan-King MKA, Wall RA, Greenwood BM. Meningococcal carriage, meningococcal disease and vaccination. *J Infect* 1988; **16**: 55–9.
18. Mackenzie IF, Nelder R, Maconachie M, Radford G. 'My ward is more deprived than yours'. *J Pub Hlth Med* 1998; **20**: 186–90.
19. Stuart JM, Cartwright KAV, Dawson JA, Rickard J, Noah ND. Risk factors for meningococcal disease: a case control study in south west England. *Commun Med* 1988; **10**: 139–46.
20. Stanwell-Smith RE, Stuart JM, Hughes AO, Robinson P, Griffin MB, Cartwright K. Smoking, the environment and meningococcal disease: a case control study. *Epidemiol Infect* 1994; **112**: 315–28.
21. Cartwright K. Meningococcal carriage and disease. In Cartwright K, ed. *Meningococcal disease*. Chichester: John Wiley and Sons, 1995, 115–46.
22. Kremastinou J, Blackwell C, Tzanakaki G, Kallergi C, Elton R, Weir D. Parental smoking and carriage of *Neisseria meningitidis* among Greek schoolchildren. *Scand J Infect Dis* 1994; **26**: 719–23.
23. Olcén P, Kjellander J, Danielsson D, Lindquist BL. Epidemiology of *Neisseria meningitidis*: prevalence and symptoms from the upper respiratory tract in family members to patients with meningococcal disease. *Scand J Infect Dis* 1981; **13**: 105–9.
24. Stuart JM, Cartwright KAV, Robinson PM, Noah ND. Effect of smoking on meningococcal carriage. *Lancet* 1989; **ii**: 723–5.
25. Darouiche R, Perkins B, Musher D, Hamill R, Tsai S. Levels of rifampicin and ciprofloxacin in nasal secretions: Correlation with MIC₉₀ and eradication of nasopharyngeal carriage of bacteria. *J Infect Dis* 1990; **162**: 1124–7.
26. Nicolle IE, Postl B, Kotelwetz, et al. Chemoprophylaxis for *Neisseria meningitidis* in an isolated arctic community. *J Infect Dis* 1981; **145**: 103–9.
27. Sivonen A, Renkonen O-V, Weckström, Koskenvuo K, Raunio V, Mäkelä PH. The effect of chemoprophylactic use of rifampicin and minocycline on rates of carriage of *Neisseria meningitidis* in army recruits in Finland. *J Infect Dis* 1978; **137**: 238–44.
28. Pearce MC, Sheridan JW, Jones DM, et al. Control of group C meningococcal disease in Australian Aboriginal children by mass rifampicin chemoprophylaxis and vaccination. *Lancet* 1995; **346**: 20–3.