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META-ANALYSIS

Antibiotics for eradicating meningococcal carriages: Network meta-analysis and investigation of evidence inconsistency

Asmaa S Abdelhamid, Yoon K Loke, Ibrahim Abubakar, Fujian Song

Asmaa S Abdelhamid, Yoon K Loke, Fujian Song, Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, United Kingdom

Ibrahim Abubakar, Institute of Epidemiology and Health, University College of London, London WC1E 6BT, United Kingdom

Author contributions: Song F had the initial idea; Abdelhamid AS and Song F extracted data from the included trials; Song F conducted data analyses; Abdelhamid AS, Loke YK and Song F investigated causes of inconsistencies, and drafted the manuscript; Abubakar I provided clinical advice on the interpretation of results and critically commented on the manuscript; all authors approved the manuscript.

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Correspondence to: Fujian Song, PhD, Professor, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ,
United Kingdom. fujian.song@uea.ac.uk
Telephone: +44-1603-591253
Fax: +44-1603-59752

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Abstract

AIM

To compare different antibiotics for eradicating the carriage of *Neisseria meningitidis* (*N. meningitidis*), and to investigate heterogeneity and evidence inconsistency.

METHODS

From a search of PubMed and published systematic reviews, we identified 23 trials evaluating 15 antibiotics that could be connected in a trial network. The outcome of interest is the eradication of *N. meningitidis*. We used WinBUGS to conduct random-effects, mixed treatment comparisons. Heterogeneity and evidence inconsistency was investigated by meta-regression modelling and examining characteristics of trial participants and interventions evaluated.

RESULTS

Rifampin, ciprofloxacin, minocycline, ceftriaxone, and azythromycin were statistically significantly ($P < 0.05$) more effective than placebo. The probability of being the best was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and below 1% for the remaining regimens. Significant inconsistency between the direct and indirect estimates was observed for the comparison of rifampin and ciprofloxacin ($P < 0.01$), which may be

caused by different types of carriers and different doses of ciprofloxacin.

CONCLUSION

A range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the other two antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines.

Key words: Chemoprophylaxis; Antibiotics; *Nersseria meningitidis*; Meningococcal infection; Network meta-analysis

Core tip: This network meta-analysis found that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages. A combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Careful investigation of significant inconsistency between direct and indirect comparison of rifampin and ciprofloxacin found that it was mainly caused by different types of carriers (persistent or any) and the varying doses of ciprofloxacin in the included trials. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

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INTRODUCTION

Neisseria meningitidis (*N. meningitidis*), a Gram-negative bacterium, is a normal inhabitant of the human pharynx. Transmission from person to person happens by droplets from the upper respiratory tract causing meningococcal disease; the severest forms of which are meningitis and septicaemia[1]. Meningococcal disease occurs usually sporadically or in small clusters all over the world as in the African "meningitis belt", from Ethiopia to Senegal, and also in overcrowded places or wherever large population movements exist[2].

Prevalence of meningococcal carriage varies greatly, from 8% to 25% in random samples of healthy individuals, and as high as 36% to 71% in military recruits, and shows a massive increase in overcrowded places[1]. Current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases irrespective of vaccination status[3-6]. The evidence behind these recommendations were mainly from published systematic reviews[7,8]. However, there is no definite evidence from the available direct comparison trials, as to which antibiotic is more effective in preventing secondary meningococcal disease cases[9].

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been developed to compare different treatment options[10-13]. Because of limited evidence from direct comparison trials, we conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *N. meningitidis*. We also reported the methodological experience obtained from this work for appropriately investigating causes of evidence inconsistencies in network meta-analysis.

MATERIALS AND METHODS

Study eligibility and identification

We included randomised controlled trials that evaluated effects of antimicrobial interventions for the prevention of meningococcal infections. Eligible studies were selected according to the following criteria: (1) it was a randomised controlled study; (2) included participants who exposed to patients with meningococcal disease or *N. meningitidis* carriers; (3) evaluated chemoprophylaxis interventions using any antibiotic regimens; and (4) reported data on eradication of meningococcal carriage. We checked references of previous systematic reviews and conducted additional literature search to identify relevant studies for this meta-analysis. Two recently published high quality systematic reviews (with pairwise meta-analysis only) were identified, in which the literature searches were updated or conducted in June 2013[7] and in December 2013[8] respectively. We assessed the eligibility of studies included in these two reviews. To identify additional eligible studies possibly published after theses systematic reviews, one reviewer (Song F) conducted a search of PubMed in April 2016. The PubMed search used the following key words: "meningococcal" or "meningitis" combined with "chemoprevent*" or "chemoprophyl*" or antibiotic*" or antimicrobial*". In addition, the search was limited to "clinical trial" and published in the last 5 years. However, all relevant studies in the current meta-analysis could be identified from existing systematic reviews, and no new eligible studies were identified from the search of PubMed. Eventually, we included 23 trials[14-35], in which 15 different antibiotics (or combinations of antibiotics) could be connected in a network of trials (Figure 1).

Data extraction

The outcome of interest in this network meta-analysis is failure to eradicate meningococcal carriage up to one week, although only the 2-wk outcome was reported in one trial[14]. From the included studies, two independent reviewers (Asmaa S Abdelhamid and Fujian Song) extracted the following data: Antibiotics evaluated, the number of carriers, the number of carriers with failed eradication at one week after antibiotic prophylaxis, study population, carrier status, reported serogroup, susceptibility of meningococci to antibiotics, study design, adequate or inadequate allocation concealment, and open or blinded. Disagreements between the two reviewers were resolved by discussion.

Methods for mixed treatment comparison

In contrast to within-trial direct comparisons, adjusted indirect comparison is a cross-trial comparison of different treatments, based on a common treatment (for example, placebo), so that the advantage of within-trial randomisation could be partially preserved[10]. Mixed treatment comparison refers to a combination of evidence from direct comparison trials and evidence based on indirect comparisons[12]. The validity of indirect and mixed treatment comparison depends on whether some basic assumptions could be fulfilled. The basic assumptions include homogeneity assumption for conventional pair-wise meta-analysis, trial similarity assumption for adjusted indirect comparison, and consistency assumption for combining direct and indirect evidence[36]. Among these basic assumptions, heterogeneity in conventional meta-analysis and inconsistency between direct and indirect evidence can be quantitatively assessed.

Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, United Kingdom) were used to conduct the random-effects, mixed treatment comparisons based on consistency assumption[37]. The WinBUGS code for Bayesian analysis is available from a report by Dias *et al*[37,38]. We used non-informative or vague priors, and obtained results by 200000 iterations after a burn-in of 100000.

Investigating heterogeneity and causes of inconsistency

When different antibiotics could be compared both directly and indirectly, we calculated the inconsistency (Δ) between the direct and indirect evidence by the following:

$$\Delta = d_{CB} - d'_{CB}$$

$$se(\Delta) = \sqrt{Var(d_{CB}) + Var(d'_{CB})}$$

Where d_{CB} and d'_{CB} are the treatment effects (*e.g.*, log odds ratio) by direct and indirect comparison of treatment *C* and *B*; $se(\Delta)$ is the standard error of the estimated inconsistency; $Var(d_{CB})$ and $Var(d'_{CB})$ are estimated variances of the treatments effects.

We used a statistical model suggested by Cooper *et al*[39] to explore treatment by covariate interactions in the network meta-analysis. It estimates a regression coefficient by assuming a single interaction term for the relative effects of all the treatments *vs* the reference treatment (*i.e.*, placebo)[38]. The effects of the following study-level covariates were investigated: Persistent carriers *vs* any carriers, household contacts *vs* other carriers, cluster/quasi randomised controlled trials *vs* randomised trials, adequate *vs* inadequate sequence generation, and open *vs* blinded design.

We also conducted narrative investigation of causes of inconsistency, which was focused on detailed comparison of rifampin and ciprofloxacin (reasons for this will be provided later). The assessment of clinical diversity and similarity among different sets of trials is a process of identifying possible effect modifiers, which was conducted by answering the following two questions[40]. First, we examined whether there were noticeable differences in study characteristics between different sets of trials. Then, we considered whether any of the observed differences in study characteristics between trials may have modified the relative treatment effects. In this study, we examined individual trials for effect modifiers with special attention to carriage status, dose of antibiotic used and length of intervention.

There were 14 trials that compared antibiotics and placebo. Using data from these placebo-controlled trials, we produced a funnel plot to investigate risk of publication bias. Asymmetry of the funnel plot was statistically tested using Harbord's test for small-study effects[41]. All statistical analyses were conducted and checked by the corresponding author (Fujian Song) who has training and experience in statistical methods.

RESULTS

The main characteristics of the 23 trials are presented in Table 1, and data used in network meta-analyses are shown in Table 2. There are 20 two-arm trials, one three-arm trial, and two four-arm trials. The 15 antibiotics evaluated in these trials are: Placebo, rifampin, ciprofloxacin, minocycline, minocycline plus rifampin, penicillin, ampicillin, ceftriaxone, sulphadiazine, sulphadimidine, azythromycin, spectinomycin, cephalexin, "Sch29482", and coumermycin A1 (Figure 1).

Carriers were mainly from household contacts of cases (six trials), military recruits (seven trials), and students or young people (six trials). Six trials recruited heavy or persistent carriers (defined as two or more sequential positive cultures before antibiotic prophylaxis). The test of susceptibility to antibiotics was done in most of the studies. The sequence generation was inadequate or unclear in 11 trials. Blinding was performed in 12 trials, and allocation concealment was adequate in only three trials (Table 1).

There were five cluster randomised trials. We could not find empirical data on intra-cluster correlation coefficient (ICC) for the included cluster randomised trials, and therefore estimated the effective sample

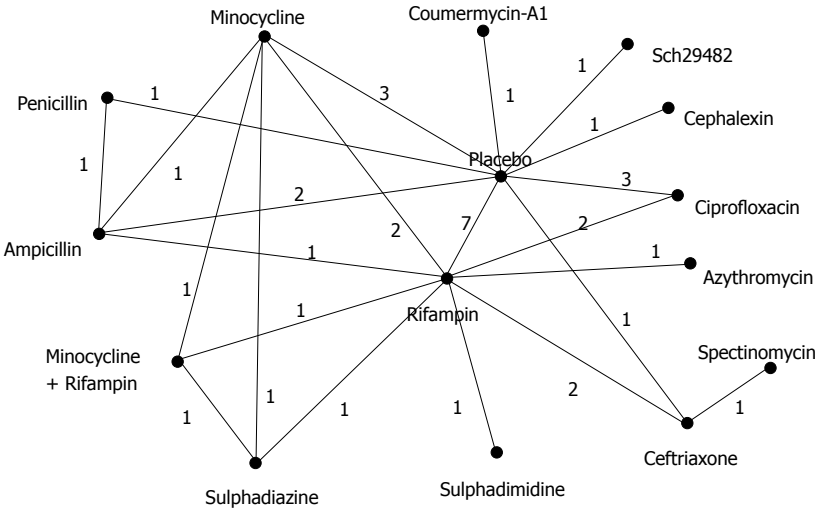

Figure 1 Network of comparisons antibiotics for preventing meningococcal infections. The lines that connect antibiotics refer the direct comparison of two antibiotics. The number beside a line is the number of trials that directly compared the two antibiotics lined by the line.

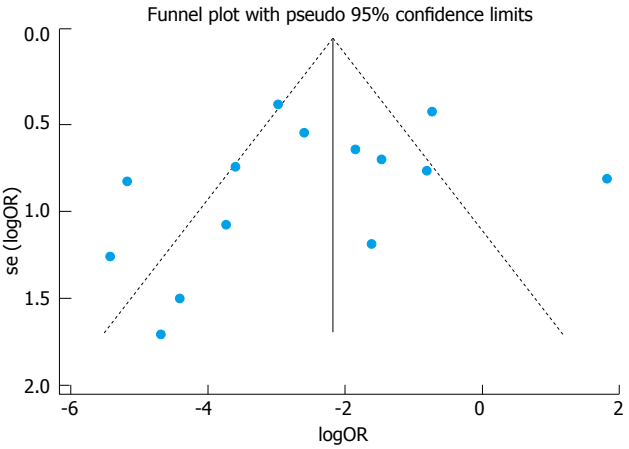

Figure 2 Funnel plot - estimated effects (log odds ratio) of antibiotics in placebo-controlled studies. Funnel plot asymmetry was not statistically significant (Harbord's test for small study effects $P = 0.600$).

sizes by assuming an ICC of 0.05[42].

Funnel plot using data from 14 placebo-controlled trials is shown in Figure 2. The funnel plot was not statistically significantly asymmetric ($P = 0.610$), indicating no concern about risk of small-study effects.

Comparison of antibiotics

The results of the network meta-analysis are shown in Table 3. Rifampin, ciprofloxacin, minocycline, ceftriaxone and azythromycin were significantly ($P < 0.05$) more effective than placebo. The probability of being the most efficacious was 67.0% for a combination of rifampin and minocycline, 25.0% for ceftriaxone, 1.7% for azythromycin, and less than 1% for the remaining antibiotics. According to evidence from the full network of trials, the combination of rifampin and minocycline was the most efficacious intervention, and ceftriaxone the second (Table 3).

The covariate effects in the network meta-analysis are shown in Table 4. Trials with persistent carriers or household contacts of cases reported significantly greater treatment effects as compared with trials of any carriers or non-household contacts of cases, while the remaining regression coefficients were not statistically significant. When the effect of persistent carrier was incorporated into the network meta-analysis, the between-study variation ($\tau = 0.434$) was much reduced as compared with the between-study variation without significant covariate adjustment ($\tau > 0.937$). Therefore, type of carriers (persistent *vs* any) may be an effect modifier[39]. However, the between-study variation was not reduced when the effect of household contacts was included in the analysis ($\tau = 0.975$).

Inconsistencies in the network meta-analysis

There is sufficient data for both direct and indirect comparisons of four pairs of antibiotics (Table 5), and the estimated inconsistencies between the direct and indirect estimates are shown in Figure 3. A statistically significant inconsistency was observed for the comparison of rifampin and ciprofloxacin. The indirect comparison based on 21 trials found that rifampin was significantly better than ciprofloxacin (OR = 0.09, 95%CI: 0.017-0.40 for failure to eradicate). In contrast, the pooling of two direct comparison trials suggested that rifampin therapy was less effective than ciprofloxacin, with a greater likelihood (non-statistically significant) of failure to eradicate (OR = 2.51, 95%CI: 0.36-15.64).

Our further investigation of causes of inconsistency was therefore focused on the comparison of rifampin and ciprofloxacin. These are also the antibiotics recommended in the current clinical guidelines. The inconsistency investigation was using data from two direct comparison trials[16,29], six placebo-controlled trials of rifampin[15,17,19,20,26,28] and three placebo-controlled trials of ciprofloxacin[24,31,33]. Figure 4 shows the results of the individual trials, with the overall estimates of direct and indirect comparisons.

While placebo controlled trials of rifampin included mostly any carriers, three placebo controlled trials of ciprofloxacin included heavy or persistent carriers (Table 1). Consequently, as shown in Figure 5, the proportion of patients with failed eradication in the placebo arm

Table 1 Main characteristics of studies included in network meta-analysis

Ref.	Antibiotics	Country and population	Carrier status	Serogroups and susceptibility	Study design	Sequence generation	Allocation concealment	Blinding
Blakebrough *et al*[14]	Rifampin: 4 × 75 mg for 0-2 yr, 4 × 150 mg for 2-4 yr, 4 × 300 mg for 5-14 yr, 4 × 600 mg for > 15 yr (bid, 2 d) Sulphadimidine: 4 × 250 mg for 0-4 yr, 4 × 500 mg for 5-14 yr, 4 × 1 g for > 15 yr (bid, 2 d)	Nigeria Household contacts	Any carriers	Group A Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Borgoño *et al*[15]	Rifampin: 2 × 10 mg/kg Placebo	Chile Children	Any carriers	Group unknown Susceptibility not tested	RCT	Unclear	Unclear	Double-blind
Cuevas *et al*[16]	Rifampin: 4 × 600 mg for > 18 yr, 4 × 20 mg/kg for 2-18 yr (bid, 2 d) Ciprofloxacin: 1 × 750 mg for > 18 yr, 1 × 15 mg/kg for 2-18 yr	Malawi Household contacts	Any carriers	Group A: 51% (unknown 49%) Susceptibility tested	Cluster RCT	Unclear	Unclear	Open
Deal *et al*[17]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Healthy students	Heavy/ Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deal *et al*[18]	Cephalexin: 12 × 500 mg (tid, 4 d) Placebo	United States Students	Persistent (3 positive cultures)	Group B Susceptibility tested	RCT	Adequate	Adequate	Double-blind
Deviatkina *et al*[19]	Rifampin: 4 × 300 mg (4 d) Placebo	Russia Unclear	Unknown	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Open
Devine *et al*[20]	Rifampin: 4 × 600 mg (4 d) Placebo	United States Army recruits	Any carriers	Group Y: 79% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[21]	Coumermycin A1: 14 × 50 mg (bid, 7 d) Placebo	United States Army recruits	Any carriers	Group unknown Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 1 × 200 mg + 9 × 100 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group Y: 63% Susceptibility tested	RCT	Adequate	Unclear	Double-blind
Devine *et al*[22]	Minocycline: 4 × 200 mg (bid, 2 d) No antibiotic	United States Army recruits	Any carriers	Group Y: Most Susceptibility tested	RCT	Adequate	Unclear	Open
Dowd *et al*[23]	Ampicillin: 30 × 500 mg (tid, 10 d) Penicillin: 30 × 462 mg (tid, 10 d) Placebo	United States Amy recruits	Any carriers	Group B and sulfadiazine-resistant	RCT	Unclear	Unclear	Double-blind
Dworzack *et al*[24]	Ciprofloxacin: 1 × 750 mg Placebo	United States Young adults	Persistent (3 positive cultures)	Group B: 41%, Z: 33% Susceptibility tested	RCT	Unclear	Unclear	Double-blind
Girgis *et al*[25]	Rifampin: 4 × 600 mg (bid, 2 d) Azithromycin: 1 × 500 mg	Egypt Nursing students	Any carriers	Group A: 37%; B: 33% Susceptibility tested	RCT	Adequate	Unclear	Open
Guttler *et al*[26]	Rifampin: 5 × 600 mg (5 d) Minocycline 10 × 100 mg (bid, 5 d) Ampicillin 10 × 500 mg (bid, 5 d) Placebo	United States Army recruits	Any carriers	Group B or C: 31% (non-groupable 67%) Susceptibility tested	Cluster RCT	Adequate	Unclear	Open
Judson *et al*[27]	Ceftriaxone: im 1 × 125 mg Spectinomycin: im 1 × 2 g	United States Patients with gonorrhoea	Any carriers	Group unknown Susceptibility tested	RCT	Unclear	Unclear	Outcome assessment blinded

Kaiser *et al*[28]	Rifampin: 4 × 600 mg for weight ⩾ 66 lb, or 4 × 300 mg for weight < 66 lb (4 d) Placebo	United States Household contacts	Any carriers	Group C: 35% Susceptibility tested	RCT	Adequate	Unclear	Open
Kaya *et al*[29]	Rifampin: 4 × 600 mg (bid, 2 d) Ciprofloxacin: 1 × 750 mg	Turkey Healthy adults	Any carriers	Group unknown Susceptibility not tested	Quasi RCT	Inadequate	Inadequate	Open
Munford *et al*[30]	Rifampin: 4 × 600 mg (bid, 2 d) Minocycline: 1 × 200 mg + 5 × 100 mg (bid, 3 d) Rifampin + Minocycline: as above Sulphadiazine: 4 × 1 g (bid, 2 d)	Brazil Household contacts	Any carriers	Group C: Most Susceptibility tested	Cluster quasi-RCT	Inadequate	Inadequate	Open
Pugsley *et al*[32]	Sch29482: 16 × 250 mg (every 6 h for 4 d) Placebo	United States	Persistent carriers (2 positive cultures)	Group Z: 36%; B: 24%	RCT	Adequate	Unclear	Double-blind
Pugsley *et al*[31]	Ciprofloxacin: 10 × 500 mg (bid, 5 d) Placebo	Young men United States	Persistent (2 positive cultures)	Susceptibility tested Group B: 79%	RCT	Adequate	Unclear	Double-blind
Renkonen *et al*[33]	Ciprofloxacin: 4 × 250 mg (bid, 2 d) Placebo	Young adults Finland	Heavy (> 100 colonies per plate)	Susceptibility tested Group B: 45%	RCT	Adequate	Adequate	Double-blind
Schwartz *et al*[34]	Rifampin: 4 × 600 mg or 4 × 10 mg/kg (bid, 2 d)	Army recruits Saudi Arabia	Any carriers	Susceptibility tested Group A	Cluster RCT	Unclear	Unclear	Open
Simmons *et al*[35]	Ceftriaxone: im 1 × 250 mg (or 125 mg for < 15 yr) Rifampin: 4 × 600 mg for adults, 4 × 5 mg/kg for children < 1 mo, and 4 × 10 mg for children > 1 mo (bid, 2 d) Ceftriaxone: im 1 × 250 mg, or 1 × 125 mg for < 12 yr	Household contacts New Zealand Household contacts	Any carriers	Susceptibility tested Group B: 53% Susceptibility tested	RCT	Unclear	Unclear	Open

im: Intramuscular; bid: Twice a day; tid: Three times a day; RCT: Randomized controlled trials.

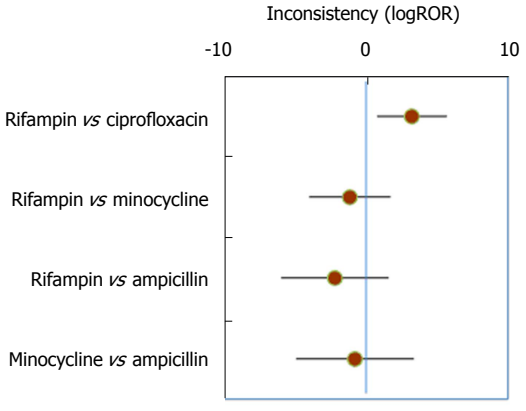

Figure 3 Inconsistencies (and 95%CIs) between direct and indirect estimates for comparisons with closed loops. logROR: 0 indicates no difference between the direct and indirect estimates.

trials of rifampin (83% *vs* 55%). If the absolute results of antibiotic interventions were not influenced by the proportion of participants with persistent carriage, trials that included persistent carriers will show greater relative treatment effects purely because of the high failure rates in the placebo group (Figure 5). Therefore, imbalanced distribution of types of carriers across different sets of trials may invalid the similarity assumption in the network meta-analysis, which raises a question whether the indirect comparison is valid in this case.

In addition, the use of ciprofloxacin in the direct comparison trials[16,29] was different from its use in the placebo-controlled trials of ciprofloxacin[24,31,33]. A single dose of ciprofloxacin was compared with multiple doses of rifampin in the two direct comparison trials, while two of the three placebo-controlled trials of ciprofloxacin compared placebo and multiple doses of ciprofloxacin (Table 1). Therefore, the effect of ciprofloxacin (with multiple doses) in the placebo-controlled trials may be enhanced as compared to the single dose in the two direct comparison trials. The eradication failure in the ciprofloxacin arm at one week was 10.5% in the direct comparison trials, as compare with only 3.0% in the placebo-controlled trials (Figure 5). The different doses of ciprofloxacin used in the direct comparison trials and in the placebo-controlled trials also contributed to the significant inconsistency observed.

DISCUSSION

According to this network meta-analysis, a range of

Table 2 Antibiotics compared and data from the included trials for network meta-analysis

Trial	Regimen	*n*	Failure to eradicate
Guttler *et al*[26]	Placebo	18 (146)	8 (65)
	Rifampin	18 (147)	2 (13)
	Minocycline	18 (147)	1 (12)
	Ampicillin	18 (147)	3 (22)
Munford *et al*[30]	Rifampin	65 (67)	6 (6)
	Sulphadiazine	79 (82)	37 (38)
	Minocycline	56 (58)	6 (6)
	Rifampin + Minocycline	59 (61)	0 (0)
Schwartz *et al*[34]	Rifampin	34 (36)	9 (9)
	Ceftriaxone	65 (68)	2 (2)
Dowd *et al*[23]	Placebo	47	26
	Penicillin	20	9
	Ampicillin	26	8
Borgoño *et al*[15]	Placebo	110	71
	Rifampin	118	10
Deal *et al*[17]	Placebo	15	13
	Rifampin	15	2
Deviatkina *et al*[19]	Placebo	43	10
	Rifampin	46	3
Devine *et al*[20]	Placebo	28	25
	Rifampin	38	7
Kaiser *et al*[28]	Placebo	6	6
	Rifampin	13	1
Dworzack *et al*[24]	Placebo	22	20
	Ciprofloxacin	24	1
Pugsley *et al*[31]	Placebo	21	14
	Ciprofloxacin	21	0
Renkonen *et al*[33]	Placebo	53	46
	Ciprofloxacin	56	2
Deal *et al*[18]	Placebo	15	14
	Cephalexin	15	11
Devine *et al*[22]	Placebo	48	42
	Minocycline	41	14
Devine *et al*[22]	Placebo	29	27
	Minocycline	53	16
Devine *et al*[21]	Placebo	39	28
	Coumermycin A1	33	31
Pugsley *et al*[32]	Placebo	29	26
	Sch29482	29	23
Cuevas *et al*[16]	Rifampin	84 (88)	3 (3)
	Ciprofloxacin	75 (79)	9 (9)
Kaya *et al*[29]	Rifampin	25	1
	Ciprofloxacin	26	2
Girgis *et al*[25]	Rifampin	59	3
	Azythromycin	60	4
Simmons *et al*[35]	Rifampin	82	4
	Ceftriaxone	100	3
Blakebrough *et al*[14]	Rifampin	46 (48)	11 (11)
	Sulphadimidine	33 (34)	33 (34)
Judson *et al*[27]	Ceftriaxone	29	0
	Spectinomycin	9	8

For cluster trials, ICC = 0.05 was assumed for estimating effective sample sizes, and original sample size and events in cluster trials are shown in brackets.

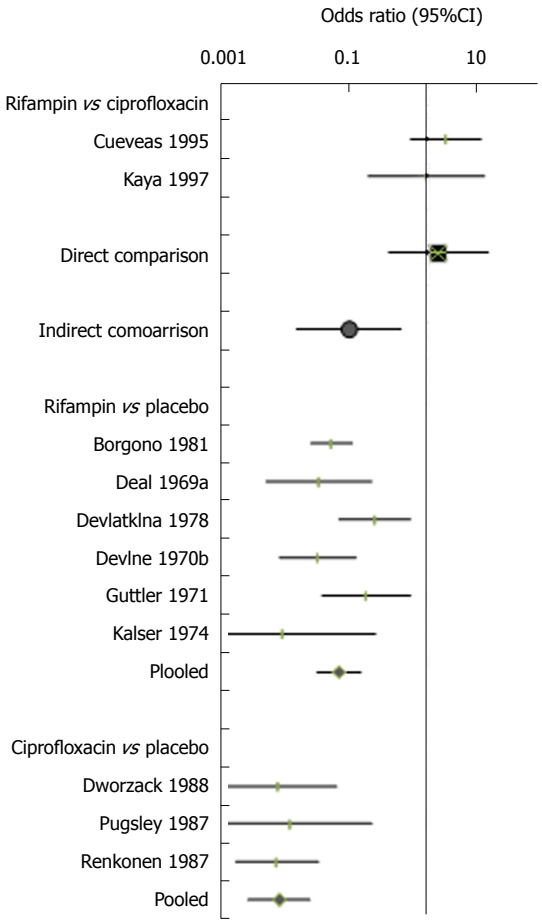

Figure 4 Rifampin *vs* ciprofloxacin for preventing meningococcal infections. The outcome is the failure to eradicate at 1 wk. Pooled direct and indirect estimates were the results of mixed treatment comparison, and other results were from DerSimonian-Laird meta-analyses.

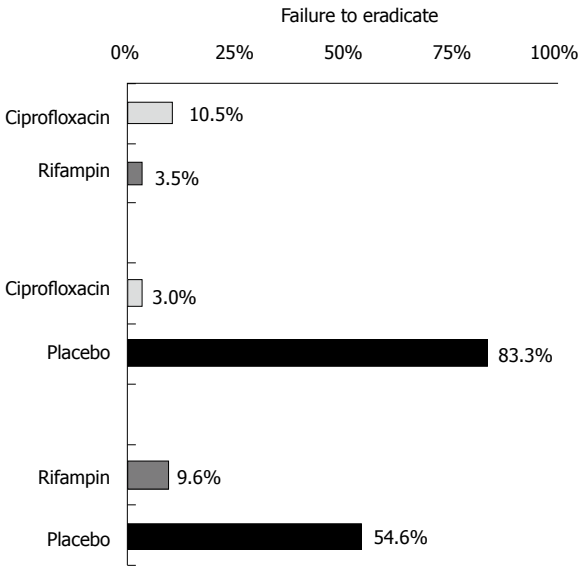

Figure 5 Proportions of failure to eradicate in individual arms of trials for the direct and indirect comparison of rifampin and ciprofloxacin.

antibiotic regimens are effective for preventing meningococcal infections in carriers. The simultaneous analysis of all randomised controlled trials that could be connected in a coherent network provided results that were not available from the conventional pair-wise meta-analysis[43]. The network meta-analysis revealed that a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than the antibiotics (ciprofloxacin or rifampin) recommended by the current guidelines[4-6]. The network

Table 3 Results of network meta-analysis of antibiotics for preventing meningococcal infections (odds ratio of failure to eradicate)

	2 Rifampin	3 Ciprofloxacin	4 Cephalexin	5 Minocycline	6 Ampicillin	7 Penicillin	8 Ceftriaxone	9 Rifampin + minocycline	10 Azythromycin	11 Spectinomycin	12 Coumermycin A1	13 Sch29482	14 Sulphadiazine	15 Sulphadimidine
1 Placebo	0.038[a]	0.020[a]	0.274	0.058[a]	0.267	0.611	0.009[a]	0.004[a]	0.071[a]	5.971	5.524	0.498	0.487	23.17
2 Rifampin		0.53	7.201	1.536	7.028[a]	16.20[a]	0.247	0.098	1.89	156.2[a]	146.2[a]	13.15[a]	12.88[a]	601[a]
3 Ciprofloxacin			13.7	2.911	13.29[a]	30.67[a]	0.467	0.184	3.54	301.0[a]	278.0[a]	24.87[a]	24.4[a]	1174[a]
4 Cephalexin				0.214	0.980	2.26	0.035[a]	0.013[a]	0.262	22.42	20.6	1.826	1.825	91.1[a]
5 Minocycline					4.577	10.52	0.161	0.064	1.212	102.3[a]	95.57[a]	8.53	8.42[a]	396[a]
6 Ampicillin						2.291	0.035[a]	0.014[a]	0.266	22.54	20.85[a]	1.864	1.84	88.6[a]
7 Penicillin							0.015[a]	0.006[a]	0.116	9.808	9.128	0.81	0.8	39.09
8 Ceftriaxone								0.385	7.566	620[a]	597[a]	53.17[a]	52.94[a]	2493[a]
9 Rifampin + minocycline									20.15	1776[a]	1584[a]	140.2[a]	134.3[a]	7088[a]
10 Azythromycin										83.64[a]	78.9[a]	7.03	7	334[a]
11 Spectinomycin											0.924	0.082	0.084	4.032
12 Coumermycin A1												0.089	0.088	4.372
13 Sch29482													0.992	48.75
14 Sulphadiazine														47.14

[a]95%CIs did not contain zero.

meta-analysis also revealed significant inconsistency between direct and indirect estimates for the comparison of rifampin and ciprofloxacin. We investigated causes of the observed inconsistency and found that it was likely due to the following two effect modifiers: Types of carriers (persistent *vs* any), and the varying doses of ciprofloxacin.

The superior efficacy of rifampin and minocycline means it should be considered for areas where there is high degree of resistance to other agents, or in groups of patients where high rates of eradication are considered to be essential. The most efficacious regimen (rifampin and minocycline) was reported to have a significantly increased risk of adverse effects as compared to either drug alone[30]. Headache, dizziness, nausea, or vomiting were specific adverse effects noted more frequently in patients receiving the rifampin-minocycline combination. Nevertheless, patients who consider eradication of carriage to be their top priority may choose to put up with these adverse effects in order to have the best chance of treatment success.

Equally, the effectiveness of single dose intramuscular ceftriaxone, without any need to worry about patient adherence to oral regimens, makes it particularly suitable for patients when there are concerns surrounding the likelihood of the patient being able to regularly take several oral doses as prescribed. For instance, ceftriaxone would be an efficacious option in younger children who have difficulty taking tablets. Moreover, a single dose of ceftriaxone would appear to be less risky option than either ciprofloxacin or rifampin in women who are pregnant or breastfeeding. Use of ceftriaxone in both of these patient groups would be in-line with the United States CDC recommendations[3], and our network meta-analysis now provides the relevant evidence base to support this guidance.

Although the current guidelines in the United Kingdom recommend ciprofloxacin because it can be conveniently used as a single dose regimen, the results of inconsistency investigation indicate that single dose ciprofloxacin may be less effective than either multiple dose ciprofloxacin or rifampin. A regimen of multiple doses of ciprofloxacin seems preferable for persistent carriers (according to evidence from placebo-controlled trials). However, the emergence of ciprofloxacin-resistant *N. meningitidis* should also be taken into consideration[44].

Choice of optimal antibiotic strategy will be inevitably influenced by considering many factors such as cost, convenience, adherence, tolerability and bacterial resistance in a trade-off against the rate of failed eradication. For example, rifampin has been an important antibiotic agent in tuberculosis treatment, and to minimise the risk of bacterial resistance, it is not recommended as a prophylactic agent for household contacts in sub-Saharan Africa[6].

Table 4 Results of covariate effects in network meta-analysis: Regression coefficient and between study variation

Covariate	Regression coefficient, β (95%CI)	Between-study variation (τ)
Persistent carrier (1) *vs* any carriers (0)	-2.904 (-4.695 to -1.186)	0.434
Household (1) *vs* other (0)	-6.178 (-16.79 to -0.069)	0.975
Cluster/quasi RCT (1) *vs* RCT (0)	0.405 (-2.235 to 2.881)	1.082
Sequence generation inadequate (1) *vs* adequate (0)	0.461 (-1.301 to 2.014)	1.025
Open design (1) *vs* blinded (0)	0.055 (-1.877 to 1.662)	1.087

β > 0 indicating that treatment effect is smaller when the covariate exists. RCT: Randomized controlled trial.

Table 5 Results of different methods for four comparisons that provided sufficient trials for both direct and indirect comparisons

	MTC estimate		Direct estimate		Indirect estimate	
Comparison	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)	No. of trials	OR (95%CrI)
Rifampin *vs* ciprofloxacin	23	0.52 (0.13, 1.89)	2	2.51 (0.36, 15.64)	21	0.09 (0.017, 0.40)
Rifampin *vs* minocycline	23	1.55 (0.40, 6.07)	2	0.85 (0.11, 5.59)	21	2.27 (0.28, 19.89)
Rifampin *vs* ampicillin	23	6.94 (1.21, 37.53)	1	1.62 (0.09, 29.82)	20	12.23 (1.04, 146.9)
Minocycline *vs* ampicillin	23	4.52 (0.67, 28.30)	1	3.46 (0.16, 91.10)	20	6.50 (0.41, 93.6)

MTC: Mixed treatment comparison based on all data in the network of trials.

Methodological implications

One of the main advantages of network meta-analysis is pooling of all connected trials into a coherent network of evidence. However, a study found that the inconsistency between direct and indirect evidence may be more prevalent than previously observed[45], and it has been generally accepted that causes of inconsistency in network meta-analysis should be carefully investigated[36,46-48]. In the current study, statistical meta-regression analyses found that the type of carriers (persistent *vs* any, and household contacts *vs* other) may be a cause of heterogeneity in the network meta-analysis. However, the usefulness of statistical methods for investigating causes of inconsistency is often limited because of the small number of trials, inadequate reporting of relevant variables, and modelling complexity.

The narrative investigation of causes of inconsistency is difficult for a complex network. The existence of evidence inconsistencies in a network meta-analysis does not mean that the whole network is inconsistent[46]. Therefore, we focused on the investigation of statistically significant inconsistencies. To further simplify the narrative investigation, a sub-network of trials was formed after excluding those that are only remotely connected to the target comparison.

We demonstrated that focused examination of characteristics of trial participants and interventions evaluated may reveal the clinically meaningful causes of inconsistency in network meta-analysis. The detailed examination of trial participants and interventions evaluated is similar to the investigation of heterogeneity in conventional pair-wise meta-analysis. Although the type of carriers (persistent *vs* any) can be identified by both statistical covariate analysis and narrative investigation, the difference in doses of ciprofloxacin as a possible cause of inconsistency could not be investigated by the statistical models we used. However, the narrative investigation mainly relies on subjective judgement, is restricted by available data from published studies, and a good understanding of the topic is required.

Study limitations

In order to include as many studies as possible in the trial network, we focused on eradication failure and did not consider other important outcomes such as adverse effects and new cases of meningococcal disease. Included studies were mostly conducted in 1970s or 1980s, and the most recent study was published in 2000[35]. Therefore, it is a question about whether the results of previous randomised controlled trials are applicable to the present. Although we included only randomised controlled trials, the quality of the included trials was poor, with considerable risk of bias. According to the results of meta-regression analyses (Table 4), the treatment effects were not significantly associated with whether a trial was cluster or quasi randomised, whether the sequence generation was inadequate, and whether it was blinded. In addition, publication and outcome reporting bias was possible. Funnel plot using data from placebo-controlled trials indicated that there was no statistically significant small-study effect.

Conclusion

The network meta-analysis confirms that a range of prophylactic antibiotic regimens are effective for eradicating meningococcal carriages, and treatment choice will depend on the individual priorities of the patients and physicians. In clinical situations where complete eradication is considered to be of the utmost importance, a combination of rifampin and minocycline seems to offer the highest likelihood of success. Ceftriaxone as a single intramuscular injection is also likely to be more effective as compared with the two

recommended antibiotics (ciprofloxacin or rifampin) by the current guidelines. Variation in the type of carriage and dosage regimens of ciprofloxacin may account for the observed inconsistency in the direct and indirect comparisons of rifampin and ciprofloxacin. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in network meta-analysis.

COMMENTS

Background

The current public health guidelines recommend chemoprophylaxis to be offered to close contacts of cases of meningococcal meningitis. Because of limited evidence from direct comparison trials, the authors conducted a network meta-analysis of randomised controlled trials that evaluated different antibiotics for eradicating carriages of *Neisseria meningitidis* (*N. meningitidis*).

Research frontiers

With the ever increasing number of competing interventions and a shortage of direct comparison trials, methods for indirect comparison and network meta-analysis have been widely used to compare different treatment options.

Innovations and breakthroughs

This is the first network meta-analysis to compare the efficacy of competing antibiotics for eradicating the carriage of *N. meningitidis*. Methodological experience obtained from this network meta-analysis was also reported.

Applications

For eradicating meningococcal carriages, a combination of rifampin and minocycline seems the most efficacious, and ceftriaxone is also likely to be more effective than ciprofloxacin or rifampin alone. Detailed examination of characteristics of relevant studies should be conducted for investigating causes of inconsistency in all network meta-analysis.

Terminology

Network meta-analysis can be used to combine evidence from direct comparison trials and evidence based on indirect comparisons.

Peer-review

This is a well-performed network meta-analysis regarding the effects of antibiotics for eradicating carriages of *N. meningitidis*. The methodology is clear, the meta-analysis was performed well, the article was well-written, and the limitations of the study have been adequately discussed. The findings of this meta-analysis should be useful for the scientific and clinical community.

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