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Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis (Review)

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[Intervention Review]

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Approximately 2.5% of all hospitalisations in people with liver cirrhosis are for spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis is associated with significant short-term mortality; therefore, it is important to prevent spontaneous bacterial peritonitis in people at high risk of developing it. Antibiotic prophylaxis forms the mainstay preventive method, but this has to be balanced against the development of drug-resistant spontaneous bacterial peritonitis, which is difficult to treat, and other adverse events. Several different prophylactic antibiotic treatments are available; however, there is uncertainty surrounding their relative efficacy and optimal combination.

Objectives

To compare the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis using a network meta-analysis and to generate rankings of the different prophylactic antibiotic treatments according to their safety and efficacy.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers to November 2018 to identify randomised clinical trials in people with cirrhosis at risk of developing spontaneous bacterial peritonitis.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or status) in adults with cirrhosis undergoing prophylactic treatment to prevent spontaneous bacterial peritonitis. We excluded randomised clinical trials in which participants had previously undergone liver transplantation, or were receiving antibiotics for treatment of spontaneous bacterial peritonitis or other purposes.

Data collection and analysis

We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio, rate ratio, and hazard ratio (HR) with 95% credible intervals (CrI) based on an available-case analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance.

Main results

We included 29 randomised clinical trials (3896 participants; nine antibiotic regimens (ciprofloxacin, neomycin, norfloxacin, norfloxacin plus neomycin, norfloxacin plus rifaximin, rifaximin, rufloxacin, sparfloxacin, sulfamethoxazole plus trimethoprim), and 'no active intervention' in the review. Twenty-three trials (2587 participants) were included in one or more outcomes in the review. The trials that provided the information included people with cirrhosis due to varied aetiologies, with or without other features of decompensation, having ascites with low protein or previous history of spontaneous bacterial peritonitis. The follow-up in the trials ranged from 1 to 12 months. Many of the trials were at high risk of bias, and the overall certainty of evidence was low or very low. Overall, approximately 10% of trial participants developed spontaneous bacterial peritonitis and 15% of trial participants died.

There was no evidence of differences between any of the antibiotics and no intervention in terms of mortality (very low certainty) or number of serious adverse events (very low certainty). However, because of the wide CrIs, clinically important differences in these outcomes cannot be ruled out. None of the trials reported health-related quality of life or the proportion of people with serious adverse events.

There was no evidence of differences between any of the antibiotics and no intervention in terms of proportion of people with 'any adverse events' (very low certainty), liver transplantation (very low certainty), or the proportion of people who developed spontaneous bacterial peritonitis (very low certainty). The number of 'any' adverse events per participant was fewer with norfloxacin (rate ratio 0.74, 95% CrI 0.59 to 0.94; 4 trials, 546 participants; low certainty) and sulfamethoxazole plus trimethoprim (rate ratio 0.19, 95% CrI 0.02 to 0.81; 1 trial, 60 participants; low certainty) versus no active intervention. There was no evidence of differences between the other antibiotics and no intervention in the number of 'any' adverse events per participant (very low certainty). There were fewer other decompensation events with rifaximin versus no active intervention (rate ratio 0.61, 65% CrI 0.46 to 0.80; 3 trials, 575 participants; low certainty) and norfloxacin plus neomycin (rate ratio 0.06, 95% CrI 0.00 to 0.33; 1 trial, 22 participants; low certainty). There was no evidence of differences between the other antibiotics and no intervention in the number of decompensations events per participant (very low certainty). None of the trials reported health-related quality of life or development of symptomatic spontaneous bacterial peritonitis.

One would expect some correlation between the above outcomes, with interventions demonstrating effectiveness across several outcomes. This was not the case. The possible reasons for this include sparse data and selective reporting bias, which makes the results unreliable. Therefore, one cannot draw any conclusions from these inconsistent differences based on sparse data.

There was no evidence of any differences in the subgroup analyses (performed when possible) based on whether the prophylaxis was primary or secondary.

Funding: the source of funding for five trials were organisations who would benefit from the results of the study; six trials received no additional funding or were funded by neutral organisations; and the source of funding for the remaining 18 trials was unclear.

Authors' conclusions

Based on very low-certainty evidence, there is considerable uncertainty about whether antibiotic prophylaxis is beneficial, and if beneficial, which antibiotic prophylaxis is most beneficial in people with cirrhosis and ascites with low protein or history of spontaneous bacterial peritonitis.

Future randomised clinical trials should be adequately powered, employ blinding, avoid postrandomisation dropouts (or perform intention-to-treat analysis), and use clinically important outcomes such as mortality, health-related quality of life, and decompensation events.

PLAIN LANGUAGE SUMMARY

Use of antibiotics to prevent spontaneous bacterial peritonitis in people with advanced liver disease

What was the aim of this Cochrane Review?

People with advanced liver disease (liver cirrhosis, or late-stage scarring of the liver with complications) are at risk of developing an abnormal build-up of fluid in the tummy, called ascites. This fluid may get infected with bacteria, without one knowing the cause. This is called 'spontaneous bacterial peritonitis'. It is important to prevent spontaneous bacterial peritonitis in people at high risk of developing it, because it is associated with a significant risk of death. Antibiotics are often used in people with advanced liver disease and ascites as a means to help prevent spontaneous bacterial peritonitis, but it is unclear whether they are effective and if effective, which antibiotic is the most effective.

We aimed to determine the best available antibiotic treatment (if any) for the prevention of spontaneous bacterial peritonitis in people with advanced liver disease. We collected and analysed all relevant research studies and found 29 randomised clinical trials (participants

are randomly assigned to one of two treatment groups). During analysis of data, we used standard Cochrane techniques, allowing direct comparison of only two treatments at a time. We also used advanced techniques, allowing indirect comparisons of more than two treatments simultaneously (usually referred as 'network meta-analysis'). The aim was to gather reliable direct and indirect evidence.

Date of literature search

November 2018.

Key messages

Only two small studies were conducted without flaws, and because of the very high uncertainty in the obtained analysis results, the authors could not say whether antibiotics work and, if they work, which one to use. Out of 1564 participants, 10% of people with cirrhosis and ascites developed spontaneous bacterial peritonitis, and out of 2169 participants, about 15% died within 12 months.

Funding source was unclear in 18 studies. Drug companies funded five studies. There were no concerns regarding the source of funding for the remaining six studies.

What did the review study?

We studied adults with advanced liver disease due to various causes, and who were undergoing preventive treatment to avoid developing spontaneous bacterial peritonitis. Participants received different antibiotics or no antibiotics. We excluded studies in people who had previously undergone liver transplantation, and where people received antibiotics for the treatment of spontaneous bacterial peritonitis or for any other reason. The average age of participants, when reported, ranged from 42 to 63 years. The administered antibiotic types were quinolones, rifamycins, sulfonamides, and aminoglycosides. The authors wanted to gather and analyse data on death, quality of life, serious and non-serious side effects, time to liver transplantation, time to development of spontaneous bacterial peritonitis, time to development of other complications of advanced liver disease, and length of hospital stay.

What were the main results of the review?

The 29 studies included a small number of participants (3896 participants). Study data were sparse. Twenty-three studies with 2587 participants provided data for analyses. The follow-up in the trials ranged from 1 to 12 months. The review shows that:

- of the 10 different antibiotics compared in the trials, norfloxacin and rifaximin were most commonly used;
- 15 of every 100 people died within 12 months, and 10 of every 100 people developed spontaneous bacterial peritonitis;
- giving preventive antibiotics may make no difference to the percentage of deaths or people with serious complications; however, potentially important differences cannot be ruled out;
- none of the trials reported quality of life or symptomatic development of spontaneous bacterial peritonitis;
- there was evidence showing that the percentage of people who developed spontaneous bacterial peritonitis as per laboratory criteria may be reduced with sulfonamides compared with no use of antibiotics (difficult to estimate how much reduction);
- there was evidence of differences in other outcomes such as any complications, liver transplantation, and other signs of liver failure, but these differences were not consistent. Therefore, the results are unreliable, and we cannot draw any conclusions about how effective antibiotics are;
- future well-designed trials are needed.

Quality of the evidence

We cannot draw any conclusions from these trials due to the sparse data.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Patient or population: people with liver cirrhosis

Settings: secondary or tertiary care

Intervention: various interventions

Comparison: no active intervention

Follow-up period: 1–12 months

Network geometry plots: Figure 1

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Certainty of evidence
		No active intervention	Various interventions	Difference	
All-cause mortality **Total studies: 17** **Total participants: 2169**					
No active intervention	**Reference**	—	—	—	
Rifaximin (3 RCTs, 479 participants)	**HR 0.57** (0.33 to 1.00) **Network estimate**	**184 per 1000**	**105 per 1000** (61 to 184)	**79 fewer per 1000** (123 fewer to 0 fewer)	**Very low**[a,b,c]
Norfloxacin (4 RCTs, 546 participants)	**HR 0.74** (0.49 to 1.09) **Network estimate**	**184 per 1000**	**136 per 1000** (90 to 201)	**48 fewer per 1000** (94 fewer to 17 more)	**Very low**[a,b,c]
Ciprofloxacin (3 RCTs, 255 participants)	**HR 0.61** (0.31 to 1.16) **Network estimate**	**184 per 1000**	**113 per 1000** (57 to 213)	**71 fewer per 1000** (126 fewer to 29 more)	**Very low**[a,b,c]
Sulfamethoxazole +trimethoprim (1 RCT, 60 participants)	**HR 0.47** (0.20 to 1.00) **Network estimate**	**184 per 1000**	**85 per 1000** (38 to 184)	**98 fewer per 1000** (146 fewer to 0 more)	**Very low**[a,b,c]

Norfloxacin +rifaximin (no direct RCT)	**HR 0.40** (0.12 to 1.17) **Network estimate**	**184 per 1000**	**73 per 1000** (22 to 215)	**111 fewer per 1000** (161 fewer to 32 more)	**Very low**[a,b,c]
Rufloxacin (no direct RCT)	**HR 1.45** (0.27 to 8.21) **Network estimate**	**184 per 1000**	**265 per 1000** (50 to 1000)	**82 more per 1000** (133 fewer to 816 more)	**Very low**[a,b,c]
Health-related quality of life					
None of the trials reported this outcome.					
Serious adverse events (proportion of participants with one or more serious adverse event)					
None of the trials with no active intervention as control group reported this outcome.					
Serious adverse events (number of serious events per participant) **Total studies: 2** **Total participants: 353**					
No active intervention	**Reference**	—	—	—	
Rifaximin (2 RCTs, 353 participants)	**Rate ratio 1.66** (0.98 to 2.90) **Direct estimate**	**132 per 1000**	**219 per 1000** (129 to 383)	**87 more per 1000** (3 fewer to 251 more)	**Very low**[a,b,c]
Any adverse events (proportion of participants with one or more adverse event) **Total studies: 3** **Total participants: 631**					
No active intervention	**Reference**	—	—	—	
Rifaximin (1 RCT, 299 participants)	**OR 1.01** (0.00 to 853.21) **Network estimate**	**799 per 1000**	**800 per 1000** (5 to 1000)	**1 more per 1000** (201 fewer to 201 more)	**Very low**[a,b,c]
Norfloxacin (no direct RCT)	**OR 11.85** (0.01 to 263,023.85) **Network estimate**	**799 per 1000**	**979 per 1000** (26 to 1000)	**180 more per 1000** (201 fewer to 201 more)	**Very low**[a,b,c]
Any adverse events (number of events per participant) **(Only direct estimates presented as there was evidence of inconsistency in the network meta-analysis involving the main interventions being compared in this review)**					

No active intervention	**Reference**	—	—	—	
Rifaximin (3 RCTs, 418 participants)	**Rate ratio 1.15** (0.98 to 1.34) **Direct estimate**	**531 per 1000**	**609 per 1000** (522 to 710)	**78 more per 1000** (9 fewer to 169 more)	**Very low**[a,b,c]
Norfloxacin (4 RCTs, 546 participants)	**Rate ratio 0.74** (0.59 to 0.94) **Direct estimate**	**531 per 1000**	**393 per 1000** (312 to 498)	**138 fewer per 1000** (219 fewer to 33 fewer)	**Low**[a,b]
Ciprofloxacin (3 RCT; 255 participants)	**Rate ratio 0.72** (0.49 to 1.05) **Direct estimate**	**531 per 1000**	**384 per 1000** (261 to 555)	**152 fewer per 1000** (270 fewer to 24 more)	**Very low**[a,b,c]
Sulfamethoxazole + trimethoprim (1 RCT, 60 participants)	**Rate ratio 0.19** (0.02 to 0.81) **Direct estimate**	**531 per 1000**	**102 per 1000** (13 to 431)	**138 fewer per 1000** (219 fewer to 33 fewer)	**Low**[a,b]
Liver transplantation **Total studies: 3** **Total participants: 260**					
No active intervention	**Reference**	—	—	—	
Norfloxacin (1 RCT, 68 participants)	**HR 0.93** (0.31 to 3.44) **Network estimate**	**182 per 1000**	**168 per 1000** (56 to 625)	**14 fewer per 1000** (126 fewer to 443 more)	**Very low**[a,b,c]
Ciprofloxacin (no direct RCT)	**HR 0.62** (0.12 to 3.31) **Network estimate**	**182 per 1000**	**113 per 1000** (22 to 602)	**69 fewer per 1000** (160 fewer to 420 more)	**Very low**[a,b,c]
Sulfamethoxazole + trimethoprim (no direct RCT)	**HR 2.62** (0.62 to 11.91) **Network estimate**	**182 per 1000**	**477 per 1000** (114 to 1000)	**295 more per 1000** (68 fewer to 818 more)	**Very low**[a,b,c]
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis) **Total studies: 15** **Total participants: 1504** **(Only direct estimates presented as there was evidence of inconsistency in the network meta-analysis involving the main interventions being compared in this review)**					
No active intervention	**Reference**	—	—	—	

Rifaximin (2 RCTs, 106 participants)	**HR 7.80** (0.13 to 4647.11) **Direct estimate**	**140 per 1000**	**1000 per 1000** (19 to 1000)	**860 more per 1000** (121 fewer to 860 more)	**Very low**[a,b,c]
Norfloxacin (3 RCTs, 255 participants)	**HR 0.16** (0.00 to 1.56) **Direct estimate**	**140 per 1000**	**23 per 1000** (0 to 219)	**117 fewer per 1000** (140 fewer to 79 more)	**Very low**[a,b,c]
Ciprofloxacin (3 RCTs, 255 participants)	**HR 0.56** (0.02 to 60.64) **Direct estimate**	**140 per 1000**	**78 per 1000** (2 to 1000)	**62 fewer per 1000** (138 fewer to 860 more)	**Very low**[a,b,c]
Sulfamethoxazole + trimethoprim (1 RCT, 60 participants)	**HR not estimable** Direct estimate	**140 per 1000**	**Not estimable**	**Not estimable**	**Very low**[a,b,c]
Number of decompensation episodes (per participant) **Total studies: 8** **Total participants: 1275**					
No active intervention	**Reference**	—	—	—	
Norfloxacin + neomycin (1 RCT, 22 participants)	**Rate ratio 0.06** (0.00 to 0.33) **Network estimate**	**459 per 1000**	**25 per 1000** (1 to 152)	**434 fewer per 1000** (458 fewer to 307 fewer)	**Low**[a,b]
Norfloxacin + rifaximin (no direct RCT)	**Rate ratio 0.33** (0.04 to 1.40) **Network estimate**	**459 per 1000**	**151 per 1000** (19 to 643)	**308 fewer per 1000** (440 fewer to 184 more)	**Very low**[a,b,c]
Rifaximin (3 RCTs, 575 participants)	**Rate ratio 0.61** (0.46 to 0.80) **Network estimate**	**459 per 1000**	**280 per 1000** (209 to 365)	**179 fewer per 1000** (250 fewer to 94 fewer)	**Low**[a,b]
Norfloxacin (3 RCTs, 439 participants)	**Rate ratio 0.81** (0.58 to 1.12) **Network estimate**	**459 per 1000**	**372 per 1000** (268 to 515)	**87 fewer per 1000** (192 fewer to 56 more)	**Very low**[a,b,c]

*Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the weighted median risk of the control group.

CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; **RCT:** randomised clinical trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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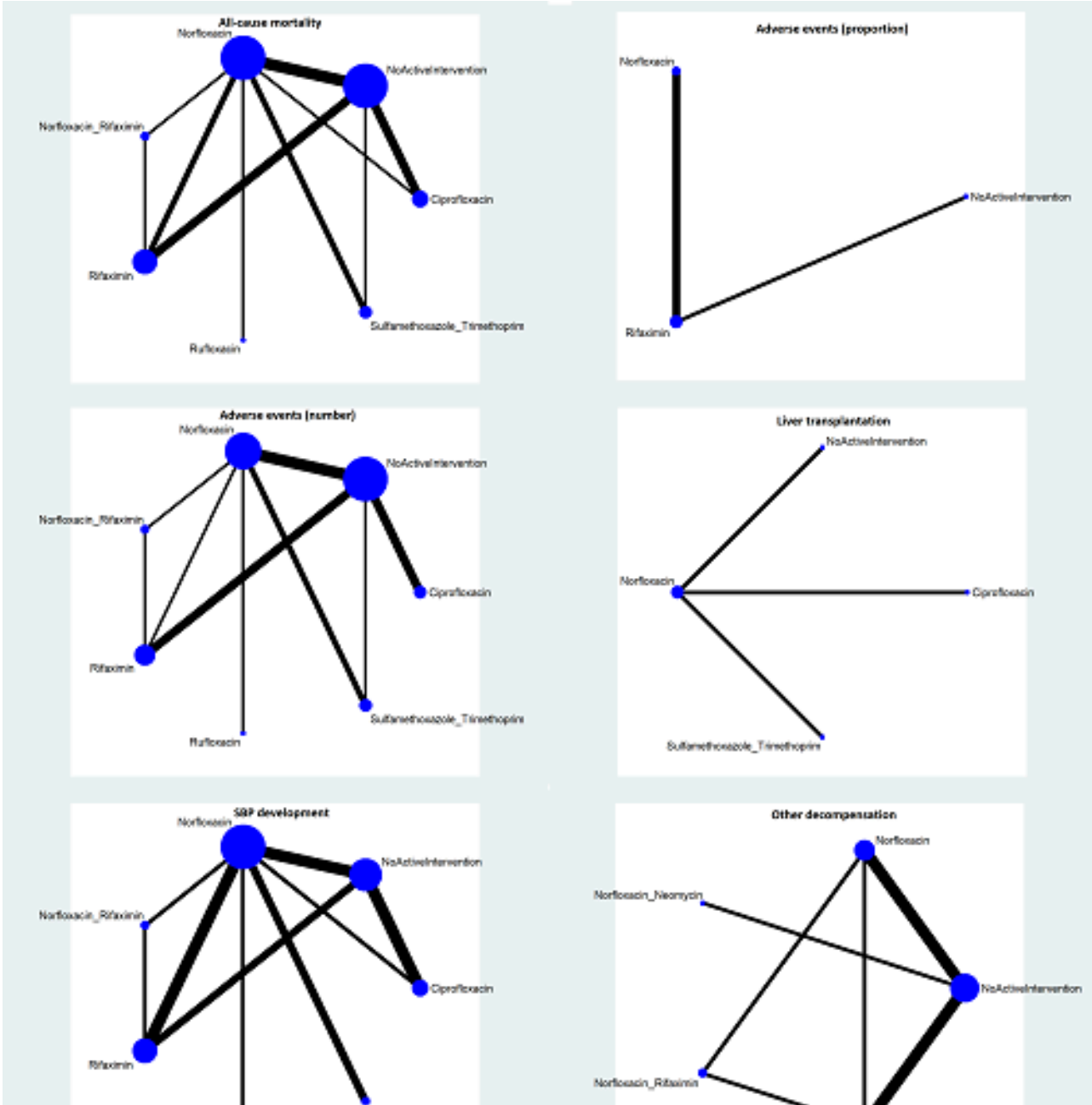
[a]Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level because the sample size was small.
[c]Downgraded one level because the credible intervals were wide (included clinical benefit and harms).

Figure 1. A high resolution image is available at https://doi.org/10.5281/zenodo.3603056. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (Interventions) _: plus; Adverse events (proportion): the proportion of participants who developed 'any adverse events'; NoActiveIntervention: 'no active intervention'; SBP: spontaneous bacterial peritonitis.



Summary of findings 2. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Patient or population: people with liver cirrhosis

Settings: secondary or tertiary care

Intervention: various interventions

Comparison: no active intervention

Follow-up period: 1–12 months

Network geometry plots: Figure 1

Outcomes	Rifaximin		Norfloxacin		Ciprofloxacin	
All-cause mortality						
No active intervention 184 per 1000 (18.4%)	**HR 0.57** (0.33 to 1.00) **Network estimate**	**79 fewer per 1000** (123 fewer to 0 fewer)	**HR 0.74** (0.49 to 1.09) **Network estimate**	**48 fewer per 1000** (94 fewer to 17 more)	**HR 0.61** (0.31 to 1.16) **Network estimate**	**71 fewer per 1000** (126 fewer to 29 more)
—	**Very low**[a,b,c]		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	Based on 479 participants (3 RCTs)		Based on 546 participants (4 RCTs)		Based on 255 participants (3 RCTs)	
Serious adverse events (number of events per participant)						
No active intervention 132 per 1000 (13.2 per 100 participants)	**Rate ratio 1.66** (0.98 to 2.90) **Direct estimate**	**87 more per 1000** (3 fewer to 253 more)	—		—	
—	**Very low**[a,b,c]		—		—	
—	Based on 353 participants (2 RCTs)		—		—	
Any adverse events (proportion of participants with one or more adverse event)						

No active intervention 799 per 1000 (79.9%)	**OR 1.01** (0.00 to 853.21) **Network estimate**	**1 more per 1000** (201 fewer to 201 more)	**OR 11.85** (0.01 to 263023.85) **Network estimate**	**180 more per 1000** (201 fewer to 201 more)	—	
—	**Very low**[a,b,c]		**Very low**[a,b,c]		—	
—	Based on 299 participants (1 RCT)		No direct RCTs		—	
Any adverse events (number of events per participant)						
No active intervention 531 per 1000 (53.1 per 100 participants)	**Rate ratio 1.15** (0.98 to 1.34) **Direct estimate**	**78 more per 1000** (9 fewer to 169 more)	**Rate ratio 0.74** (0.59 to 0.94) **Direct estimate**	**138 fewer per 1000** (219 fewer to 33 fewer)	**Rate ratio 0.72** (0.49 to 1.05) **Direct estimate**	**152 fewer per 1000** (270 fewer to 24 more)
—	**Very low**[a,b,c]		**Low**[a,b]		**Very low**[a,b,c]	
—	Based on 418 participants (3 RCTs)		Based on 546 participants (4 RCTs)		Based on 255 participants (3 RCTs)	
Liver transplantation						
No active intervention 182 per 1000 (18.2%)	—		**HR 0.93** (0.31 to 3.44) **Network estimate**	**14 fewer per 1000** (126 fewer to 443 more)	**HR 0.62** (0.12 to 3.31) **Network estimate**	**69 fewer per 1000** (160 fewer to 420 more)
—	—		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	—		Based on 68 participants (1 RCT)		No direct RCT	
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis)						
No active intervention 140 per 1000 (14%)	**HR 7.80** (0.13 to 4647.11) **Direct estimate**	**860 more per 1000** (121 fewer to 860 more)	**HR 0.16** (0.00 to 1.56) **Direct estimate**	**117 fewer per 1000** (140 fewer to 79 more)	**HR 0.56** (0.02 to 60.64) **Direct estimate**	**62 fewer per 1000** (138 fewer to 860 more)
—	**Very low**[a,b,c]		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	Based on 106 participants (2 RCTs)		Based on 255 participants (3 RCTs)		Based on 255 participants (3 RCTs)	

Number of decompensation episodes (per participant)						
No active intervention 459 per 1000 (45.9%)	**Rate ratio 0.61** (0.46 to 0.80) **Network estimate**	**179 fewer per 1000** (250 fewer to 94 fewer)	**Rate ratio 0.81** (0.58 to 1.12) **Network estimate**	**87 fewer per 1000** (192 fewer to 56 more)	—	
—	**Low**[a,b]		**Very low**[a,b,c]		—	
—	Based on 575 participants (3 RCTs)		Based on 439 participants (3 RCTs)		—	
Length of hospital stay						
No active intervention 17.6 days	—		—		**MD –8.29 days** (–11.09 to –5.50) **Network estimate**	**8.29 fewer days** (11.09 fewer to 5.5 fewer)
—	—		—		**Low**[a,b]	
—	—		—		Based on 60 participants (1 RCT)	

CrI: credible interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised clinical trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level because the sample size was small.
[c]Downgraded one level because the credible intervals were wide (included clinical benefit and harms).

BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions including carbohydrate metabolism, fat metabolism, protein metabolism, drug metabolism, synthetic functions, storage functions, digestive functions, excretory functions, and immunological functions (Read 1972). Liver cirrhosis is a liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered, with fibrous septa surrounding regenerated or regenerating parenchymal nodules (Tsochatzis 2014; NCBI 2018a). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol related fatty liver disease, autoimmune liver diseases, and metabolic liver diseases (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the US, the prevalence of chronic liver disease varies between 0.3% and 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis caused an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries, such as the UK, while there is a decreasing trend in other countries, for example France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is due to the development of clinically significant portal hypertension (hepatic venous pressure gradient at least 10 mmHg) (de Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (de Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Spontaneous bacterial peritonitis

Ascites is accumulation of free fluid in the abdomen (peritoneal cavity) (NCBI 2018b), and it is a feature of liver decompensation (Tsochatzis 2017; EASL 2018). Approximately 20% of people with cirrhosis have ascites (D'Amico 2014). Approximately 1% to 4% of people with cirrhosis develop ascites each year (D'Amico 2006; D'Amico 2014). Ascites is the first sign of liver decompensation in about a third of people with compensated liver cirrhosis (D'Amico 2014). When the ascitic fluid is infected with bacteria without gastrointestinal disease or trauma, it is termed spontaneous bacterial peritonitis. However, because of the poor sensitivity of ascitic fluid culture, spontaneous bacterial peritonitis is diagnosed by a polymorphonuclear leukocyte count of more than 250 per mm^3 in the ascitic fluid (Rimola 2000; EASL 2018). In the presence of haemorrhagic ascites (ascites with red blood cell count of more than 10,000 per mm^3), one polymorphonuclear leukocyte should be subtracted for every red blood cell 250 to account for the presence of blood in the ascitic fluid (Rimola 2000). Spontaneous bacterial peritonitis may or may not be symptomatic, with symptoms of peritonitis such as abdominal pain, systemic infection, fever and chills, and hypotension (Rimola 2000; Nousbaum 2007; EASL 2010).

The overall incidence and prevalence of spontaneous bacterial peritonitis in people with cirrhosis is difficult to estimate. Approximately 2.5% of all hospitalisations of people with cirrhosis are for spontaneous bacterial peritonitis (Devani 2019). The incidence of spontaneous bacterial peritonitis in people with decompensated liver cirrhosis is about 20% over a period of 1 to 12 months (Saab 2009).

The short-term mortality (that is, death within 30 days of diagnosis or death in hospital) after spontaneous bacterial peritonitis is about 15% to 40% (Khan 2009; Tandon 2011; Devani 2019). Spontaneous bacterial peritonitis is associated with significant resource utilisation: one study conducted in the US showed that the mean length of hospital stay was approximately six days and the mean hospital costs per patient were approximately USD 17,000 (Devani 2019).

Pathophysiology of spontaneous bacterial peritonitis

Increased bacterial translocation (gut bacteria or bacterial products migrating outside the intestinal lumen) and decreased local and systemic immune responses in people with cirrhosis are believed to be the cause of spontaneous bacterial peritonitis (Bernardi 2010).

Description of the intervention

Antibiotic prophylaxis in the form of norfloxacin (fluoroquinolone) is recommended for people without previous episodes of spontaneous bacterial peritonitis but for people who have ascites with low protein (primary prophylaxis), and for people with one or more previous episodes of spontaneous bacterial peritonitis (secondary prophylaxis) (EASL 2010; Runyon 2013; EASL 2018). Alternative antibiotic prophylaxis recommended in these people include ciprofloxacin (fluoroquinolone) and a combination of trimethoprim and sulfamethoxazole (folic acid synthesis inhibitors) (EASL 2010; Runyon 2013). Rifaximin is another antibiotic that has been tried (Goel 2017), but it is not currently recommended by the European Association for the Study of the Liver (EASL) for the prophylaxis of spontaneous bacterial peritonitis (EASL 2018).

How the intervention might work

Different antibiotic classes have different mechanisms of action. Cephalosporins inhibit bacterial cell wall synthesis (Yotsuji 1988). Fluoroquinolones are type II topoisomerase inhibitors: type II topoisomerases at appropriate levels are required for normal cellular processes, and altering their levels leads to bacterial cell death (Aldred 2014). Folic acid synthesis inhibitors inhibit folic acid, which is necessary for DNA and bacterial cell replication (Gleckman 1981). Rifaximin inhibits bacterial ribonucleic acid (RNA) synthesis (DuPont 2015).

Why it is important to do this review

Spontaneous bacterial peritonitis is associated with significant short-term mortality (Khan 2009; Tandon 2011; Devani 2019). It is important to prevent spontaneous bacterial peritonitis in people at high risk of developing it. This has to be balanced against the development of drug-resistant spontaneous bacterial peritonitis, which is difficult to treat. Active spontaneous bacterial peritonitis may preclude liver transplantation as liver transplantation is not performed during sepsis. Several different prophylactic antibiotic treatments are available; however, their relative efficacy and

optimal combination are not known. There have been two Cochrane Reviews on the role of prophylactic antibiotics in people with cirrhosis (Cohen 2009; Chavez-Tapia 2010); however, there have been no previous network meta-analyses on the topic. Network meta-analysis allows for a combination of direct and indirect evidence and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis, we aimed to provide the best level of evidence for the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis. If it was not possible to perform this review with network meta-analysis methods, we performed head-to-head comparison meta-analysis whenever possible. We also presented results from direct comparisons whenever possible, even when we could perform the network meta-analysis.

OBJECTIVES

To compare the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis using a network meta-analysis and to generate rankings of the different prophylactic antibiotic treatments according to their safety and efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials (including cluster-randomised trials and cross-over randomised trials) for this network meta-analysis, irrespective of language, publication status, or date of publication. We excluded studies of other designs because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events.

Types of participants

We included randomised clinical trials with adults with liver cirrhosis, who were undergoing prophylactic treatment to prevent spontaneous bacterial peritonitis. We excluded randomised clinical trials in which participants had previously undergone liver transplantation, or were receiving antibiotics for treatment of spontaneous bacterial peritonitis or other purposes, for example, treatment of hepatic encephalopathy.

Types of interventions

We included any of the following different antibiotic interventions for comparison with one another or against 'no active intervention', either alone or in combination.

- Cephalosporins.
- Quinolones.
- Folic acid synthesis inhibitors.
- Rifaximin.
- Other classes of antibiotics.

We used 'no active intervention' (either placebo or no antibiotic treatment) as the reference group. We considered each antibiotic as a different treatment node. We considered variations in doses, frequency, and duration of antibiotics as the same treatment node. We treated each different combination of the antibiotics as different treatment nodes.

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the studies. Transitivity assumption means that participants included in the different trials with different antibiotic prophylaxis can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect-modifiers, such as the reason why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis), is the same across trials. Since there was no concern about the transitivity assumption, we did not perform a separate meta-analysis for people considered at high risk of spontaneous bacterial peritonitis due to different reasons.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death).
- Health-related quality of life using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018), at maximal follow-up
- Serious adverse events (during or within six months after cessation of intervention). We defined a serious adverse event as any event that would increase mortality; was life-threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might have jeopardised the person or required intervention to prevent it (ICH-GCP 1997). However, none of the trial authors defined serious adverse events. Therefore, we used the list provided by trial authors for serious adverse events (as indicated in the protocol; Gurusamy 2018).
  - Proportion of people with one or more serious adverse event.
  - Number of serious adverse events per participant.

Secondary outcomes

- Any adverse events (during or within six months after cessation of intervention): we defined an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of the intervention) (ICH-GCP 1997). However, none of the trial authors defined 'adverse event'. Therefore, we used the list provided by trial authors for adverse events (as indicated in the protocol; Gurusamy 2018).
  - Proportion of people with one or more adverse event.
  - Number of any adverse events per participant.
- Time to liver transplantation (maximal follow-up).

- Time to development of spontaneous bacterial peritonitis (however, defined by study authors at maximal follow-up).
  - According to definitions used for spontaneous bacterial peritonitis.
  - Symptomatic spontaneous bacterial peritonitis.
- Number of decompensation episodes (maximal follow-up).

Exploratory outcomes

- Length of hospital stay (all hospital admissions until maximal follow-up).
- Number of days of lost work (in people who work) (maximal follow-up).
- Treatment costs (including the cost of the treatment and any resulting complications).

We chose the above outcomes based on their importance to patients, having made a survey related to research priorities for people with liver diseases (Gurusamy 2019), based on feedback of the patient and public representatives of the project, and based on an online survey about the outcomes promoted through the Cochrane Consumer Network.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to November 2018, without applying any language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), which included various trial registers, including ISRCTN and ClinicalTrials.gov. We also searched the European Medical Agency (EMA) (www.ema.europa.eu/ema/) and US Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials on 10 November 2018. The search strategies are provided in Appendix 1.

Searching other resources

We searched the references of the identified trials and the existing Cochrane Reviews on prophylactic antibiotic treatments in liver cirrhosis to identify additional trials for inclusion (Cohen 2009; Chavez-Tapia 2010).

Data collection and analysis

Selection of studies

Two review authors (KG and OK) independently identified trials for inclusion by screening the titles and abstracts, and sought full-text articles for any references identified by at least one of the review authors for potential inclusion. We selected trials for inclusion based on the full-text articles. We provided the list of references that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We provided a list of ongoing trials identified primarily through the search of the clinical trial registers for further follow-up in the Characteristics of ongoing studies table. We resolved any discrepancies through discussion.

It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, because of the exponentially increased amount of work required for non-randomised studies, we planned to register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events if there was uncertainty in the balance of benefits and harms of effective treatment(s). We did not perform this because of the findings of the review, that is, the credible intervals (CrI) were wide and there was considerable uncertainty about the benefits of the different antibiotics used as prophylaxis.

Data extraction and management

Two review authors (KG and OK) independently extracted the data in a piloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - natural logarithm of hazard ratio and its standard error, if this was reported, rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, and variceal bleeding), the aetiology for cirrhosis, and the interval between diagnosis of ascites and prophylactic treatment;
  - details of the intervention and control (including dose, frequency, and duration);
  - length of follow-up;
  - information related to 'Risk of bias' assessment (see Assessment of risk of bias in included studies).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria.

We collected outcomes at maximum follow-up but also at short-term (up to three months) and medium-term (from three months to five years) if applicable.

We attempted to contact the trial authors in the case of unclear or missing information. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), to assess the risk of bias in the included trials. Specifically, we assessed sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the study. In general, we classified the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (e.g. use of interactive voice response system).
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We excluded such quasi-randomised studies.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it was likely that the investigators who assigned the participants knew the allocation sequence. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or there was rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information to permit a judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but it was likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information to permit a judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for prophylactic antibiotic treatment of people with cirrhosis, namely, all-cause mortality, incidence of spontaneous bacterial peritonitis, and adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully; or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

Other bias

- Low risk of bias: the trial appeared free of other components that could have put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Unclear risk of bias: the trial may or may not have been free of other components that could have put it at risk of bias.
- High risk of bias: there were other factors in the trial that could have put it at risk of bias (e.g. baseline differences, early stopping).

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed bias risk domains. Otherwise, we considered trials to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation; allocation concealment; blinding of participants, healthcare professionals, and outcome assessors; incomplete outcome data; and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018). We did not

use additional items for cross-over or clustered RCTs, as we did not identify any that met the inclusion criteria.

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we calculated the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if the included trials had used different scales. If we calculated the SMD, we planned to convert it to a common scale, for example, EQ5D or SF-36 (using the standard deviation of the common scale) for the purpose of interpretation. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio (RaR) with 95% CrI. This assumes that the events were independent of each other, that is, if a person has had an event they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated the hazard ratio (HR) with 95% CrI.

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each outcome when network meta-analysis was performed. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities for each outcome when network meta-analysis was performed (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant receiving antibiotic prophylaxis for spontaneous bacterial peritonitis according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

If we had identified any cluster-randomised clinical trials, we planned to include them provided that the effect estimate adjusted for cluster correlation was available or if there was sufficient information available to calculate the design effect (which would allow us to take clustering into account). We also planned to assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

If we had identified any cross-over randomised clinical trials, we planned to include only the outcomes after the period of first intervention because the included treatments could have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes we used for analysis accounted for the correlation between the effect sizes from trials with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we used the data available to us. When intention-to-treat analysis was not used and the data were not missing at random (e.g. treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), it could lead to biased results; therefore, we conducted best-worst case scenario analysis (assuming a good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (assuming a bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible for binary and time-to-event outcomes, where binomial likelihood was used.

For continuous outcomes, we planned to impute the standard deviation from P values, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available; otherwise, we planned to simply provide a median and interquartile range of the difference in medians. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of MDs and may bias the effect estimate to no effect for calculation of SMDs (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We also planned to assess the presence of clinical heterogeneity by comparing effect estimates (see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, reasons why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis), different aetiologies for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the cointerventions (e.g. both groups received albumin). Different study designs and risk of bias could contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2, and comparing this with values reported in a study of the distribution of between-study heterogeneity estimates) (Turner 2012), and by calculating the I^2 statistic (Jackson 2014) using Stata 15.1. If we identified substantial clinical, methodological, or statistical heterogeneity, we planned to explore and address the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: reasons

why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis, that is, ascites with low protein or previous episodes of spontaneous bacterial peritonitis; methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we planned to perform a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older treatments) or higher risk of bias in older studies (comparing older treatments with placebo) (Chaimani 2012). As there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we judged the reporting bias by the completeness of the search (Chaimani 2012). We also considered lack of reporting of outcomes as a form of reporting bias.

Data synthesis

Methods for indirect and mixed comparisons

We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the network meta-analysis, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log OR for binary outcomes, MD or SMD for continuous outcomes, log RaR for count outcomes, and log HR for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters'), using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of 'at risk' individuals at the point when they were censored) for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We used 'no active intervention' as the reference group across the networks. We used a fixed-effect model and random-effects model for the network meta-analysis. We reported both models for comparison with the reference group in a forest plot when the results were different between the models. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model, that is, usually using the random-effects model in the absence of 'small-study' bias.

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation to assist with the assessment of convergence, employing codes provided by the NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 iterations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. checked whether the values in different chains mix very well by visualisation), and ran the models for another 10,000 iterations to obtain effect estimates. If we did not obtain convergence, we increased the number of iterations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we planned to use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We estimated the probability that each intervention ranks at each of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and inconsistency factor plots to assess inconsistency when applicable (Higgins 2012; Chaimani 2013). We used Stata 15.1 to create inconsistency factor plots. In the presence of inconsistency, we planned to assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section.

If there was evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials, and, when appropriate, limited network meta-analysis to a more compatible subset of trials.

Direct comparison

We performed the direct comparisons using the same codes and the same technical details.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups, and investigate heterogeneity and inconsistency using meta-regression using the codes provided in the NICE DSU guidance (Dias 2012a), if we included a sufficient number of trials (when there were at least two trials in at least two of the subgroups) and when the interaction term could be calculated. We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias (risk of bias in all domains were low) compared to trials at high risk of bias (risk of bias was unclear or high in at least one of the domains).

- The reasons why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis).
- The aetiology for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease).
- The interval between the diagnosis of ascites and the start of prophylactic treatment.
- Different types of cointervention (e.g. both groups received treatment for ascites or vasoactive drugs to decrease portal pressure, as cointerventions).
- The period of follow-up (short-term: up to three months, medium term: more than three months to five years, long-term: more than five years).
- The definition used by authors for serious adverse events and any adverse event (ICH-GCP 1997) versus other definitions.

We planned to calculate a single common interaction term (which assumed each relative treatment effect versus a common comparator treatment ('no active intervention') was impacted in the same way by the covariate in question) when applicable (Dias 2012a). If the 95% CrI of the interaction term did not overlap zero, we would have considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

If there were postrandomisation dropouts, we reanalysed the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses whenever possible. We also planned to perform a sensitivity analysis excluding the trials in which mean or standard deviation (or both) were imputed, and we planned to use the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention was within the top two, the probability that the intervention was within the top three, etc.), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks) in graphs (SUCRA) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks).

We uploaded all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo; zenodo.org/record/3457887#.Xe5_nG52uIU).

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the three interventions (rifaximin, norfloxacin, and ciprofloxacin) which most trials compared (Table 1).

Recommendations for future research

We provided recommendations for future research regarding the population, intervention, control, outcomes, period of follow-up, and study design, based on the uncertainties that we identified from the existing research.

RESULTS

Description of studies

Results of the search

We identified 1322 references through electronic searches of CENTRAL (183 references), MEDLINE Ovid (501 references), Embase Ovid (238 references), Science Citation Index Expanded (316 references), ClinicalTrials.gov (35 references) and WHO Trials register (49 references). After removing duplicate references, there were 1050 references. We excluded 978 clearly irrelevant references through reading titles and abstracts. We did not identify any additional eligible trial by reference searching or by searching the EMA or FDA. We retrieved 72 full-text references for further assessment in detail. We excluded 22 references (21 studies) for the reasons stated in the Characteristics of excluded studies table. Thus, we included 29 trials described in 50 references (Characteristics of included studies table). The reference flow is shown in Figure 2.

Figure 2. Study flow diagram.

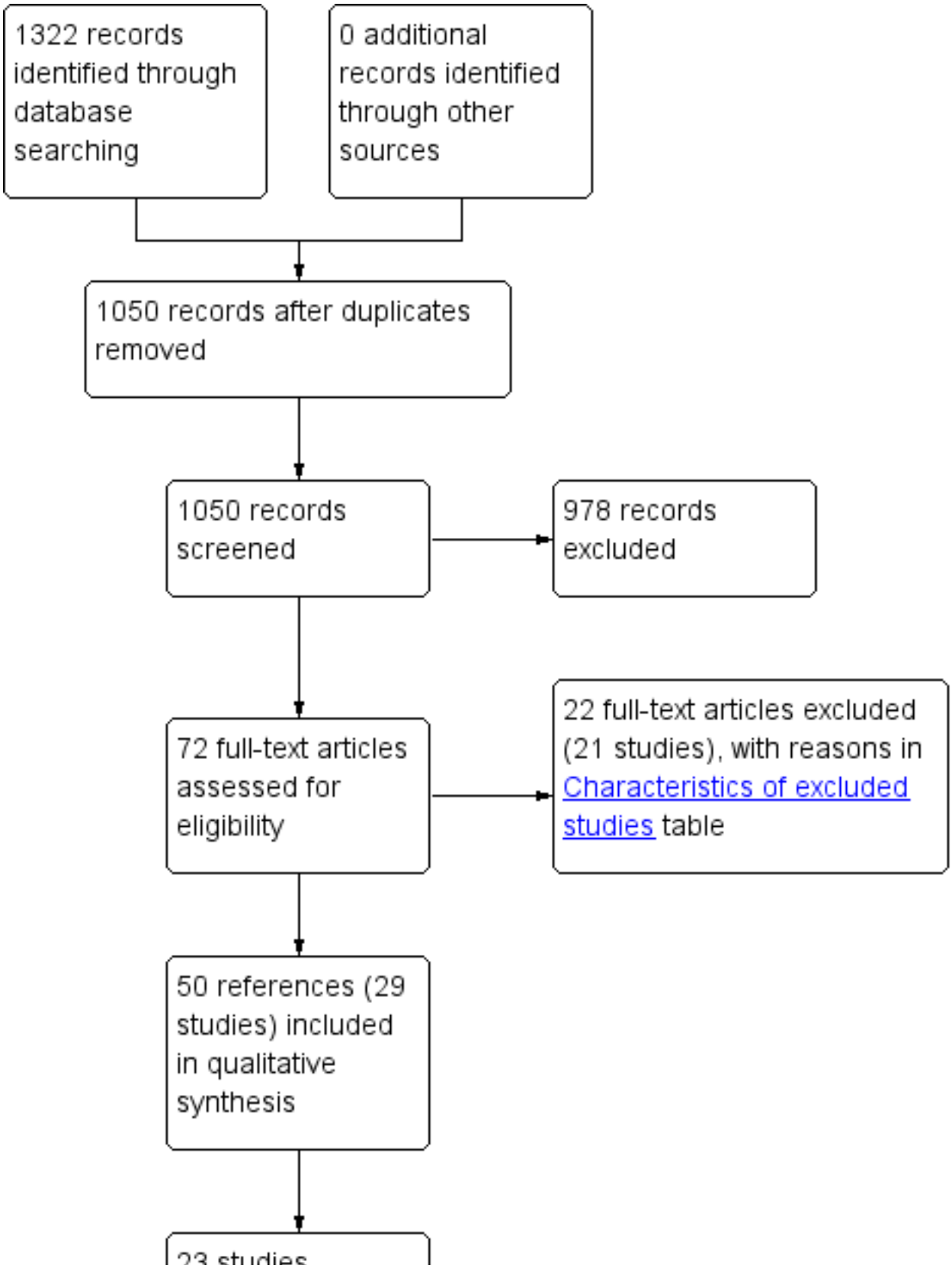
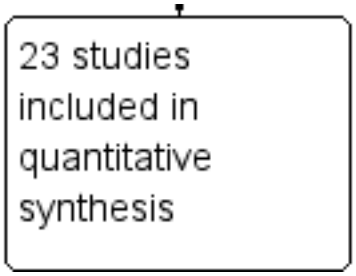


Figure 2. (Continued)



Included studies

We included 29 trials (Ginés 1990; Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Mostafa 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Assem 2016; Bajaj 2016; Elfert 2016; Latif 2016; Ibrahim 2017; Kimer 2017; Praharaj 2017; Yim 2018). A total of 3896 participants were randomised to different interventions. The number of participants ranged from 20 to 518. A total of 2587 participants from 23 trials provided data for one or more outcomes (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Assem 2016; Elfert 2016; Kimer 2017; Praharaj 2017; Yim 2018). The mean or median age in the trials ranged from 42 to 63 years in the trials that reported this information (Ginés 1990; Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Mostafa 2014; Tellez-Avila 2014; Assem 2016; Bajaj 2016; Elfert 2016; Latif 2016; Ibrahim 2017; Kimer 2017). The proportion of females ranged from 16.7% to 61.1% in the trials that reported this information (Ginés 1990; Rolachon 1995; Miglio 1997; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Bass 2010; Ali 2014; Lontos 2014; Mostafa 2014; Tellez-Avila 2014; Assem 2016; Elfert 2016; Latif 2016; Ibrahim 2017; Kimer 2017).

The follow-up period in the trials ranged from 1 to 12 months. Five trials had short-term follow-up (Singh 1995; Baik 2015; Latif 2016; Ibrahim 2017; Kimer 2017); 24 trials had medium-term follow-up (Ginés 1990; Rolachon 1995; Miglio 1997; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Mostafa 2014; Tellez-Avila 2014; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Assem 2016; Bajaj 2016; Elfert 2016; Praharaj 2017; Yim 2018); and none of the trials had long-term follow-up.

Nine trials reported the proportion of participants who had other features of decompensation: in five trials, all the participants had other features of decompensation (Miglio 1997; Bass 2010; Ali 2014; Nawaz 2015; Abdel Motelleb 2016); in the remaining four trials, the proportion of participants who had other features of decompensation ranged from 13.8% to 65.8% (Bauer 2002; Fernandez 2007; Assem 2016; Ibrahim 2017).

Seven trials reported the proportion of participants who had ascites with low protein: in one trial, none of the participants had ascites with low protein (Tellez-Avila 2014); in four trials, all the participants had ascites with low protein (Rolachon 1995; Fernandez 2007; Terg 2008; Abdel Motelleb 2016); in the remaining two trials, the proportion of participants who had ascites with low protein ranged from 49.1% to 86.3% (Alvarez 2005; Lontos 2014).

Eighteen trials reported the proportion of participants who had primary prophylaxis: in six trials, none of the participants had primary prophylaxis (Ginés 1990; Bauer 2002; Mostafa 2014; Mostafa 2015; Elfert 2016; Praharaj 2017); in eight trials, all the participants had primary prophylaxis (Grangie 1998; Fernandez 2007; Terg 2008; Tellez-Avila 2014; Abdel Motelleb 2016; Assem 2016; Bajaj 2016; Ibrahim 2017); in the remaining four trials, the proportion of participants who had primary prophylaxis ranged from 61.4% to 88.3% (Rolachon 1995; Singh 1995; Alvarez 2005; Lontos 2014).

Nineteen trials reported the proportion of participants who had alcohol-related cirrhosis: in three trials, none of the participants had alcohol-related cirrhosis (Mostafa 2014; Mostafa 2015; Latif 2016); in one trial, all the participants had alcohol-related cirrhosis (Trespi 1999); in the remaining 15 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 3.2% to 91.7% (Ginés 1990; Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Ali 2014; Lontos 2014; Tellez-Avila 2014; Moreau 2015; Bajaj 2016; Kimer 2017).

Sixteen trials reported the proportion of participants who had viral-related cirrhosis: in one trial, none of the participants had viral-related cirrhosis (Trespi 1999); in two trials, all the participants had viral-related cirrhosis (Mostafa 2014; Mostafa 2015); in the remaining 13 trials, the proportion of participants who had viral-related cirrhosis ranged from 1.7% to 95.2% (Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Madrid 2001; Bauer 2002; Ali 2014; Lontos 2014; Tellez-Avila 2014; Assem 2016; Bajaj 2016; Ibrahim 2017; Kimer 2017).

Six trials reported the proportion of participants who had autoimmune disease-related cirrhosis: in four trials, none of the participants had autoimmune disease-related cirrhosis (Trespi 1999; Mostafa 2014; Tellez-Avila 2014; Mostafa 2015); in the remaining two trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 3.3% to 3.7% (Rolachon 1995; Kimer 2017).

Nineteen trials reported the proportion of participants who had other-causes for cirrhosis: in two trials, none of the participants had other-causes for cirrhosis (Trespi 1999; Mostafa 2015); in the remaining 17 trials, the proportion of participants who had other causes for cirrhosis ranged from 1.6% to 64.9% (Ginés 1990; Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Madrid 2001;

Bauer 2002; Alvarez 2005; Fernandez 2007; Ali 2014; Lontos 2014; Tellez-Avila 2014; Moreau 2015; Assem 2016; Bajaj 2016; Ibrahim 2017; Kimer 2017).

In the only trial that reported the proportion of participants who had treatment for ascites in addition to antibiotics, all the participants had treatment for ascites in addition to antibiotics (Trespi 1999).

The trials compared nine antibiotic regimens (ciprofloxacin, neomycin, norfloxacin, norfloxacin plus neomycin, norfloxacin plus rifaximin, rifaximin, rufloxacin, sparfloxacin, sulfamethoxazole plus trimethoprim), and 'no active intervention'.

Twenty-three trials reported one or more outcomes for this review (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Assem 2016; Elfert 2016; Kimer 2017; Praharaj 2017; Yim 2018). The important characteristics, potential effect modifiers, and follow-up in each trial is reported in Table 1. Overall, there did not seem to be any systematic differences between the comparisons.

Funding: the source of funding for five trials was industrial organisations who could benefit from the results of the study (Ginés 1990; Bass 2010; Tellez-Avila 2014; Moreau 2015; Bajaj 2016); six trials were funded by neutral organisations who had no vested interests in the results of the study (Madrid 2001; Fernandez 2007; Terg 2008; Assem 2016; Kimer 2017; Yim 2018); the source of funding for the remaining 18 trials was unclear (Rolachon 1995; Singh 1995; Miglio 1997; Grangie 1998; Trespi 1999; Bauer 2002; Alvarez 2005; Ali 2014; Lontos 2014; Mostafa 2014; Baik 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Elfert 2016; Latif 2016; Ibrahim 2017; Praharaj 2017).

Excluded studies

We excluded 21 studies, with reasons (Anonymous 1971; Boccardi 1974; Rimola 1985; Schubert 1991; Henrion 1992; Pateron 1992; Bode 1997; Gerbes 1997; Novella 1997; Gines 1998; Assy 2005; Bendtsen 2005; Lata 2005; Anonymous 2006; Vibert 2008; Kemp 2009; Jalan 2010; Siddique 2010; Bajaj 2012; Gupta 2013; Kumar 2014; see Characteristics of excluded studies table).

Risk of bias in included studies

The risk of bias is summarised in Figure 3, Figure 4, and Table 2. Two trials were at low risk of trials in all domains (Terg 2008; Kimer 2017). All the remaining trials were at unclear or high risk of bias in at least one of the domains and were considered to be at high risk of bias.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

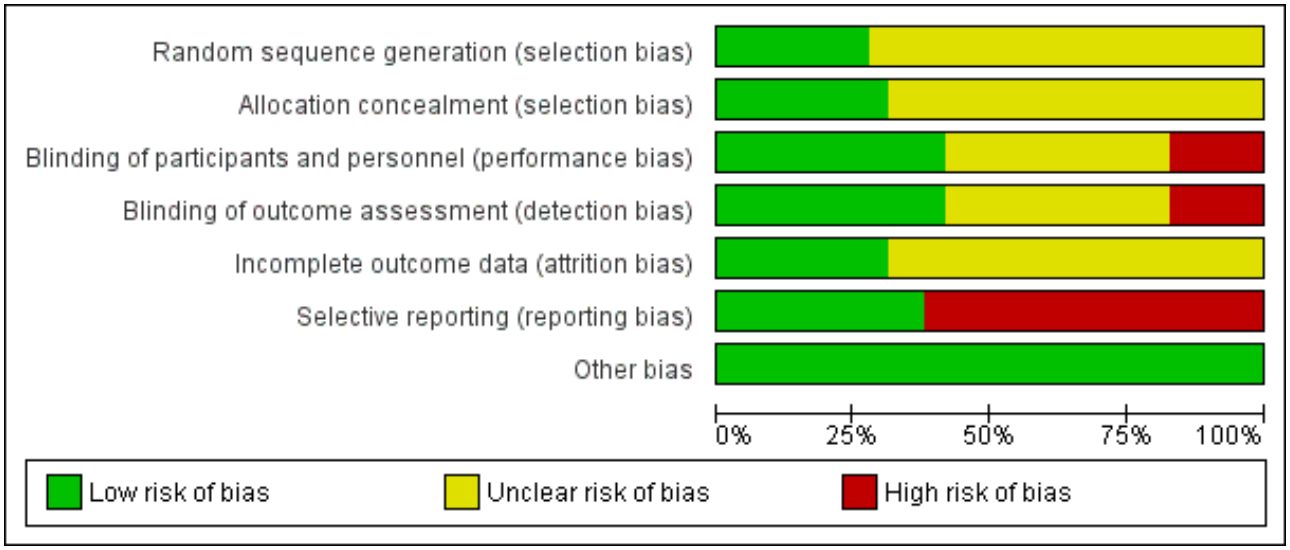


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

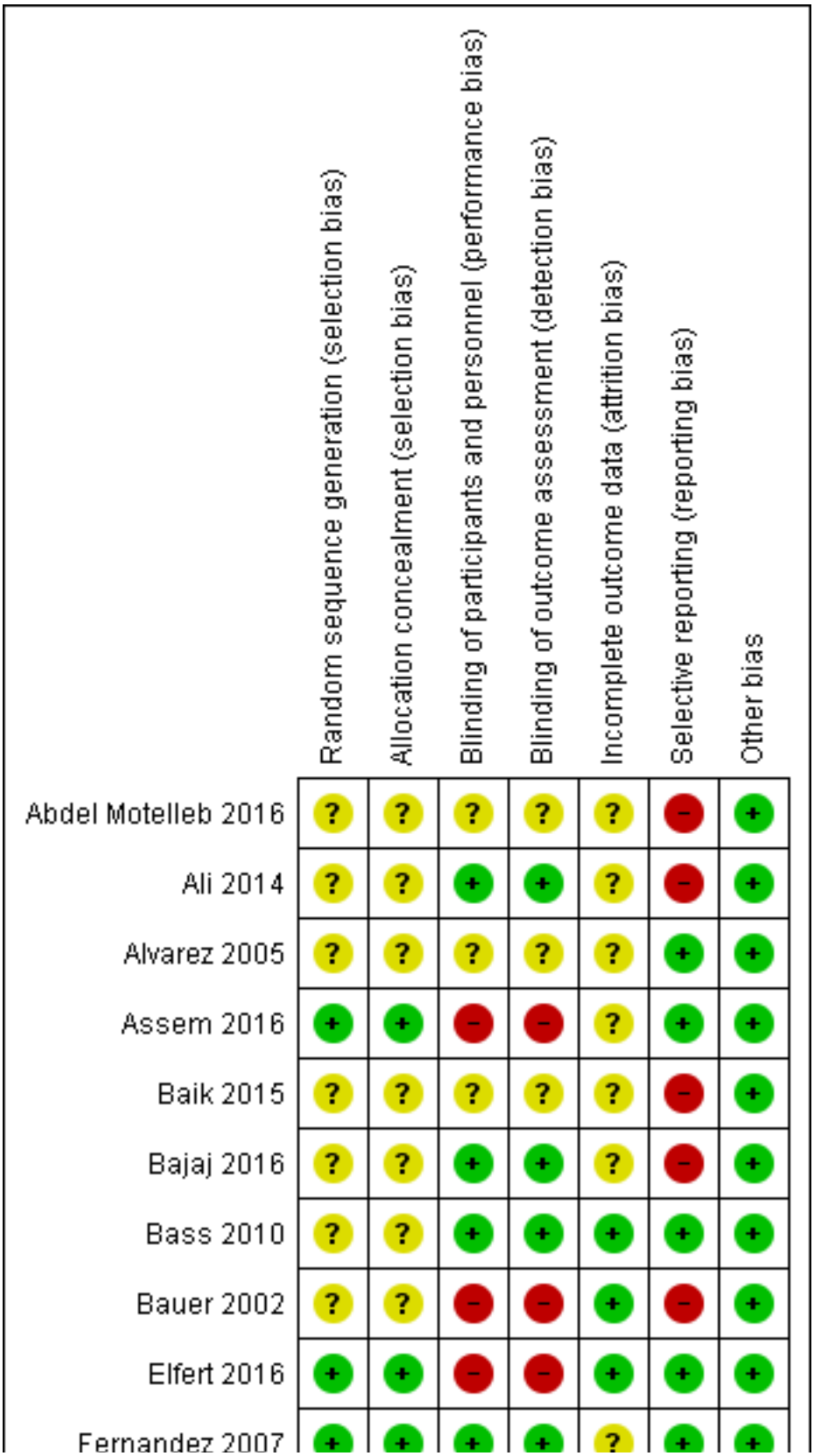
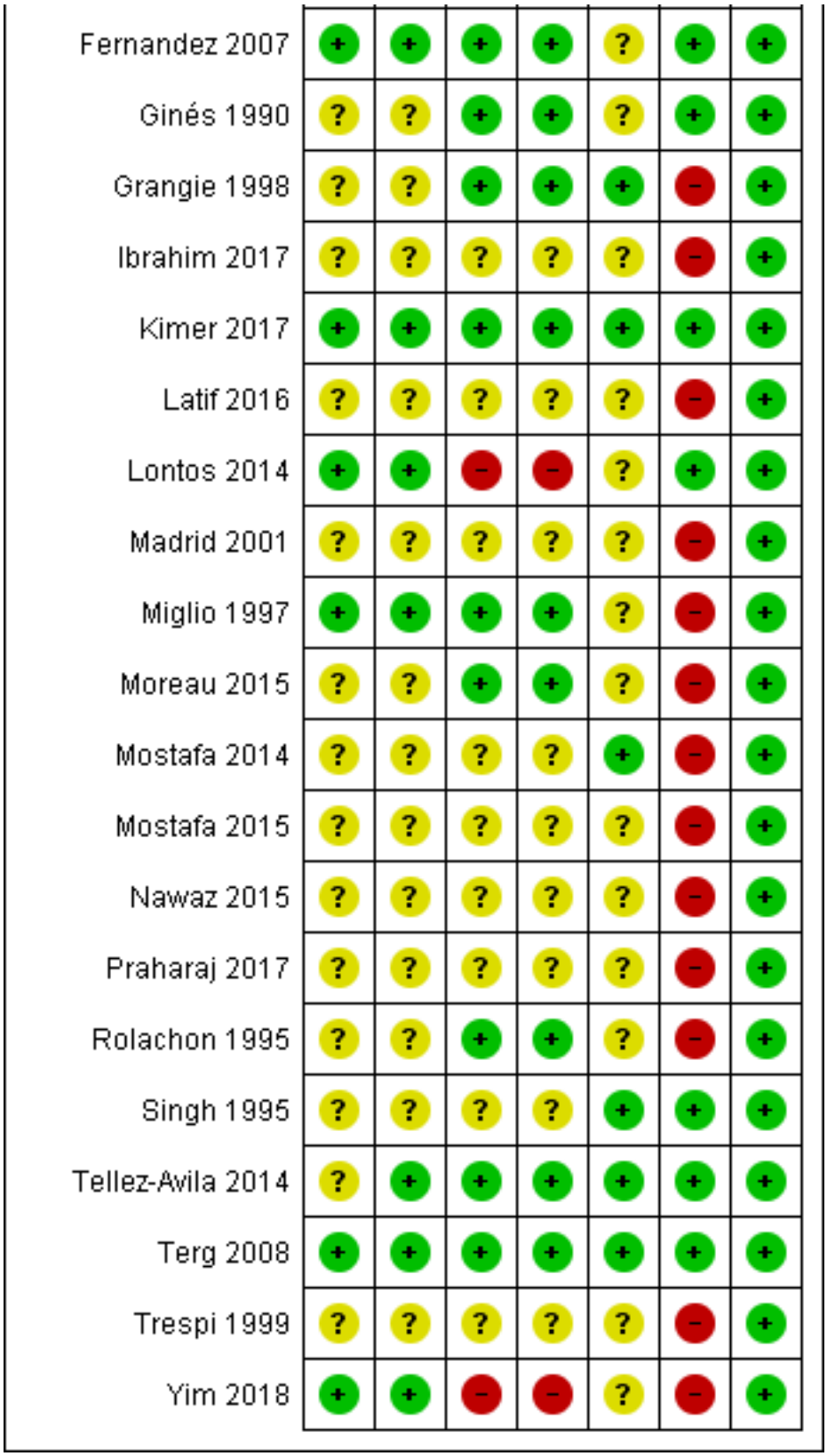


Figure 4. (Continued)



Allocation

Eight trials were at low risk of sequence generation bias (Miglio 1997; Fernandez 2007; Terg 2008; Lontos 2014; Assem 2016; Elfert 2016; Kimer 2017; Yim 2018); the remaining 21 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Bass 2010; Ali 2014; Mostafa 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Bajaj 2016; Latif 2016; Ibrahim 2017; Praharaj 2017).

Nine trials were at low risk of allocation concealment bias (Miglio 1997; Fernandez 2007; Terg 2008; Lontos 2014; Tellez-Avila 2014; Assem 2016; Elfert 2016; Kimer 2017; Yim 2018); the remaining 20 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Bass 2010; Ali 2014; Mostafa 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Bajaj 2016; Latif 2016; Ibrahim 2017; Praharaj 2017).

Blinding

Twelve trials were at low risk of blinding of trial participants and healthcare providers bias (Ginés 1990; Rolachon 1995; Miglio 1997; Grangie 1998; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Tellez-Avila 2014; Moreau 2015; Bajaj 2016; Kimer 2017); 12 trials, which did not provide sufficient information, were at unclear risk of blinding of participants and healthcare providers bias (Singh 1995; Trespi 1999; Madrid 2001; Alvarez 2005; Mostafa 2014; Baik 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Latif 2016; Ibrahim 2017; Praharaj 2017); the remaining five trials were at high risk of blinding of participants and healthcare providers bias (Bauer 2002; Lontos 2014; Assem 2016; Elfert 2016; Yim 2018).

The risk of blinding of outcome assessors' bias was the same as the risk of blinding of trial participants and healthcare providers' bias in the trials.

Incomplete outcome data

Nine trials were at low risk of incomplete outcome data bias (Singh 1995; Grangie 1998; Bauer 2002; Terg 2008; Bass 2010; Mostafa 2014; Tellez-Avila 2014; Elfert 2016; Kimer 2017); the remaining 20 trials were at unclear risk of incomplete outcome data bias, because it was not clear whether there were postrandomisation dropouts or whether the postrandomisation dropouts were related to the outcomes (if there were postrandomisation dropouts) (Ginés 1990; Rolachon 1995; Miglio 1997; Trespi 1999; Madrid 2001; Alvarez 2005; Fernandez 2007; Ali 2014; Lontos 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Assem 2016; Bajaj 2016; Latif 2016; Ibrahim 2017; Praharaj 2017; Yim 2018).

Selective reporting

Eleven trials were at low risk of selective outcome reporting bias (Ginés 1990; Singh 1995; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Lontos 2014; Tellez-Avila 2014; Assem 2016; Elfert 2016; Kimer 2017), as the protocol published prior to recruitment was available and the outcomes were reported or the important clinical outcomes expected to be reported in such trials were reported; the remaining 18 trials were at high risk of selective outcome reporting bias, as the trials did not report the reasonably expected clinical outcomes in the absence of a protocol published prior to recruitment (Rolachon 1995; Miglio 1997; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Ali 2014; Mostafa 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Abdel Motelleb 2016; Bajaj 2016; Latif 2016; Ibrahim 2017; Praharaj 2017; Yim 2018).

Other potential sources of bias

There was no other bias noted in the trials.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis; **Summary of findings 2** Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

The network plots (where relevant) are available in Figure 1. The inconsistency factor plots (where relevant) are available in Figure 5. The differences in the fixed-effect versus random-effects model where relevant are available in Figure 6. The model fit is available in Table 2. The effect estimates are available in Table 3.

Figure 5. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency for all-cause mortality and other decompensation, but there was evidence of inconsistency for adverse events number and SBP development. SBP: spontaneous bacterial peritonitis.
Note: The full images are available at doi.org/10.5281/zenodo.3457886.

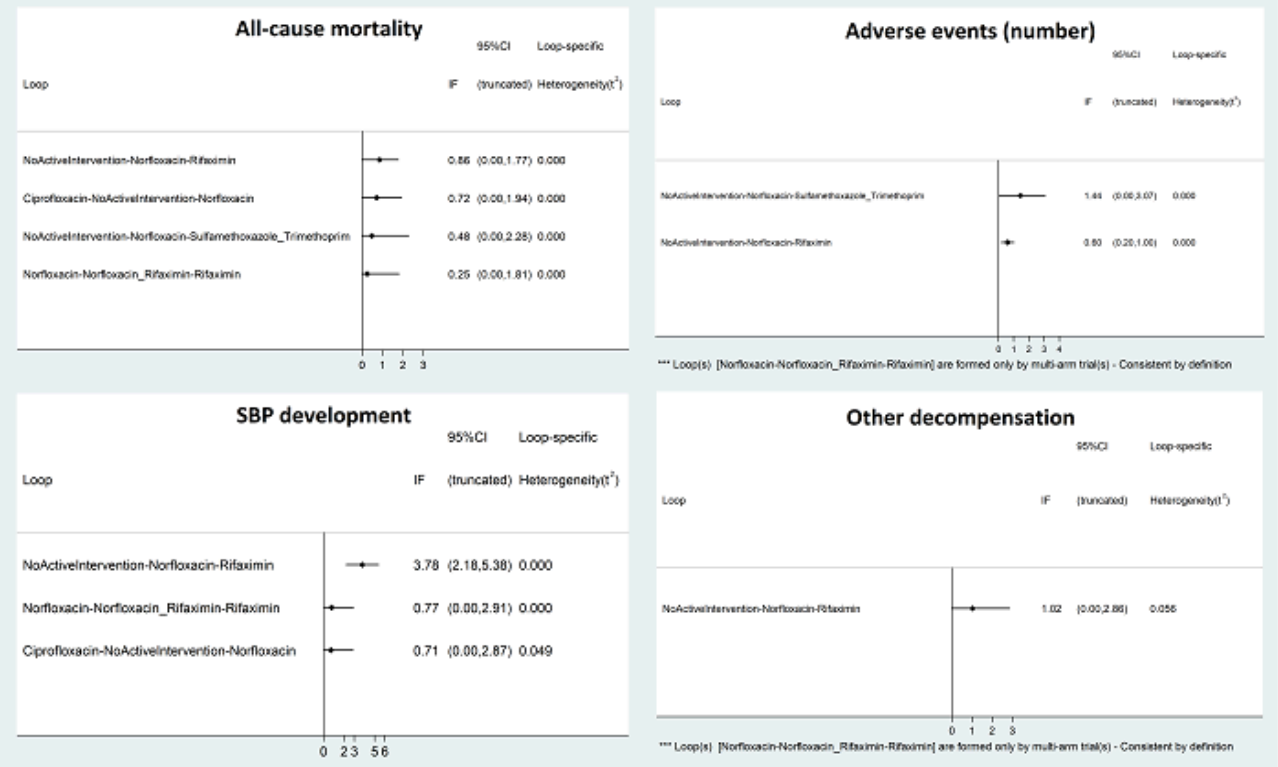
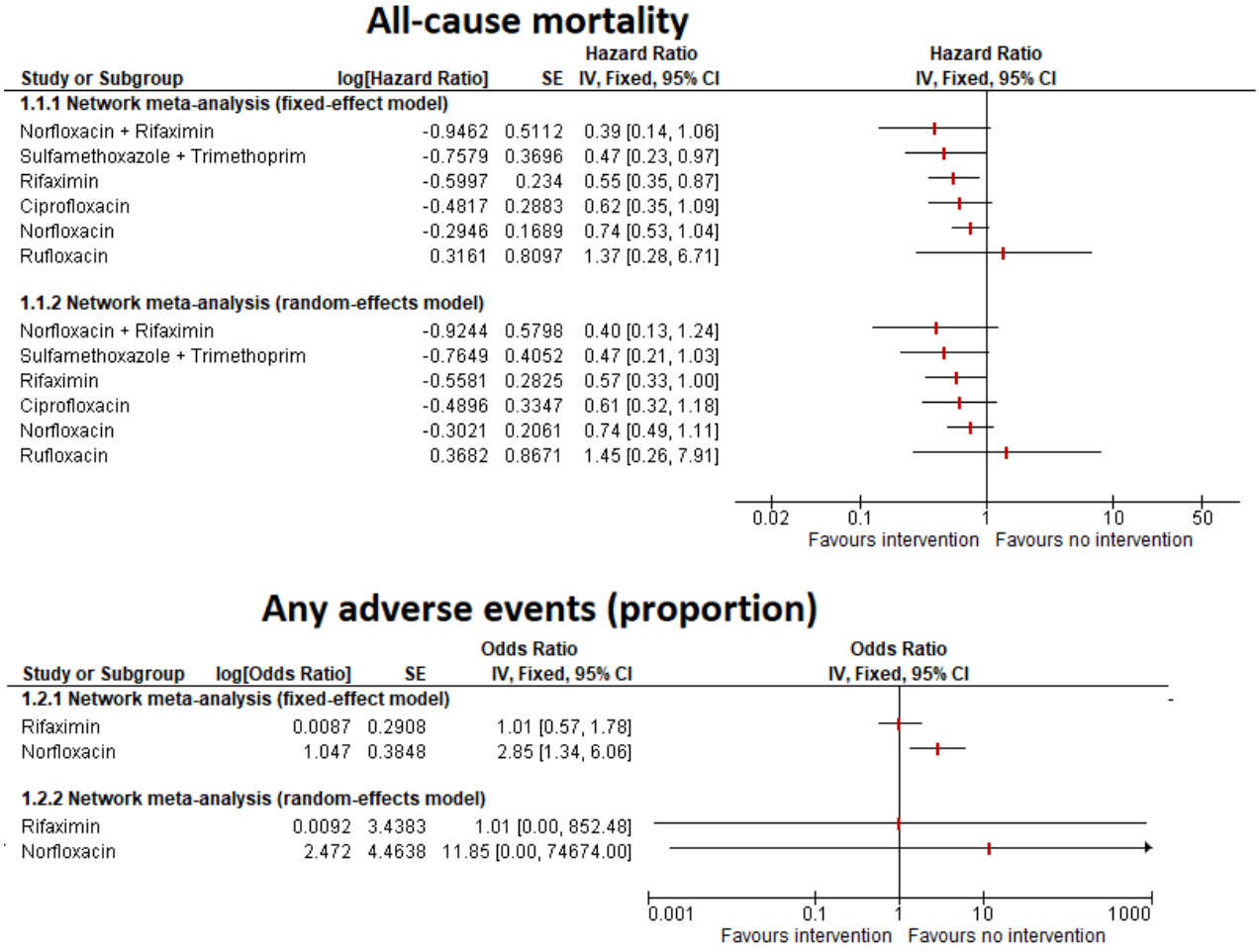


Figure 6. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used.



The 95% CrIs of the probability ranks were wide and included 0 and 1 in all the comparisons for all the primary and secondary outcomes. This was probably because of the sparse data from small trials. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots as we considered that presenting this information would be unhelpful and potentially misleading and ignore the differences in systematic errors in the trials.

The certainty of evidence was very low for all the comparisons. This was because 27 trials (all except Terg 2008 and Kimer 2017) were at unclear or high risk of bias for one or more risk of bias domains at the outcome level (downgraded one level), the sample size was small (downgraded one level), and the wide CrIs overlapping significant clinical effect and no effect (downgraded one level).

All-cause mortality

Seventeen trials (2169 participants) reported all-cause mortality (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Tellez-Avila 2014; Moreau 2015; Assem 2016; Elfert 2016; Kimer 2017; Yim 2018). These trials compared seven treatments (ciprofloxacin, neomycin, norfloxacin, norfloxacin plus neomycin, norfloxacin plus rifaximin, rifaximin, rufloxacin, sparfloxacin, sulfamethoxazole plus trimethoprim, and no active intervention). All the trials were connected to the network.

There was no evidence of inconsistency according to model fit (Table 2), 'between-design' variance (0.17, 95% CrI 0.00 to 3.49), or in the inconsistency factor plot (Figure 5). The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The 'between-study variance' was 0.03 (95% CrI 0.00 to 0.39).

There was no evidence of differences in any of the direct comparisons or in the network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons) (all comparisons: very low certainty evidence) (Table 3). The sensitivity analysis indicated that the different scenarios (best-worst and worst-best scenarios) for imputing missing data indicated different interpretation of results; therefore, the results were sensitive to the postrandomisation dropouts, and have to be interpreted with caution.

Health-related quality of life

None of the trials reported health-related quality of life.

Serious adverse events

Two trials (332 participants) reported proportion of people with serious adverse events (Mostafa 2015; Elfert 2016). Both trials compared rifaximin versus norfloxacin. There were no serious events in either group in the two trials (Mostafa 2015; Elfert 2016) (very low certainty evidence).

Five trials (797 participants) reported number of serious adverse events per participant (Bass 2010; Mostafa 2015; Elfert 2016; Kimer 2017; Yim 2018). These trials compared four treatments. Two trials (332 participants) comparing rifaximin and norfloxacin were not connected to the network because they had zero events in both arms (Mostafa 2015; Elfert 2016); one trial was not connected to the network because of unconnected treatments once the trials with zero events in both arms was excluded (Yim 2018): therefore, these three trials were excluded from the network. Only two treatments (rifaximin versus no active intervention) were compared in the remaining two trials. Therefore, network meta-analysis or checking for inconsistency was not applicable. The fixed-effect model was used because it had equivalent results and model fit as random-effects model. There was no evidence of differences (i.e. there was no statistically significant difference in any of the comparisons) between rifaximin and no active intervention (RaR 1.66, 95% CrI 0.98 to 2.90; 2 trials, 353 participants; very low-certainty evidence) or between ciprofloxacin and norfloxacin (RaR 1.63, 95% CrI 0.85 to 3.24; 1 trial, 112 participants; very low-certainty evidence).

Any adverse events

Three trials (631 participants) reported proportion of people with any adverse events (Bass 2010; Mostafa 2015; Elfert 2016). These trials compared three treatments. All the trials were connected to the network. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because it was more conservative and there was significant between-study heterogeneity (the 'between-study variance' was 9.28, 95% CrI 0.12 to 24.10), even though the model fit was similar to the fixed-effect model. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons) (Table 3). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Fifteen trials (1734 participants) reported number of any adverse events per participant (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Lontos 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Assem 2016; Kimer 2017). These trials compared seven treatments. All the trials were connected to the network. There was evidence of inconsistency according to model fit, inconsistency factor (one loop involving 'no active intervention', norfloxacin, and rifaximin), and the 'between-design' variance (1.51, 95% CrI 0.03 to 18.25); therefore, there is uncertainty in the validity of the network meta-analysis results. The direct comparisons are more reliable. We did not attempt to exclude the studies causing the inconsistency since the three interventions in the inconsistent loop were the three main interventions compared in this review and the differences may be due to the different definitions used for adverse events across the comparisons (none of the trials used the ICH-GCP definition). Therefore, only the direct comparison results are presented. The fixed-effect model was used because it had equivalent results and model fit as random-effects model.

The following direct comparisons were statistically significant favouring antibiotic prophylaxis:

- Norfloxacin versus 'no active intervention': RaR 0.74 (95% CrI 0.59 to 0.94; 4 trials, 546 participants; low-certainty evidence).
- Sulfamethoxazole plus trimethoprim versus 'no active intervention': RaR 0.19 (95% CrI 0.02 to 0.81; 1 trial, 60 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant).

- Rifaximin versus 'no active intervention': RaR 1.15 (95% CrI 0.98 to 1.34; 3 trials, 418 participants; very low-certainty evidence).
- Ciprofloxacin versus 'no active intervention': RaR 0.72 (95% CrI 0.49 to 1.05; 3 trials, 255 participants; very low-certainty evidence).
- Norfloxacin versus rifaximin: RaR 1.18 (95% CrI 0.88 to 1.58; 1 trial, 160 participants; very low-certainty evidence).
- Norfloxacin plus rifaximin versus rifaximin: RaR 0.95 (95% CrI 0.71 to 1.29; 1 trial, 161 participants; very low-certainty evidence).
- Sulfamethoxazole plus trimethoprim versus norfloxacin: RaR 1.27 (95% CrI 0.79 to 2.11; 2 trials, 137 participants; very low-certainty evidence).
- Norfloxacin plus rifaximin versus norfloxacin: RaR 0.81 (95% CrI 0.60 to 1.08; 1 trial, 157 participants; very low-certainty evidence).
- Rufloxacin versus norfloxacin: RaR 1.60 (95% CrI 0.79 to 3.54; 1 trial, 79 participants; very low-certainty evidence).

Liver transplantation

Four trials (339 participants) reported liver transplantation (Bauer 2002; Fernandez 2007; Lontos 2014; Yim 2018). These trials compared five treatments. There were 55 liver transplants in total (16.2%). One trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the arms (Bauer 2002), and therefore excluded from the network. The network had four connected treatments. The three connected trials included 260 participants. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. Only one trial was included in each of the comparisons; therefore, only fixed-effect model is applicable.

The following direct comparisons were statistically significant.

- There were more liver transplants with sulfamethoxazole plus trimethoprim versus norfloxacin: HR 2.71 (95% CrI 1.10 to 7.59; 1 trial, 80 participants; low-certainty evidence).
- There were fewer liver transplants with rufloxacin versus norfloxacin: there were 0/39 (0%) liver transplants in the rufloxacin group compared to 8/40 (20%) in the norfloxacin group (1 trial, 79 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant).

In the network meta-analysis, the following comparison was statistically significant.

- Sulfamethoxazole plus trimethoprim versus norfloxacin: HR 2.74 (95% CrI 1.12 to 7.08; low-certainty evidence). This was consistent with that of the direct comparison.

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (Table 3). The sensitivity analysis indicated that the different scenarios (best-worst and worst-best scenarios) for imputing missing data indicated different interpretation of results; therefore, the results have to be interpreted with caution.

Proportion with spontaneous bacterial peritonitis

None of the trials reported proportion with symptomatic spontaneous bacterial peritonitis. Sixteen trials (1564 participants) reported proportion with spontaneous bacterial peritonitis (as per definition) (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Lontos 2014; Tellez-Avila 2014; Assem 2016; Elfert 2016; Kimer 2017; Praharaj 2017; Yim 2018). These trials compared seven treatments. One trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the arms (Singh 1995), and therefore was excluded from the network. All the seven treatments were connected. Fifteen trials (1504 participants) were included in the network.

There was evidence of inconsistency according to inconsistency factor (one loop involving 'no active intervention', norfloxacin, and rifaximin), and the 'between-design' variance 4.34 (95% CrI 0.29 to 21.57), but not by model fit. We did not attempt to exclude the studies causing the inconsistency since the three interventions in the inconsistent loop were the three main interventions compared in this review; the definitions used for spontaneous bacterial peritonitis development was similar in the trials, suggesting that the differences across comparisons could not be explained by the heterogeneity in the definitions used across comparisons. Therefore, only the direct comparison results are presented.

In the direct comparison, the incidence of spontaneous bacterial peritonitis was 0/30 in the sulfamethoxazole plus trimethoprim group versus 4/30 in the no active intervention group (1 trial, 60 participants). The HR could not be estimated because of zero events in the sulfamethoxazole plus trimethoprim group and the upper and lower CrI of the HR was very close to zero (very low-certainty evidence).

There was no evidence of differences in the remaining direct comparisons.

- Rifaximin versus no active intervention: HR 7.80 (95% CrI 0.13 to 4647.11; 2 trials, 106 participants; very low-certainty evidence).
- Norfloxacin versus no active intervention: HR 0.16 (95% CrI 0.00 to 1.56; 3 trials, 255 participants; very low-certainty evidence).
- Ciprofloxacin versus no active intervention: HR 0.56 (95% CrI 0.02 to 60.64; 3 trials, 255 participants; very low-certainty evidence).
- Norfloxacin versus rifaximin: HR 3.59 (95% CrI 0.46 to 33.18; 3 trials, 481 participants; very low-certainty evidence).
- Norfloxacin plus rifaximin versus rifaximin: HR 0.59 (95% CrI 0.11 to 2.51 ; 1 trial, 161 participants; very low-certainty evidence).
- Ciprofloxacin versus norfloxacin: HR 0.68 (95% CrI 0.12 to 3.49; 1 trial, 112 participants; very low-certainty evidence).
- Sulfamethoxazole plus trimethoprim versus norfloxacin: HR 1.48 (95% CrI 0.42 to 5.45; 2 trials, 137 participants; very low-certainty evidence).
- Norfloxacin plus rifaximin versus norfloxacin: HR 0.29 (95% CrI 0.06 to 1.04; 1 trial, 157 participants; very low-certainty evidence).
- Rufloxacin versus norfloxacin: HR 2.31 (95% CrI 0.88 to 6.70; 1 trial, 79 participants; very low-certainty evidence).

Number of decompensation episodes

Eight trials (1275 participants) reported number of other decompensation events (Ginés 1990; Madrid 2001; Fernandez 2007; Bass 2010; Ali 2014; Moreau 2015; Nawaz 2015; Assem 2016). From the information available in the trials, it was unclear whether each participant developed only one decompensation event. Therefore, we analysed this outcome as a count outcome. These trials compared five treatments. All the trials were connected to the network. There was no evidence of inconsistency according to the 'between-design' variance: 1.49 (95% CrI 0.00 to 21.25), inconsistency factor, or model fit. The fixed-effect model was used because it had equivalent results and model fit as random-effects model.

The following direct comparisons were statistically significant (Table 3).

- Rifaximin versus 'no active intervention': RaR 0.63 (95% CrI 0.48 to 0.82; 3 trials, 575 participants; low-certainty evidence).
- Norfloxacin plus neomycin versus 'no active intervention': RaR 0.05 (95% CrI 0.00 to 0.34; 1 trial, 22 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) (very low certainty evidence).

In the network meta-analysis, the following comparisons were statistically significant (Table 3).

- Rifaximin versus 'no active intervention': RaR 0.61 (95% CrI 0.46 to 0.80; low-certainty evidence).
- Norfloxacin plus neomycin versus 'no active intervention': RaR 0.06 (95% CrI 0.00 to 0.33; low-certainty evidence).
- Norfloxacin plus neomycin versus rifaximin: RaR 0.09 (95% CrI 0.00 to 0.55; low-certainty evidence).
- Norfloxacin plus neomycin versus norfloxacin: RaR 0.07 (95% CrI 0.00 to 0.43; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (very low-certainty evidence).

Length of hospital stay

Two trials (139 participants) reported length of hospital stay (Rolachon 1995; Bauer 2002). These trials compared four different treatments. The trials were not connected by common treatments. Therefore, only direct comparisons were performed. Only one trial

was included in each of the comparisons; therefore, we estimated the effect estimates from a single trial for each comparison.

Ciprofloxacin had lower length of hospital stay versus 'no active intervention' (MD −8.29 days, 95% CrI −11.09 to −5.50; 1 trial, 60 participants; low-certainty evidence). There was no evidence of a difference between the treatments in the remaining direct comparison between rufloxacin and norfloxacin (MD −0.70 days, 95% CrI −5.07 to 3.65; 1 trial, 79 participants; very low-certainty evidence). There was no imputation of mean or standard deviation; therefore, sensitivity analysis was not applicable.

Number of days of lost work

None of the trials reported number of days of lost work.

Treatment costs

None of the trials reported treatment costs.

Subgroup analysis

Data were sufficient to perform the following subgroup analyses: ascites with low protein; primary prophylaxis; and duration of follow-up (short-term versus medium term). There was insufficient data for the remaining subgroup analyses or only one subgroup was represented in the analyses. There were no subgroup differences for any of the outcomes where there was at least two different subgroups represented in the analyses (all-cause mortality, number of serious adverse events per participant, or other decompensation events). There was no convergence for model fit procedures of the subgroup analysis for proportion of any adverse events, probably because of the complex model with sparse data (only three trials with three connected treatments) and liver transplantation (only three trials with four connected treatments). Only direct comparisons were performed for number of 'any adverse events' per participant and spontaneous bacterial peritonitis; the number of studies included in each direct comparison was insufficient to perform the subgroup analyses.

Assessment of reporting biases

Since there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we were unable to perform the comparison-adjusted funnel plot. Many trials did not report outcomes such as mortality, adverse events, or decompensation events, outcomes that are likely to have been recorded in a trial of this nature.

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of all the antibiotic prophylaxis for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis. We included 29 trials including 3896 participants. The trials compared 10 interventions. A total of 23 trials including 2587 participants were included for one or more outcomes of this review (Ginés 1990; Rolachon 1995; Singh 1995; Grangie 1998; Trespi 1999; Madrid 2001; Bauer 2002; Alvarez 2005; Fernandez 2007; Terg 2008; Bass 2010; Ali 2014; Lontos 2014; Tellez-Avila 2014; Baik 2015; Moreau 2015; Mostafa 2015; Nawaz 2015; Assem 2016; Elfert 2016; Kimer 2017; Praharaj 2017; Yim 2018).

Overall, 15% of the trial participants died within one year. There was no evidence of a difference in mortality or serious adverse events in any of the direct comparisons or network meta-analysis. However, the CrIs were wide, and clinically important differences in mortality or serious adverse events could not be ruled out. The number of any adverse events per participant was fewer with norfloxacin and sulfamethoxazole plus trimethoprim than with no active intervention. There were some comparisons in which there were differences in any adverse events per participant; liver transplantation; spontaneous bacterial peritonitis development; other decompensation events; and length of hospital stay. One would expect some correlation between outcomes (i.e. if the intervention was effective, it is expected to be effective across these outcomes). This was not the case. The possible reasons for this include sparse data and selective reporting bias. Since these outcomes are likely to be measured routinely in a clinical trial of this nature, but were not reported in many of the trials, one has to suspect selective outcome reporting bias strongly (i.e. the trial authors were reporting outcomes based on the direction of the results). This makes the results unreliable. Therefore, one cannot draw any conclusions from these inconsistent differences based on sparse data.

In terms of the design of a future trial to answer the research question, the median control group (no active intervention) mortality within 12 months was 18.4%. The sample size required to detect a relative risk reduction of 20% in the experimental group, type I error of 5%, and type II error of 20% was 3202 participants. Given that approximately 20% of people with liver cirrhosis develop ascites, the conduct of this trial is feasible. Development of spontaneous bacterial peritonitis may not be a good primary outcome in such a trial since the median control group (no active intervention) was 14.0%, which was less than the mortality. Since similar trials reported development of spontaneous bacterial peritonitis, it appears that people with ascites were dying of other causes besides spontaneous bacterial peritonitis. In the trials that reported the causes of mortality, the cause of death was due to spontaneous bacterial peritonitis and other decompensation events. There were approximately 46 other decompensation events per 100 participants (in addition to spontaneous bacterial peritonitis development) in the 'no active intervention' group (i.e. about 60 events in total in the 'no active intervention group'). In addition to causing death, decompensation usually results in hospital admissions and significant costs. Therefore, 'any decompensation event' is another possible primary outcome. Assuming that the variance was equal to the mean in an ordinary Poisson distribution commonly used to analyse recurrent events (that happen independently, although this is a questionable assumption), a 20% relative risk reduction in the experimental group, type I error of 5%, and type II error of 20%, the sample size required in a trial using any decompensation event is 786 participants.

In terms of the interventions to be compared, the American Association For the Study of Liver Diseases (AASLD) and the EASL both suggest that people with ascites with low protein or those who had previous episodes of spontaneous bacterial peritonitis receive norfloxacin as antibiotic prophylaxis. Despite the uncertainty in its effectiveness, it could be one of the interventions in a future trial, as it might prove to be difficult to recruit participants into a trial with 'no active intervention' because of the recommendations in these

guidelines. However, this might be possible in people with cirrhosis at low risk of spontaneous bacterial peritonitis.

Rifaximin is potentially effective in preventing recurrent hepatic encephalopathy (Bass 2010). Therefore, rifaximin can be one of the other interventions compared. While there is no high-certainty evidence indicating that these interventions are better than no antibiotics for major outcomes such as mortality and the trials included for different outcomes were different suggesting the possibility of selective reporting bias, it is unclear whether patients will accept to be randomised to 'no active intervention' ('no intervention' or 'placebo') and clinicians will randomise participants in a trial with 'no active intervention' as one of the arms. Therefore, further involvement of patients and clinicians in qualitative research is necessary in the design of such as trial.

Overall completeness and applicability of evidence

The trials included a wide variety of people with cirrhosis having ascites with low protein or previous history of spontaneous bacterial peritonitis. However, it was unclear whether any of the trials included participants with no previous history of spontaneous bacterial peritonitis and had normal protein in their ascites. Therefore, the findings of this review are applicable only in people with cirrhosis having ascites with low protein or previous history of spontaneous bacterial peritonitis.

There did not seem to be any restrictions based on the aetiology or the presence of other features of decompensation in the trials that provided this information. Therefore, the results of the study are applicable in all people with cirrhosis having ascites with low protein or previous history of spontaneous bacterial peritonitis. We excluded trials in which participants had undergone liver transplantation. Therefore, the findings of this review are not applicable in people with ascites secondary to liver decompensation after liver transplantation.

Quality of the evidence

The overall certainty (quality) of evidence was low or very low. One of the main reasons for the very low certainty of evidence was the unclear or high risk of bias in many of the trials. It is possible to perform trials of low risk of bias in the field. To perform a low risk of bias trial, randomisation can be performed using standard methods, for example, web-based central randomisation; blinding of parties involved can be achieved by using double-placebo design even if two interventions at different frequencies are given (i.e. a placebo for intervention and a placebo for control); an intention-to-treat analysis can be performed; and a protocol can be published prior to recruitment. None of these have any major ethical considerations; therefore, a low risk of bias trial is very much feasible.

Another major reason for very low certainty of evidence was imprecision: the trials had small sample sizes and the CrIs overlapped clinically significant benefits and clinically significant harms for most comparisons. Therefore, future trials should be adequately powered with sample sizes as described in the Summary of main results section.

We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons (i.e. there was no concern about transitivity assumption). There was no evidence of inconsistency in most of the outcomes (except number of 'any adverse events'). However, one cannot rule out inconsistency ('incoherence' according to GRADE terminology). There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. However, different sets of trials were included for different outcomes. It is extremely likely that trials in this group of patients measured adverse events, decompensation events, and liver transplantation during the follow-up period; nevertheless, many trials did not report these outcomes suggesting reporting bias.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions and conducted the network meta-analysis where appropriate according to NICE DSU guidance. In addition, we analysed data using the fixed-effect model and random-effects model, and assessed and reported inconsistency whenever possible. These are the strengths of the review process.

We excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation is better than another. Another major limitation of this review was the paucity of data: the trials were small. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials, most of which were at high risk of bias. However, the potential effect modifiers in the trials that reported them were broadly similar across comparisons. The results of direct comparisons and indirect comparisons were similar for the outcomes where we could assess this. Therefore, the concern about transitivity assumption was low. However, lack of transitivity could not be ruled out.

We included only randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. Therefore, it is possible that we missed a large number of non-randomised studies addressing reporting of harms. A significant effort is required to identify the non-randomised studies and assess the risk of bias in those studies. Since it is possible to conduct future studies powered on mortality (which is likely to be sufficient to identify any clinically meaningful differences in health-related quality of life), a systematic review on adverse events appears to be unnecessary. This is because of the uncertainty in the benefits of different treatments; in addition, the patients are likely to give more importance to mortality and quality of life than adverse events.

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on the topic. There have been several systematic reviews on antibiotic prophylaxis in people with cirrhosis having ascites with low protein or previous history of spontaneous bacterial peritonitis (Cohen 2009; Goel 2017; Kamal 2017; Sidhu 2017).

Cohen 2009 pooled all antibiotic prophylaxis versus no prophylaxis. They found that the trials, which were at high risk of bias, found lower mortality and incidence of spontaneous bacterial peritonitis

with antibiotic prophylaxis, but they highlighted that there is uncertainty about the effectiveness because of the risk of bias in the trials. We have treated different antibiotic prophylaxes as different interventions in this review and used Bayesian analysis (which is more conservative than frequentist meta-analysis (unpublished data by the Cochrane Methods Group), which may be the reason for finding that there was no evidence of difference in mortality.

The other systematic reviews compared rifaximin versus other antibiotics or 'no active treatment' (Goel 2017; Kamal 2017; Sidhu 2017). All three systematic reviews included randomised and non-randomised studies and found that rifaximin may be more effective in preventing spontaneous bacterial peritonitis than other antibiotics and 'no active treatment'. Inclusion of non-randomised studies and pooling all systemic antibiotics into one group may be the reason for the differences in their conclusions and those of our systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

Based on very low-certainty evidence, there is considerable uncertainty about whether antibiotic prophylaxis is beneficial and if beneficial, which antibiotic prophylaxis is most beneficial in people with cirrhosis having ascites with low protein or history of spontaneous bacterial peritonitis.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials are as follows.

Study design: placebo-controlled, parallel, randomised clinical trial.

Participants: people with liver cirrhosis and ascites.

Intervention: rifaximin, norfloxacin, or a combination of the two.

Control: no active intervention (if it is feasible to include this as one of the control groups). No active intervention may be as feasible as control in people at low risk of spontaneous bacterial peritonitis.

Outcomes:

Primary outcome: medium-term mortality (one-year all-cause mortality).

Secondary outcomes: health-related quality of life; decompensation events; adverse events; incidence of spontaneous bacterial peritonitis; and resource utilisation measures including length of hospital stay.

Minimum length of follow-up: one year.

Sample size: for a simple two-arm parallel randomised clinical trial, the sample size required to detect a relative risk reduction of 20% in the experimental group from the control group proportion of 18.4% mortality, type I error of 5%, and type II error of 20%, 3202 participants are required. For participants at low risk of spontaneous bacterial peritonitis, there is no information to calculate the sample size from this systematic review. A feasibility randomised clinical trial can provide the potential effect size and allow sample size calculations.

Other aspects: trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and CONSORT statement (Schulz 2010).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdel Motelleb 2016

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: not stated Number randomised: 333 Postrandomisation dropouts: not stated Revised sample size: 333 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 333 (100%) Ascites with low protein: 333 (100%) Primary prophylaxis: 333 (100%)

Abdel Motelleb 2016 *(Continued)*

	Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated
Interventions	Participants randomly assigned to 3 groups. Group 1: norfloxacin + rifaximin (n = not stated) Further details: norfloxacin + rifaximin (no further details) for 6 months Group 2: norfloxacin (n = not stated) Further details: norfloxacin (no further details) for 6 months Group 3: rifaximin (n = not stated) Further details: rifaximin (no further details) for 6 months No information on the number of participants in each group
Outcomes	None of the outcomes of interest were reported. Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Single-blind." Comment: further information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Single-blind." Comment: further information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Ali 2014

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2012–2013 Number randomised: 126 Postrandomisation dropouts: not stated Revised sample size: 126 Mean age (years): 42 Females: 66 (52.4%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 126 (100%) Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 4 (3.2%) Viral-related cirrhosis: 120 (95.2%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 2 (1.6%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • ≥ 2 episodes of hepatic encephalopathy Exclusion criteria: • hypersensitivity to rifamycin and its products • calcium level > 10 mg/dL • hepatocellular carcinoma • comorbidities such as chronic kidney disease, respiratory insufficiency, and cerebrovascular injury
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 63) Further details: rifaximin 550 mg BD for 6 months or until recurrence of hepatorenal syndrome Group 2: no active intervention (n = 63) Further details: placebo for 6 months
Outcomes	Outcomes reported: all-cause mortality; number of other decompensation events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.
Risk of bias	

Ali 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Triple blind randomized placebo-controlled trial… The patients, the investigator and the statistician did not know which patients were receiving Rifaximin and which were being given placebo."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Triple blind randomized placebo-controlled trial… The patients, the investigator and the statistician did not know which patients were receiving Rifaximin and which were being given placebo."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Alvarez 2005

Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 1999–2001 Number randomised: 57 Postrandomisation dropouts: not stated Revised sample size: 57 Mean age (years): 48 Females: 19 (33.3%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: 28 (49.1%) Primary prophylaxis: 35 (61.4%) Alcohol-related cirrhosis: 20 (35.1%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 37 (64.9%)

Alvarez 2005 *(Continued)*

	Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated
Interventions	Participants randomly assigned to 2 groups. Group 1: sulfamethoxazole + trimethoprim (n = 25) Further details: sulfamethoxazole 160 mg + trimethoprim 800 mg daily for 5 days a week (duration not stated, but probably until follow-up Group 2: norfloxacin (n = 32) Further details: norfloxacin 400 mg daily for 5 days a week (duration not stated, but probably until follow-up)
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Assem 2016

Methods	Randomised clinical trial
Participants	Country: Saudi Arabia and Egypt Period of recruitment: 2014–2015 Number randomised: 239

Assem 2016 *(Continued)*

	Postrandomisation dropouts: not stated Revised sample size: 239 Mean age (years): 57 Females: 63 (26.4%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 56 (23.4%) Ascites with low protein: not stated Primary prophylaxis: 239 (100%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 222 (92.9%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 17 (7.1%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • people with resolving ascites for 1 month after diuretic therapy • uncontrolled diabetes mellitus • liver malignancy • organic renal disease • HIV infection • known hypersensitivity to planned drugs
Interventions	Participants randomly assigned to 3 groups. Group 1: rifaximin + norfloxacin (n = 79) Further details: rifaximin 550 mg BD orally for 1 month, alternating with norfloxacin 400 mg OD for 1 month, total duration 6 months Group 2: norfloxacin (n = 78) Further details: norfloxacin 400 mg OD orally for 6 months Group 3: rifaximin (n = 82) Further details: rifaximin 550 mg BD orally for 6 months
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition); number of other decompensation events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Enrolled patients were randomly allocated to three groups by using consecutively numbered, computer-generated envelopes."

Assem 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Enrolled patients were randomly allocated to three groups by using consecutively numbered, computer-generated envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open-label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: appeared some people were excluded from some outcomes, but information not clear.
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Baik 2015

Methods	Randomised clinical trial
Participants	Country: South Korea Period of recruitment: 2011–2013 Number randomised: 65 Postrandomisation dropouts: not stated Revised sample size: 65 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • people with advanced cirrhosis (no further details on how advanced cirrhosis was defined)

Baik 2015 *(Continued)*

Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 17) Further details: rifaximin 1200 mg/day for 3 months Group 2: no active intervention (n = 48) Further details: no treatment Additional details: both groups received propranolol
Outcomes	Outcomes reported: number of any adverse events per participant Follow-up (months): 3
Notes	Attempted to contact authors in November 2018, but received no replies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Bajaj 2016

Methods	Randomised clinical trial
Participants	Country: USA and Russia Period of recruitment: not stated Number randomised: 518 Postrandomisation dropouts: 2 (0.4%)

Bajaj 2016 *(Continued)*

	Revised sample size: 516 Reasons for postrandomisation dropouts: not stated Mean age (years): 57 Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 516 (100%) Alcohol-related cirrhosis: 125 (24.2%) Viral-related cirrhosis: 160 (31.0%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 231 (44.8%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • people with Grade I ascites Exclusion criteria: • history of oesophageal bleeding
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 422) Further details: rifaximin 40–160 mg (immediate release and soluble solid dispersion) for 24 weeks Group 2: no active intervention (n = 94) Further details: placebo for 24 weeks
Outcomes	None of the outcomes of interest were reported. Follow-up (months): 6
Notes	Trial name/trial registry number: NCT01904409 Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double-blind placebo-controlled trial."

Bajaj 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind placebo-controlled trial."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Bass 2010

Methods	Randomised clinical trial
Participants	Country: USA, Canada, Russia Period of recruitment: 2005–2008 Number randomised: 299 Postrandomisation dropouts: 0 (0%) Revised sample size: 299 Mean age (years): 56 Females: 117 (39.1%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 299 (100%) Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • ≥ 2 episodes of overt hepatic encephalopathy Exclusion criteria: • gastrointestinal bleeding • recent portosystemic shunt or transjugular intrahepatic portosystemic shunt • comorbidities such as chronic renal insufficiency or respiratory insufficiency • electrolyte insufficiency

Bass 2010 *(Continued)*

Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 140) Further details: rifaximin 550 mg BD for 6 months or until recurrence of hepatorenal syndrome Group 2: no active intervention (n = 159) Further details: placebo for 6 months
Outcomes	Outcomes reported: all-cause mortality; number of serious adverse events per participant; proportion of people with any adverse events; number of any adverse events per participant; number of other decompensation events. Follow-up (months): 6
Notes	Trial name/trial registry number: NCT00298038 Attempted to contact authors in November 2018, but received no replies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind placebo-controlled trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind placebo-controlled trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Bauer 2002

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: 79

Bauer 2002 *(Continued)*

	Postrandomisation dropouts: 0 (0%) Revised sample size: 79 Mean age (years): 60 Females: 24 (30.4%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 52 (65.8%) Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: 24 (30.4%) Viral-related cirrhosis: 51 (64.6%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 3 (3.8%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • advanced liver failure • chronic hepatic encephalopathy • moderate or severe renal failure • presence of hepatocellular carcinoma • known or suspected hypersensitivity to quinolones • selective intestinal decontamination with norfloxacin prior to the index episode of spontaneous bacterial peritonitis
Interventions	Participants randomly assigned to 2 groups. Group 1: rufloxacin (n = 39) Further details: rufloxacin 400 mg once weekly (after loading doses) orally (duration not stated, but appeared continuous) Group 2: norfloxacin (n = 40) Further details: norfloxacin 400 mg OD orally (duration not stated, but appeared continuous)
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; liver transplantation; proportion with spontaneous bacterial peritonitis (as per definition); length of hospital stay. Follow-up (months): 7
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Bauer 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open randomized clinical trial."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open randomized clinical trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Elfert 2016

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: 2014 Number randomised: 262 Postrandomisation dropouts: 0 (0%) Revised sample size: 262 Mean age (years): 54 Females: 120 (45.8%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • previous allergy to quinolones • recent gastrointestinal bleeding • hepatocellular carcinoma or other neoplasias that could shorten life expectancy • people who had already taken antibiotics • recent intake of quinolones in the last 6 weeks

Elfert 2016 *(Continued)*

- HIV infection
- hepatic encephalopathy
- pregnant and lactating women

Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 131) Further details: norfloxacin 400 mg daily for 6 months Group 2: rifaximin (n = 131) Further details: rifaximin 400 mg TDS for 6 months
Outcomes	Outcomes reported: all-cause mortality; proportion of people with serious adverse events; number of serious adverse events per participant; proportion of people with any adverse events; proportion with spontaneous bacterial peritonitis (as per definition). Follow-up (months): 6
Notes	Trial name/trial registry number: NCT02120196 Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized using a computer random number generator."
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered, opaque, sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open-label."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Fernandez 2007

Methods	Randomised clinical trial
Participants	Country: Spain

Fernandez 2007 *(Continued)*

	Period of recruitment: 2000–2004 Number randomised: 74 Postrandomisation dropouts: 6 (8.1%) Revised sample size: 68 Reasons for postrandomisation dropouts: not stated Mean age (years): 62 Females: 23 (33.8%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 24 (35.3%) Ascites with low protein: 68 (100%) Primary prophylaxis: 68 (100%) Alcohol-related cirrhosis: 36 (52.9%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 5 (7.4%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • previous spontaneous bacterial peritonitis or norfloxacin prophylaxis • allergy to quinolones • hepatocellular carcinoma • organic renal failure • HIV infection
Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 35) Further details: norfloxacin 400 mg daily (duration not stated, but probably to end of follow-up) Group 2: no active intervention (n = 33) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; liver transplantation; proportion with spontaneous bacterial peritonitis (as per definition); number of other decompensation events. Follow-up (months): 12
Notes	Trial name/trial registry number: NCT00359853 Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement

Fernandez 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using consecutively numbered, computer-generated envelopes containing treatment assignment."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using consecutively numbered, computer-generated envelopes containing treatment assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, randomized, placebo-controlled trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, randomized, placebo-controlled trial."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts; unclear whether these could be related to treatment.
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Ginés 1990

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1987–1989 Number randomised: 80 Postrandomisation dropouts: not stated Revised sample size: 80 Mean age (years): 58 Females: 26 (32.5%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: 46 (57.5%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 34 (42.5%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated
Interventions	Participants randomly assigned to 2 groups.

Ginés 1990 *(Continued)*

	Group 1: norfloxacin (n = 40) Further details: norfloxacin 400 mg daily (duration not stated, but probably to end of follow-up) Group 2: no active intervention (n = 40) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition); number of other decompensation events. Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, multicenter, placebo-controlled study… Each patient's assigned drug was known only by the pharmacy."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, multicenter, placebo-controlled study… Each patient's assigned drug was known only by the pharmacy."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Grangie 1998

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1991–1993 Number randomised: 107 Postrandomisation dropouts: 0 (0%) Revised sample size: 107 Mean age (years): 55

Grangie 1998 *(Continued)*

	Females: 38 (35.5%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 107 (100%) Alcohol-related cirrhosis: 93 (86.9%) Viral-related cirrhosis: 10 (9.3%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 4 (3.7%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • active gastrointestinal bleeding • hepatocellular carcinoma or other life-threatening disease
Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 53) Further details: norfloxacin 400 mg daily (duration not stated, but probably to end of follow-up) Group 2: no active intervention (n = 54) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo-controlled."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, placebo-controlled."
Incomplete outcome data (attrition bias)	Low risk	Comment: no postrandomisation dropouts

Grangie 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Ibrahim 2017

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: not stated Number randomised: 80 Postrandomisation dropouts: not stated Revised sample size: 80 Mean age (years): 59 Females: 29 (36.3%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 11 (13.8%) Ascites with low protein: not stated Primary prophylaxis: 80 (100%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 74 (92.5%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 6 (7.5%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • renal impairment • chronic kidney disease • recent exposure to radioactive materials • sepsis • nephrotoxic drugs • hepatocellular carcinoma
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 40) Further details: rifaximin 550 mg BD for 3 months Group 2: no active intervention (n = 40) Further details: no treatment

Ibrahim 2017 *(Continued)*

Outcomes	None of the outcomes of interest were reported. Follow-up (months): 3
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report mortality or adverse events, which are expected to be reported in such trials.
Other bias	Low risk	Comment: no other bias noted

Kimer 2017

Methods	Randomised clinical trial
Participants	Country: Denmark Period of recruitment: 2013–2015 Number randomised: 54 Postrandomisation dropouts: 0 (0%) Revised sample size: 54 Mean age (years): 56 Females: 9 (16.7%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated

Kimer 2017 *(Continued)*

	Alcohol-related cirrhosis: 42 (77.8%) Viral-related cirrhosis: 6 (11.1%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 2 (3.7%) Other causes for cirrhosis: 4 (7.4%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • portal hypertension with an hepatic venous pressure gradient ≥ 10 mmHg Exclusion criteria: • cardiac or respiratory failure • invasive cancer within the past 5 years • infection • antibiotic treatment 14 days prior to inclusion • overt hepatic encephalopathy • kidney failure with serum creatinine > 200 µmol/L • transfusion-requiring bleeding within 1 week prior to inclusion • anaemia • continuous abuse of alcohol with symptoms of withdrawal • expected survival < 3 months
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 36) Further details: rifaximin 550 mg BD for 4 weeks Group 2: no active intervention (n = 18) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of serious adverse events per participant; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition). Follow-up (months): 1
Notes	Trial name/trial registry number: NCT01769040 Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated logarithm provided by our external data manager."
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated logarithm provided by our external data manager."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double-blind, randomized, and placebo-controlled trial… All patients and personnel were blinded to the treatment."

Kimer 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, randomized, and placebo-controlled trial… All patients and personnel were blinded to the treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Latif 2016

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: not stated Number randomised: 280 Postrandomisation dropouts: not stated Revised sample size: 280 Mean age (years): 50 Females: 113 (40.4%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 0 (0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • history of hepatorenal syndrome Exclusion criteria: • history of psychiatric illness or history of tranquilliser intake • portal vein thrombosis • history of alcohol intake • altered conscious level due to drug poisoning • hypersensitive to neomycin or ciprofloxacin

Latif 2016 *(Continued)*

- comorbid condition such as glomerulonephritis, renal failure, and congestive heart failure
- people already receiving oral antibiotics on regular basis
- contraindication for use of aminoglycosides and fluoroquinolones

Interventions	Participants randomly assigned to 2 groups. Group 1: neomycin (n = not stated) Further details: neomycin (no further details on dose or duration) Group 2: ciprofloxacin (n = not stated) Further details: ciprofloxacin (no further details on dose or duration) Additional details: no information on the number of participants in each group.
Outcomes	None of the outcomes of interest were reported. Follow-up (months): 1
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Lontos 2014

Methods	Randomised clinical trial
Participants	Country: Australia Period of recruitment: 2005

Lontos 2014 *(Continued)*

	Number randomised: 80 Postrandomisation dropouts: not stated Revised sample size: 80 Mean age (years): 53 Females: 20 (25.0%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: 69 (86.3%) Primary prophylaxis: 59 (73.8%) Alcohol-related cirrhosis: 34 (42.5%) Viral-related cirrhosis: 29 (36.3%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 17 (21.3%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • allergies to sulphur-containing drugs or quinolones • documented failure of either study drug in the past while on prophylaxis • antibiotic therapy in the 2 weeks prior to the inclusion • severe renal impairment • hepatocellular carcinoma or other conditions with an expected survival < 3 months • current bacterial infection • secondary peritonitis • active autoimmune hepatitis • HIV infection • previous liver transplantation
Interventions	Participants randomly assigned to 2 groups. Group 1: sulfamethoxazole + trimethoprim (n = 40) Further details: sulfamethoxazole 160 mg + trimethoprim 800 mg daily (duration not stated, but probably until follow-up) Group 2: norfloxacin (n = 40) Further details: norfloxacin 400 mg daily (duration not stated, but probably until follow-up)
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; liver transplantation; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 12
Notes	Trial name/trial registry number: ACTRN12605000560695 Attempted to contact authors in November 2018, but received no replies.
Risk of bias	

Lontos 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was achieved with computer generated and sealed in opaque envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was achieved with computer generated and sealed in opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was non-blinded to both investigators and patients."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was non-blinded to both investigators and patients."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Madrid 2001

Methods	Randomised clinical trial
Participants	Country: Chile Period of recruitment: not stated Number randomised: 22 Postrandomisation dropouts: not stated Revised sample size: 22 Mean age (years): 58 Females: 11 (50.0%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 13 (59.1%) Viral-related cirrhosis: 7 (31.8%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 2 (9.1%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated

Madrid 2001 *(Continued)*

	Inclusion criteria: • people with liver cirrhosis Exclusion criteria: • diabetes mellitus • cardiovascular disorders or abnormal electrocardiograph • electrolyte disturbances • spontaneous bacterial peritonitis • previous abdominal surgery • renal failure • treated with lactulose, antibiotics, or prokinetic drugs during past 30 days
Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin + neomycin (n = 12) Further details: norfloxacin 400 mg BD alternating with neomycin 500 mg TDS, alternating every 15 days for 6 months Group 2: no active intervention (n = 10) Further details: placebo Additional details: another group which received cisapride was excluded from the analysis
Outcomes	Outcomes reported: number of other decompensation events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used but no information about blinding provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used but no information about blinding provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.

Madrid 2001 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Miglio 1997

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 60 Postrandomisation dropouts: not stated Revised sample size: 60 Mean age (years): 61 Females: 29 (48.3%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 60 (100%) Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 24 (40.0%) Viral-related cirrhosis: 35 (58.3%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 1 (1.7%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • hepatic encephalopathy
Interventions	Participants randomly assigned to 2 groups. Group 1: neomycin (n = 30) Further details: neomycin 1 g TDS for 6 months Group 2: rifaximin (n = 30) Further details: rifaximin 400 mg TDS for 6 months
Outcomes	None of the outcomes of interest were reported. Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement

Miglio 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned, following a predetermined computer-generated list supplied by Alfa Wassermann (Bologna, Italy), either to rifaximin 400 mg three times daily or neomycin 1 g three times daily… The two drugs were supplied by Alfa Wassermann, as identical tablets, indistinguishable in appearance and similar in taste; all tablet bottles were labelled with the same name."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned, following a predetermined computer-generated list supplied by Alfa Wassermann (Bologna, Italy), either to rifaximin 400 mg three times daily or neomycin 1 g three times daily… The two drugs were supplied by Alfa Wassermann, as identical tablets, indistinguishable in appearance and similar in taste; all tablet bottles were labelled with the same name."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind randomised, controlled, multicentre trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind randomised, controlled, multicentre trial."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Moreau 2015

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: not stated Number randomised: 291 Postrandomisation dropouts: not stated Revised sample size: 291 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 223 (76.6%)

Moreau 2015 *(Continued)*

	Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 68 (23.4%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • Child-Pugh class C cirrhosis
Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 144) Further details: norfloxacin 400 mg daily for 6 months Group 2: no active intervention (n = 147) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; number of other decompensation events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo-controlled."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, placebo-controlled."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Mostafa 2014

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: 2012–2013 Number randomised: 20 Postrandomisation dropouts: 0 (0%) Revised sample size: 20 Mean age (years): 51 Females: 5 (25.0%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: 0 (0%) Viral-related cirrhosis: 20 (100%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 0 (0%) Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • active gastrointestinal bleeding • hepatic encephalopathy (> grade 2) • hepatocellular carcinoma or other malignancies • allergy to quinolones
Interventions	Participants randomly assigned to 2 groups. Group 1: sparfloxacin (n = 10) Further details: sparfloxacin 200 mg alternate days for 10 days and then twice weekly for a total of 6 months Group 2: ciprofloxacin (n = 10) Further details: ciprofloxacin 750 mg/week orally for 6 months Additional details: 2 other groups that received pentoxyphylline were excluded
Outcomes	None of the outcomes of interest were reported. Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement

Mostafa 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Randomized, blind, and controlled study." Comment: further information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Randomized, blind, and controlled study" Comment: further information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Mostafa 2015

Methods	Randomised clinical trial
Participants	Country: Egypt Period of recruitment: 2013–2014 Number randomised: 70 Postrandomisation dropouts: 0 (0%) Revised sample size: 70 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: 0 (0%) Viral-related cirrhosis: 70 (100%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 0 (0%) Other causes for cirrhosis: 0 (0%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria:

Mostafa 2015 *(Continued)*

- active gastrointestinal bleeding
- encephalopathy (> grade 2)
- hepatocellular carcinoma or other malignancies
- allergy to medications used

Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 30) Further details: norfloxacin 400 mg daily for 6 months Group 2: rifaximin (n = 40) Further details: rifaximin 800 mg daily for 6 months Additional details: the information in table 1 was incorrect, so no details entered.
Outcomes	Outcomes reported: proportion of people with serious adverse events; number of serious adverse events per participant; proportion of people with any adverse events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Single-blind" Comment: further information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Single-blind" Comment: further information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether participants were excluded after randomisation.
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Nawaz 2015

Methods	Randomised clinical trial
Participants	Country: Pakistan

Nawaz 2015 *(Continued)*

	Period of recruitment: not stated Number randomised: 150 Postrandomisation dropouts: not stated Revised sample size: 150 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): 150 (100%) Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • people with ≥ 2 episodes of hepatic encephalopathy
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 75) Further details: rifaximin 550 mg BD for 6 months Group 2: no active intervention (n = 75) Further details: placebo
Outcomes	Outcomes reported: number of other decompensation events Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used, but unclear if blinding was achieved.

Nawaz 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used, but unclear if blinding was achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Praharaj 2017

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 59 Postrandomisation dropouts: not stated Revised sample size: 59 Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 0 (0%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated
Interventions	Participants randomly assigned to 2 groups. Group 1: norfloxacin (n = 33) Further details: norfloxacin 400 mg daily for 6 months Group 2: rifaximin (n = 26) Further details: rifaximin 550 mg BD for 6 months Additional details: another 58 participants with high Child-Turcotte-Pugh score were excluded as it was unclear whether these participants had clinical features of decompensated liver disease.

Praharaj 2017 *(Continued)*

Outcomes	Outcomes reported: proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Rolachon 1995

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1991–1993 Number randomised: 60 Postrandomisation dropouts: not stated Revised sample size: 60 Mean age (years): 55 Females: 28 (46.7%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: 60 (100%) Primary prophylaxis: 53 (88.3%)

Rolachon 1995 *(Continued)*

	Alcohol-related cirrhosis: 55 (91.7%) Viral-related cirrhosis: 1 (1.7%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 2 (3.3%) Other causes for cirrhosis: 2 (3.3%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated
Interventions	Participants randomly assigned to 2 groups. Group 1: ciprofloxacin (n = 28) Further details: ciprofloxacin 750 mg/week orally for 6 months Group 2: no active intervention (n = 32) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition); length of hospital stay Follow-up (months): 6
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind … placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind … placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Singh 1995

Methods	Randomised clinical trial

Singh 1995 *(Continued)*

Participants	Country: USA Period of recruitment: not stated Number randomised: 60 Postrandomisation dropouts: 0 (0%) Revised sample size: 60 Mean age (years): 45 Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: 47 (78.3%) Alcohol-related cirrhosis: 24 (40.0%) Viral-related cirrhosis: 31 (51.7%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: 5 (8.3%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • allergy to sulfonamides • renal failure • active infections
Interventions	Participants randomly assigned to 2 groups. Group 1: sulfamethoxazole + trimethoprim (n = 30) Further details: sulfamethoxazole 160 mg + trimethoprim 800 mg daily (duration not stated, but probably until follow-up) Group 2: no active intervention (n = 30) Further details: no treatment
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition). Follow-up (months): 3
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available

Singh 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Tellez-Avila 2014

Methods	Randomised clinical trial
Participants	Country: Mexico Period of recruitment: 2008–2009 Number randomised: 95 Postrandomisation dropouts: 0 (0%) Revised sample size: 95 Mean age (years): 57 Females: 58 (61.1%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: 0 (0%) Primary prophylaxis: 95 (100%) Alcohol-related cirrhosis: 17 (17.9%) Viral-related cirrhosis: 61 (64.2%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 0 (0%) Other causes for cirrhosis: 17 (17.9%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • active gastrointestinal bleeding • antibiotics within the last 30 days

Tellez-Avila 2014 *(Continued)*

- pregnancy
- encephalopathy ≥ grade 2
- immune-related comorbidities
- immunosuppressive therapy
- hepatocellular carcinoma or other malignancies
- allergy to fluoroquinolones
- bacterial infection at the time of enrolment

Interventions	Participants randomly assigned to 2 groups. Group 1: ciprofloxacin (n = 49) Further details: ciprofloxacin 500 mg/day for 1 month Group 2: no active intervention (n = 46) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 4
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Low risk	Quote: "A random allocation sequence was generated and kept in a sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomized, double-blind placebo-controlled clinical trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomized, double-blind placebo-controlled clinical trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Terg 2008

Methods	Randomised clinical trial

Terg 2008 *(Continued)*

Participants	Country: Argentina Period of recruitment: 2000–2005 Number randomised: 100 Postrandomisation dropouts: 0 (0%) Revised sample size: 100 Mean age (years): 57 Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: 100 (100%) Primary prophylaxis: 100 (100%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • antibiotics in the previous 30 days • pregnancy • active gastrointestinal bleeding • encephalopathy > grade 2 • hepatocellular carcinoma or other malignancies • allergy to quinolones • renal or liver failure • bacterial infection
Interventions	Participants randomly assigned to 2 groups. Group 1: ciprofloxacin (n = 50) Further details: ciprofloxacin 500 mg/day (duration not stated – probably until end of follow-up) Group 2: no active intervention (n = 50) Further details: placebo
Outcomes	Outcomes reported: all-cause mortality; number of any adverse events per participant; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 8
Notes	Trial name/trial registry number: CCT-NAPN-16065 Attempted to contact authors in November 2018, but received no replies.
Risk of bias	

Terg 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with sealed and consecutively numbered opaque envelopes containing the treatment option as derived from computer generated random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with sealed and consecutively numbered opaque envelopes containing the treatment option as derived from computer generated random numbers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Multicenter, randomized, double blind, and placebo-controlled study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Multicenter, randomized, double blind, and placebo-controlled study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: protocol not available, but authors reported mortality and adverse events adequately.
Other bias	Low risk	Comment: no other bias noted

Trespi 1999

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 52 Postrandomisation dropouts: not stated Revised sample size: 52 Mean age (years): 63 Females: 11 (21.2%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: 52 (100%) Viral-related cirrhosis: 0 (0%) Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): 0 (0%)

Trespi 1999 *(Continued)*

	Other causes for cirrhosis: 0 (0%) Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Inclusion criteria: • people with ascites and alcoholic cirrhosis
Interventions	Participants randomly assigned to 2 groups. Group 1: rifaximin (n = 27) Further details: rifaximin 400 mg BD for 1 week/month (duration not stated, probably until the end of the follow-up period) Group 2: no active intervention (n = 25) Further details: no treatment
Outcomes	Outcomes reported: proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 12
Notes	Attempted to contact authors in November 2018, but received no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

Yim 2018

Methods	Randomised clinical trial
Participants	Country: South Korea

Yim 2018 *(Continued)*

	Period of recruitment: not stated Number randomised: 124 Postrandomisation dropouts: 12 (9.7%) Revised sample size: 112 Reasons for postrandomisation dropouts: not stated Mean age (years): not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Ascites with low protein: not stated Primary prophylaxis: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Exclusion criteria: • hypersensitivity or intolerability with quinolones • hepatocellular carcinoma beyond Milan Criteria • hepatic encephalopathy > stage 2 • history of treatment with antibiotics within 2 weeks of enrolment • HIV infection • uncontrolled malignancy • women at child-bearing age unwilling to use effective measures for contraception • pregnant or breast-feeding women
Interventions	Participants randomly assigned to 2 groups. Group 1: ciprofloxacin (n = 57) Further details: ciprofloxacin 750 mg weekly for 12 months Group 2: norfloxacin (n = 55) Further details: norfloxacin 400 mg daily for 12 months Additional details: none of baseline characteristics were extracted as the outcomes were presented for 55 vs 57 participants, but the baseline characteristics were described for 62 participants in each group.
Outcomes	Outcomes reported: all-cause mortality; number of serious adverse events per participant; liver transplantation; proportion with spontaneous bacterial peritonitis (as per definition) Follow-up (months): 12
Notes	Trial name/trial registry number: NCT01542801 Attempted to contact authors in November 2018, but received no replies.

Yim 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization table was generated by a statistician (SSK) using the nQuery Advisor program."
Allocation concealment (selection bias)	Low risk	Quote: "Centralized web-based interactive response system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open-label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts and it was unclear whether these were related to outcomes.
Selective reporting (reporting bias)	High risk	Comment: protocol not available, and authors did not report the outcomes assessed adequately.
Other bias	Low risk	Comment: no other bias noted

AIH: autoimmune hepatitis; BD: twice daily; n: number of participants; OD: once daily; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; TDS: three times daily.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1971	Not a randomised clinical trial
Anonymous 2006	Not a randomised clinical trial
Assy 2005	Not a randomised clinical trial
Bajaj 2012	Not a randomised clinical trial
Bendtsen 2005	Not a randomised clinical trial
Boccardi 1974	Not a randomised clinical trial
Bode 1997	Not all participants had liver cirrhosis.
Gerbes 1997	Not a randomised clinical trial
Gines 1998	Not a randomised clinical trial
Gupta 2013	Not all participants had decompensated liver cirrhosis.

Study	Reason for exclusion
Henrion 1992	Not a randomised clinical trial
Jalan 2010	Not a randomised clinical trial
Kemp 2009	Cross-over trial with short duration of treatment with no information on the outcomes prior to cross-over.
Kumar 2014	Participants received a drug that is known to affect immune system; therefore, the effect estimates obtained were not relevant to the research question.
Lata 2005	Short-term antibiotics for upper gastrointestinal bleeding
Novella 1997	Comparison of 2 different regimens of the same drug
Pateron 1992	Short-term antibiotics for upper gastrointestinal bleeding
Rimola 1985	Short-term antibiotics for upper gastrointestinal bleeding
Schubert 1991	Not a randomised clinical trial
Siddique 2010	Not a randomised clinical trial
Vibert 2008	Not a randomised clinical trial

Characteristics of ongoing studies *[ordered by study ID]*

Casper 2015

Trial name or title	INCA trial
Methods	Double-blind, placebo-controlled clinical trial
Participants	People with liver cirrhosis and ascites
Interventions	Group 1: norfloxacin 400 mg once daily Group 2: placebo once daily
Outcomes	Mortality, spontaneous bacterial peritonitis, other clinically significant infections, duration of un-scheduled cirrhosis-associated hospitalisation within 12 months
Starting date	February 2014
Contact information	Dr Marcus Casper (Email: markus.casper@uks.eu)
Notes	German Clinical Trials Register DRKS00005616; EU Clinical Trials Register EudraCT 2013-001626-26

ADDITIONAL TABLES

Table 1. Characteristics of included studies and potential effect modifiers (arranged by comparison)

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3601722.

Table 2. Model fit

Parameter	Fixed-effect model	Random-effects model	Inconsistency model
All-cause mortality at maximal follow-up			
Dbar	152.6	152.1	150.5
DIC	174.4	175.9	176.2
pD	21.8	23.81	25.75
Proportion of people with one or more serious adverse events			
Dbar	152.6	152	—
DIC	174.4	175.7	—
pD	21.8	23.75	—
Number of serious adverse events per participant			
Dbar	18.46	18.41	—
DIC	21.42	21.32	—
pD	2.955	2.905	—
Any adverse events			
Dbar	33.46	29.75	—
DIC	38.49	35.41	—
pD	5.024	5.651	—
Liver transplantation			
Dbar	27.87	152	—
DIC	33.8	175.7	—
pD	5.936	23.75	—
Proportion with spontaneous bacterial peritonitis			
Dbar	150.1	121.8	121.9
DIC	170.6	149.6	147
pD	20.49	27.78	25.1

Table 2. Model fit *(Continued)*

Number of decompensation episodes			
Dbar	95.85	95.75	92.91
DIC	107.7	107.5	108.3
pD	11.83	11.77	15.37
Length of hospital stay			
Dbar	5.667	152	—
DIC	7.677	175.7	—
pD	2.011	23.75	—

Dbar: posterior mean of deviance; DIC: deviance information criteria; pD: effective number of parameters or leverage.

Table 3. Effect estimates (network meta-analysis)

All-cause mortality (hazard ratio (95% credible interval))	**No active intervention**	**Rifaximin**	**Norfloxacin**	**Ciprofloxacin**	**Sulfamethoxazole + trimethoprim**	**Norfloxacin + rifaximin**	**Rufloxacin**
No active intervention	–	0.95 (0.04 to 28.25)	0.70 (0.35 to 1.39)	0.44 (0.05 to 3.67)	0.27 (0.03 to 1.33)	–	–
Rifaximin	0.57 (0.33 to 1.00)	–	1.72 (0.07 to 40.77)	–	–	0.76 (0.25 to 2.21)	–
Norfloxacin	0.74 (0.49 to 1.09)	1.29 (0.75 to 2.12)	–	1.37 (0.55 to 3.54)	0.70 (0.02 to 22.74)	0.50 (0.17 to 1.38)	1.82 (0.43 to 10.40)
Ciprofloxacin	0.61 (0.31 to 1.16)	1.08 (0.46 to 2.33)	0.83 (0.42 to 1.63)	–	–	–	–
Sulfamethoxazole + trimethoprim	0.47 (0.20 to 1.00)	0.81 (0.33 to 1.88)	0.63 (0.29 to 1.27)	0.76 (0.29 to 2.00)	–	–	–
Norfloxacin + rifaximin	0.40 (0.12 to 1.17)	0.69 (0.22 to 1.93)	0.54 (0.17 to 1.51)	0.64 (0.18 to 2.16)	0.85 (0.22 to 3.04)	–	–
Rufloxacin	1.45 (0.27 to 8.21)	2.52 (0.47 to 15.55)	1.93 (0.39 to 10.36)	2.34 (0.41 to 13.93)	3.11 (0.53 to 19.09)	3.74 (0.54 to 29.11)	–
Proportion of people with any adverse events (odds ratio (95% credible interval))	**No active intervention**	**Rifaximin**	**Norfloxacin**	—	—	—	—
No active intervention	–	0.96 (0.04 to 23.29)	–	—	—	—	—
Rifaximin	1.01 (0.00 to 853.21)	–	12.35 (0.15 to 10678.63)	—	—	—	—
Norfloxacin	11.85 (0.01 to 263,023.85)	12.60 (0.15 to 11707.68)	–	—	—	—	—
Liver transplantation (hazard ratio	**No active intervention**	**Norfloxacin**	**Ciprofloxacin**	**Sulfamethoxazole + trimethoprim**	—	—	—

Table 3. Effect estimates (network meta-analysis) *(Continued)*

(95% credible interval))							
No active intervention	–	0.91 (0.29 to 3.01)	–	–	—	—	—
Norfloxacin	0.93 (0.31 to 3.44)	–	0.66 (0.19 to 2.12)	2.71 (1.10 to 7.59)	—	—	—
Ciprofloxacin	0.62 (0.12 to 3.31)	0.67 (0.19 to 2.12)	–	–	—	—	—
Sulfamethoxazole + trimethoprim	2.62 (0.62 to 11.91)	*2.74 (1.12 to 7.08)*	4.08 (0.92 to 19.61)	–	—	—	—
Number of decompensation episodes (rate ratio (95% credible interval))	**No active intervention**	**Rifaximin**	**Norfloxacin**	**Norfloxacin + rifaximin**	**Norfloxacin + neomycin**	—	—
No active intervention	–	*0.63 (0.48 to 0.82)*	0.78 (0.54 to 1.09)	–	*0.05 (0.00 to 0.35)*	—	—
Rifaximin	*0.61 (0.46 to 0.80)*	–	3.60 (0.75 to 27.30)	1.01 (0.10 to 10.94)	–	—	—
Norfloxacin	0.81 (0.58 to 1.12)	1.34 (0.89 to 2.01)	–	0.29 (0.03 to 1.36)	–	—	—
Norfloxacin + rifaximin	0.33 (0.04 to 1.40)	0.54 (0.07 to 2.29)	0.40 (0.05 to 1.73)	–	–	—	—
Norfloxacin + neomycin	*0.06 (0.00 to 0.33)*	*0.09 (0.00 to 0.55)*	*0.07 (0.00 to 0.43)*	0.17 (0.00 to 2.56)	–	—	—

The table provides the effect estimates of each pairwise comparison for the different outcomes. The top half of the subtable for each outcome indicates the effect estimates from the direct comparisons. The bottom half of the subtable for each outcome indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, for example A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by '–'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.
Italics indicate statistically significant results
—: comparison not performed.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 11, 2018	#1 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees #2 antibiotic* #3 antibacteri* near prophyl* #4 #1 or #2 or #3 #5 MeSH descriptor: [Liver Cirrhosis] explode all trees #6 ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #7 #5 or #6 #8 #4 and #7
MEDLINE Ovid	January 1947 to November 2018	1. exp antibiotic prophylaxis/ 2. antibiotic*.ti,ab. 3. (antibacteri* adj prophyl*).ti,ab. 4. 1 or 2 or 3 5. exp Liver Cirrhosis/ 6. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab. 7. 5 or 6 8. 4 and 7 9. randomized controlled trial.pt. 10. controlled clinical trial.pt. 11. randomized.ab. 12. placebo.ab. 13. drug therapy.fs. 14. randomly.ab. 15. trial.ab. 16. groups.ab. 17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp animals/ not humans.sh. 19. 17 not 18 20. 8 and 19
Embase Ovid	January 1974 to November 2018	1. exp antibiotic prophylaxis/

(Continued)

		2. antibiotic*.ti,ab. 3. (antibacteri* adj prophyl*).ti,ab. 4. 1 or 2 or 3 5. exp liver cirrhosis/ 6. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab. 7. 5 or 6 8. 4 and 7 9. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 10. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 11. 9 or 10 12. 8 and 11
Science Citation Index Expanded (Web of Science)	January 1945 to November 2018	#1 TS=(antibiotic*) #2 TS=(antibacteri* near prophyl*) #3 #2 OR #1 #4 TS=((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #6 #3 AND #4 AND #5
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	November 2018	Condition: cirrhosis; intervention: antibiotic*
ClinicalTrials.gov	November 2018	antibiotic | Interventional Studies | Cirrhosis | Phase 2, 3, 4
European Medical Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	November 2018	spontaneous bacterial peritonitis

Appendix 2. Data

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3601730.

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: KG
Providing general advice on the protocol: ET, PW
Securing funding for the protocol: KG
Performing previous work that was the foundation of the current study: not applicable

Review

Co-ordinating the review: KG
Study selection: KG, LP, AB, MP, DR
Data extraction: KG, LP
Writing the review: KG, DR
Providing advice on the review: PW, SF, AJS, NH, EJM, MC, DT, CSP, BRD, ET
Securing funding for the review: KG

DECLARATIONS OF INTEREST

KO: none.
DR: none.
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EJM: none.
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MC: none.
DT: none.
BRD: none.
ET: none.
KSG: none.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

  Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.

  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made some changes from our published protocol (Gurusamy 2018).

- We did not perform Trial Sequential Analysis because the risk of false positive results with Bayesian meta-analysis is probably less or at least equivalent to Trial Sequential Analysis.
- We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the 'Summary of findings' tables.
- The trials did not report the proportion of people with other episodes of decompensation but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.

- In the absence of a protocol published prior to the start of the study, we classified the risk of bias as low for selective reporting bias only when reporting mortality, adverse events, and spontaneous bacterial peritonitis, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.
- We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.
- We did not present some information such as ranking probability tables, rankograms, and surface area under the curve (SUCRA plots) because of the concern about the misinterpretation of the results. We have highlighted this clearly within the text of the review along with the reasons for not presenting them.

NOTES

The 'Methods' section of this review was based on a standard Cochrane Hepato-Biliary Group template, incorporating advice by the Complex Reviews Support Unit for a network meta-analysis review (Best 2018).